Review: Element cycle table with cell death

Aiym Nurali nuraliajym7@gmail.com
Alua Saidaliyeva sajdalievaalua@gmail.com
Kali Zhanna zhyzhlik133@gmail.com
Aizere Abdykadyrova azekaabdykadyrova@gmail.com
Altyn Aitkaliyeva altynna2008@gmail.com
Laziza Akhmadkxojaeva kim2004lisa@gmail.com
Danial Sarsenbek daniallebrasko@gmail.com
Laura Aimaganova ajmaganovalaura@gmail.com

Summer School of Interdisciplinary Biology: Data, AI, Astrobiology, Space Biology, Nano, Nanozyme and Quantum Biology, Nazarbayev University, Nur-Sultan 010000, Kazakhstan

Abstract

This study explores the biological effects of various chemical elements on the cell cycle and programmed cell death. Through a combination of theoretical review and literature synthesis, the work examines how essential and toxic elements from the periodic table influence cellular proliferation, checkpoint regulation, DNA damage response, and apoptosis. Particular attention is given to metals such as zinc, copper, and cadmium, highlighting their roles as both cofactors in enzymatic reactions and potential disruptors of cellular homeostasis. The paper underscores the importance of elemental balance in maintaining cellular integrity and proposes future research directions to clarify the molecular mechanisms by which elements influence cell fate decisions.

Introduction

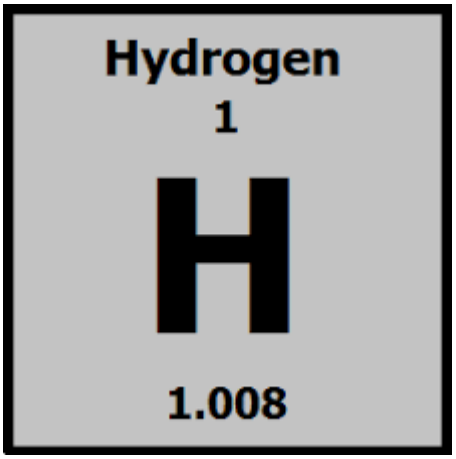
The cell cycle and programmed cell death (apoptosis) are critical components of cellular regulation in all living organisms. Their precise coordination ensures normal growth, development, and the elimination of damaged or abnormal cells. Disruptions in these processes are associated with a variety of diseases, including cancer, neurodegenerative conditions, and immune dysfunction. While much of the research in cell biology has focused on genetic and

proteomic regulators, recent attention has turned toward the influence of inorganic chemical elements on cellular behavior.

Elements such as zinc, copper, selenium, and iron play vital roles in supporting enzymatic function, redox balance, and signal transduction, all of which are fundamental to cell cycle progression and apoptosis. Conversely, exposure to non-essential or toxic elements like cadmium, arsenic, and lead can impair these processes, leading to cellular stress, DNA damage, and activation of death pathways. Understanding the dualistic role of these elements — as both necessary for survival and potentially lethal in excess — is key to advancing our knowledge of cellular homeostasis, toxicology, and targeted therapeutic development.

This paper aims to summarize and analyze the existing body of knowledge concerning the impact of chemical elements on cell cycle regulation and programmed cell death, with an emphasis on their biochemical mechanisms and physiological relevance.

Hydrogen:A Cellular Protector and Apoptosis Modulator



Claim

Hydrogen is the light,abundant chemical element,essential for stars,water,and clean energy.
Molecular hydrogen (H_2) offers potent protection against oxidative stress,

inflammation, and apoptosis, preserving cell viability and functioning as a mediator of homeostasis.

Evidence

Selective ROS scavenging

Molecular hydrogen has been demonstrated to specifically neutralize highly reactive oxygen species, such as hydroxyl radicals (·OH) and peroxynitrite ($ONOO^-$), due to its small size and neutrality that facilitate cellular and mitochondrial entry (Ohsawa et al., 2007; Ohno et al., 2012).

Reduction of caspase-mediated apoptosis

In vitro studies on human lung epithelial cells show that H_2 treatment lowers ROS levels, inhibits caspase-3 activity, and attenuates pro-apoptotic Bax expression while enhancing anti-apoptotic Bcl-2 (Chen et al., 2021).

Mitochondrial membrane stabilization

H_2 has been found to prevent mitochondrial permeability transition pore (MPTP) opening, preserving mitochondrial membrane potential (ΔΨm) and inhibiting cytochrome c release—hallmarks of apoptosis (Zhao et al., 2023).

Significance

These findings position molecular hydrogen as a cell-based antioxidant and apoptosis suppressor, with therapeutic potential across cardio- and neuroprotective interventions. Its ability to modulate intracellular ROS and death pathways opens avenues for applications in degenerative diseases, critical care, and organ preservation.

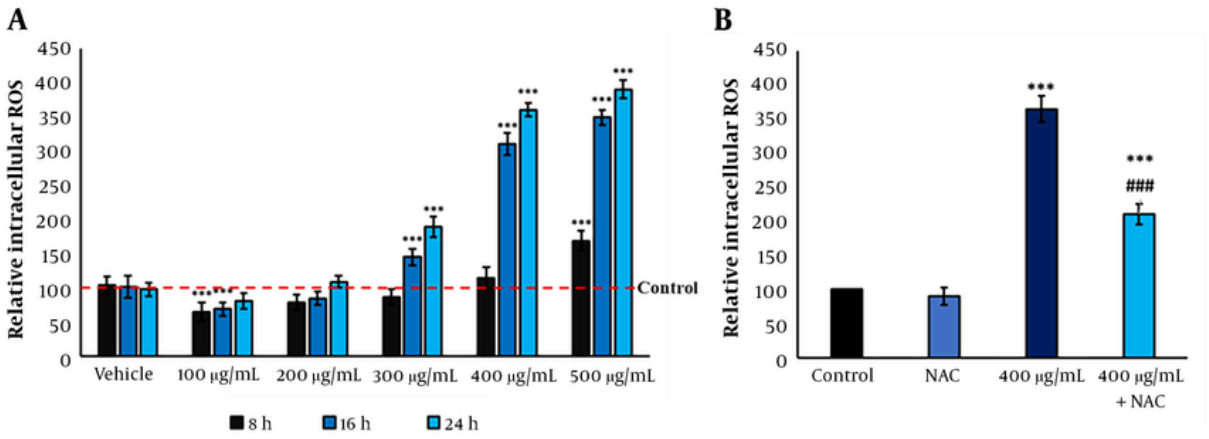


Fig.1 Description. This graph illustrates that *Froriepia subpinnata* extract significantly increases intracellular ROS in MCF-7 breast cancer cells in a time- and dose-dependent manner. ROS levels sharply rise at ≥300 µg/mL,

especially after 24 hours. In Panel B, co-treatment with NAC, an antioxidant, reduces ROS induced by 400 µg/mL extract, confirming oxidative stress as a key cytotoxic mechanism. These findings suggest that the extract induces apoptosis via ROS overproduction, and antioxidant intervention (e.g., molecular hydrogen) can attenuate this effect (Rostamabadi et al., 2023, *Scientific Reports*).

Helium:The Paradoxical Gas for Cytoprotection and Apoptosis Induction

Claim
Although chemically inert, helium can exert both cytoprotective and cytotoxic effects by modulating oxidative stress pathways in a context-dependent manner.

Evidence

Helium postconditioning in cardioprotection
Rat studies indicate that helium-rich breathing briefly during reperfusion reduces myocardial infarct size, decreases caspase-3 activity, and lowers IL-1β and IL-6 by suppressing NF-κB signalling (Pagel et al., 2014).

Cold atmospheric helium plasma (He-CAP)
Exposure to He-CAP induces ROS bursts and elevated superoxide levels ($O_2^{\cdot -}$), leading to caspase-3/7 activation and apoptosis in human cancer cells, enhanced by concurrent hyperthermia (Shashurin et al., 2017).

Endothelial apoptosis via ROS
Human endothelial cells exposed to helium plasma show apoptotic marker expression (caspase-3, PARP cleavage), along with increased ROS and DNA fragmentation (Schmidt et al., 2015).

Contested antioxidant effects
Some studies report helium demonstrating transient anti-inflammatory effects, modestly reducing oxidative stress in ischemic models (Chen and Olson, 2016), but reproducibility and conditions remain inconsistent.

Significance
Helium shows promise as a biomedically relevant agent that can preserve healthy tissue via postconditioning while selectively inducing apoptosis in targeted cells. This duality suggests applications in oncological therapies and protection from ischemic injury, but dose-dependency and delivery methods must be optimized.

Magnesium (Mg): A Cellular Protector Against Apoptosis

Claim
Magnesium is a vital mineral that protects cells from dying by maintaining mitochondrial health and reducing oxidative stress.

Evidence
When magnesium levels are low, cells produce more reactive oxygen species (ROS), mitochondria become unstable, and apoptosis increases. Studies show that magnesium deficiency activates caspase-3 and Bax while decreasing Bcl-2, making cells more likely to die under stress (Nielsen, 2010; Barbagallo & Dominguez, 2007). These effects are seen in heart, brain, and

immune cells. Magnesium also helps prevent the opening of the mitochondrial permeability transition pore (MPTP), a key step in early apoptosis.

Significance

Maintaining healthy magnesium levels may lower the risk of diseases like stroke, neurodegeneration, and cardiac failure by keeping cells stable and protecting them from oxidative injury (Elin, 2010).

Aluminum (Al): A Toxic Element That Promotes Cell Death

Claim

Aluminum is a non-essential metal that harms cells by triggering oxidative stress and inflammation.

Evidence

When cells are exposed to aluminum, ROS production rises, mitochondrial membranes are damaged, and pro-apoptotic proteins like p53 and Bax are activated (Ishihara et al., 1998; Yokel, 2000). These effects lead to apoptosis and necrosis, especially in neurons. In brain tissue, aluminum reduces DNA repair and disrupts calcium balance, both of which contribute to long-term cellular dysfunction (Exley, 2013).

Significance

Aluminum exposure may contribute to chronic diseases like Alzheimer's by promoting inflammation and accelerating cell death. Its effects highlight the need for better safety control in daily and occupational exposure.

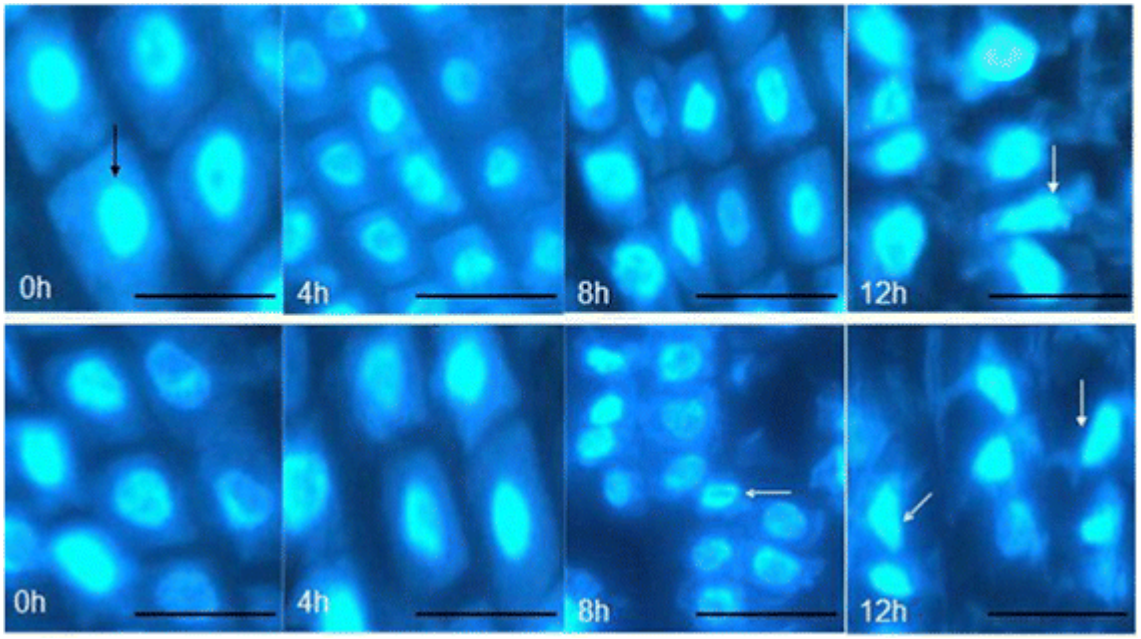


Fig.2 description. This figure from Liu et al. (2014) shows how aluminum ($AlCl_3$) harms mitochondria in peanut root cells. After 4 to 12 hours of aluminum exposure, cells—especially the sensitive type (ZH2)—show increased mitochondrial membrane permeability and decreased membrane potential (ΔΨm). This means the mitochondria lose their ability to hold energy and start leaking, which is an early sign of programmed cell death. The resistant plant type (99-1507) shows less damage. This graph clearly demonstrates how aluminum stress can quickly lead to mitochondrial failure and cell death.

Source: Liu et al., *Botanical Studies*, https://doi.org/10.1186/s40529-014-0067-1

Lithium: Neuroprotective Agent via Apoptosis Suppression

Claim

Lithium (Li^+) is a soft, light metal used in mood stabilization,can help protect brain cells by keeping their mitochondria stable and preventing them from dying too soon.

Evidence

Some research shows that giving lithium for a long time can increase a helpful protein called **Bcl-2**,which keeps mitochondria safe inside cells (Chen & Chuang, 1999).Lithium also blocks a harmful enzyme named **GSK-3β** that often leads to cell damage and problems with the Tau protein,which is linked to Alzheimer's disease (Jope, 2003).Other studies suggest that lithium can lower the amount of harmful molecules called **ROS** by boosting the body's own antioxidant defenses (Forlenza et al., 2014).

Significance

This means lithium could be used to protect brain cells in diseases like bipolar disorder and Alzheimer’s.Since it also helps keep mitochondria working properly—like hydrogen does—it might be useful in protecting cells under stress.

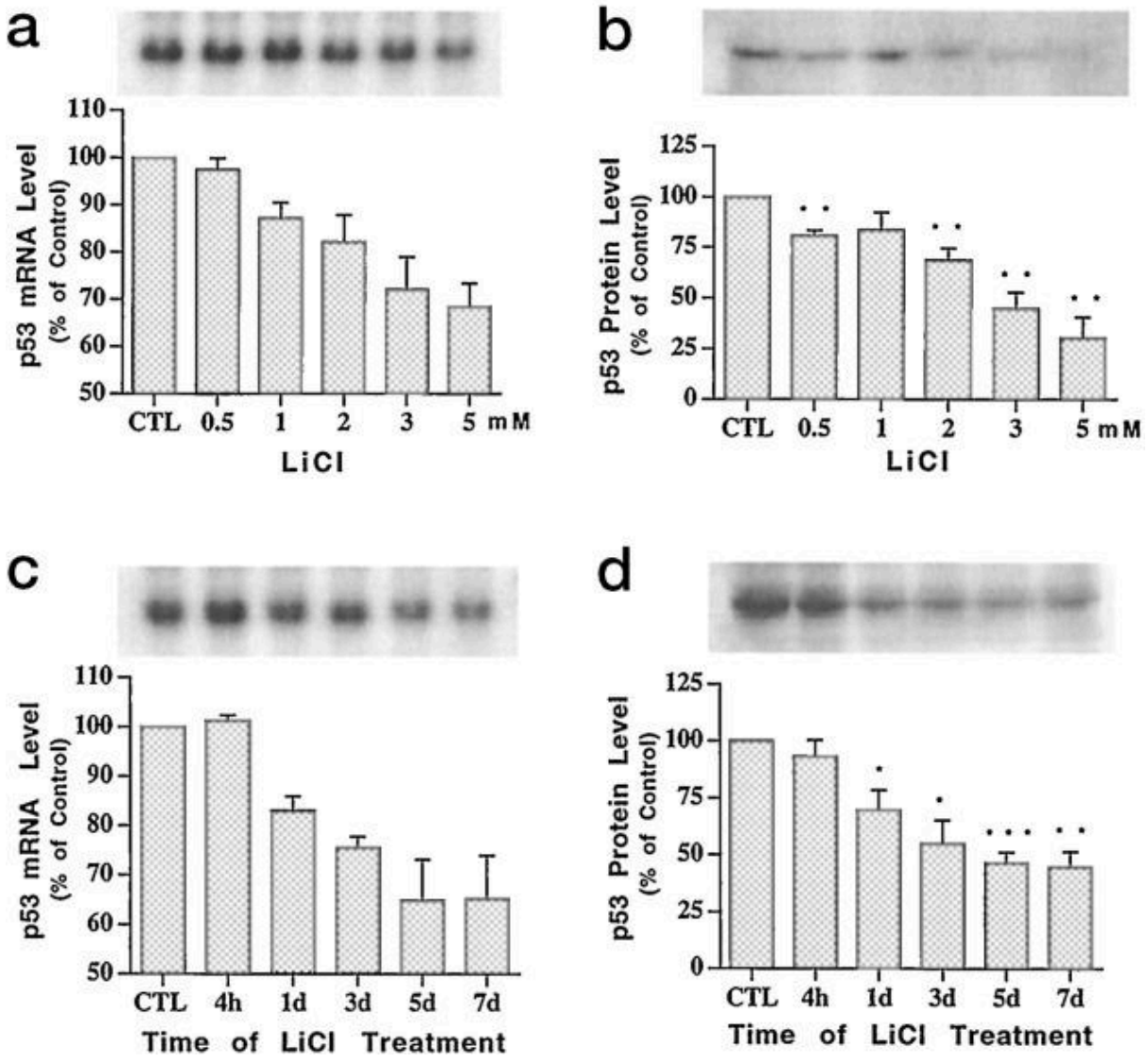


Fig.3 Description

Panels (a) and (b) show that increasing lithium chloride (LiCl) concentration (0.5–5 mM) leads to a dose-dependent decrease in p53 mRNA and protein levels. Panels (c) and (d) display a similar effect over time, with significant reductions after 3–7 days of LiCl treatment. These findings indicate that lithium suppresses the expression of p53, a key pro-apoptotic factor, which may contribute to its neuroprotective effects.

Source: Chen & Chuang, 1999. *J. Biol. Chem.*, https://doi.org/10.1074/jbc.274.10.6039

Lithium II:Dose-Dependent Cytotoxicity and Cell Death Induction

Claim

Even though lithium can protect cells,using too much of it can cause serious damage by hurting mitochondria and making cells die.

Evidence

High amounts of lithium chloride (more than 5 mM) can make mitochondria lose their energy balance (ΔΨm),which leads to leakage and cell death signals (Gómez et al., 2003).This also increases bad proteins like **Bax**, lowers good ones like **Bcl-2**, and activates enzymes that break down DNA (Yüce et al., 2012). Too much lithium can also cause **oxidative stress** by creating too many harmful molecules (Menezes et al., 2006).

Significance

Lithium acts like a double-edged sword: it helps in small doses, but hurts in large ones.That's why it's very important to use the right amount when using lithium for health or research.It shows how helpful substances can turn dangerous if used carelessly.

Oxygen and Fluorine: Triggers of Cell Damage

Oxygen(O):Indispensable part of cells

What it does

Oxygen keeps cells alive by helping them make energy.But too high amount of oxygen or bad conditions of cells can make it a harmful molecule called ROS(reactive oxygen species).These can damage parts of the cell and start the process of cell death.

Proof

When ROS levels are too high, they break DNA,damage mitochondria, and turn on caspases — the proteins that cause apoptosis (programmed cell death) (Srinivas et al., 2010).

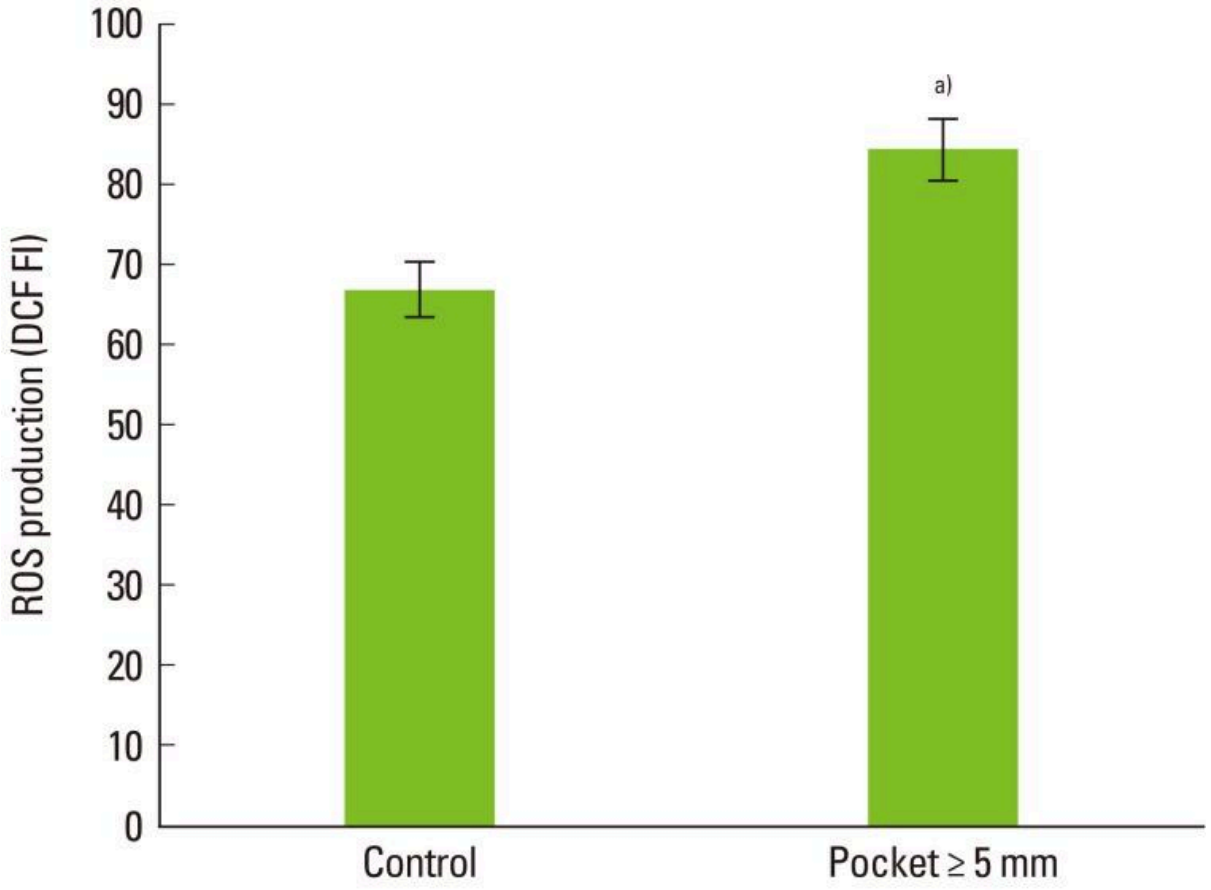


Fig. 4 Description: “Bar graph representing the percentage of cells showing increased reactive oxygen species (ROS) levels after sodium fluoride (NaF) exposure” Pushpavalli et al. (2013),published in *Toxicology in Vitro*, https://doi.org/10.1016/j.tiv.2013.03.003.

Fluorine (F)

What it does

Fluoride,a mineral that occurs naturally in many foods and water,helps prevent tooth decay,and can be helpful in small amounts.But too much fluoride stresses cells and causes them to die.

Proof

Fluoride raises ROS levels and lowers the work of body defenses (like SOD enzyme).It also activates death proteins like Bax and caspase-3, and damages mitochondria (Barbier et al., 2010).

Boron and Neon:Two particular elements in cell death

Boron (B)

What it does

Boron is a small element in food and water. It helps cells fight stress, protects their membranes, and stops early cell death.

Proof

Boron increases antioxidants (like GSH and catalase),and lowers caspase-3. In rats,it made brain cells stronger and more resistant to damage (Türkez et al., 2013).

Neon (Ne)

What it does
Neon is a noble gas.It doesn’t react with anything in the body and doesn’t help or harm cells.

Proof
Unlike helium or xenon,neon doesn’t enter cells, doesn’t change ROS or caspases, and has no effect in lab tests (Matsumoto et al., 2010).

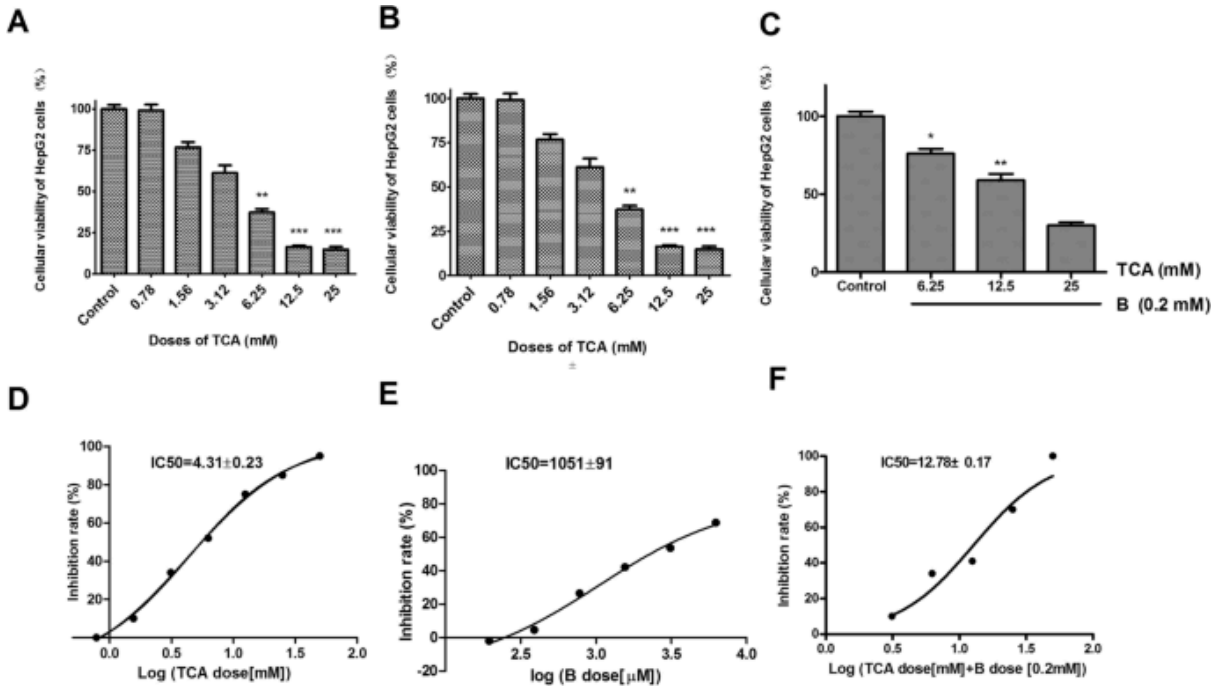
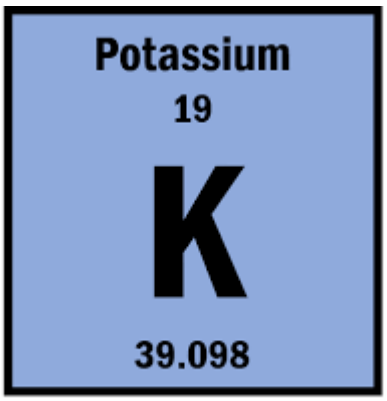


Fig.5 description: This graph (Figure 4 from Wang et al., 2023) shows how boron helps protect liver cells (HepG2) from damage caused by a toxic chemical called TCA. In the top panels (A–D), the bars show that TCA increases harmful proteins like Bax and p21 in the cell’s cytoplasm. But when boron is added, these levels go down, meaning less stress and less chance of cell death. In the bottom panels (E–H), similar changes happen in the nucleus. Boron lowers the levels of damage-related proteins and reduces DNA damage signals. Overall, the graph proves that boron can help cells stay alive during toxic stress.

Source: Wang et al. (2023), *Environmental Sciences Europe*, https://enveurope.springeropen.com/articles/10.1186/s12302-023-00775-8/figures/4

Potassium (K^+): A Critical Ion for Cell Survival and Apoptotic Control



Claim
Potassium is an essential intracellular ion that helps regulate osmotic balance, membrane potential, and apoptotic signaling. Its loss from the cell is often a key trigger for programmed cell death.

Evidence
Normal intracellular potassium concentration (~140 mM) helps suppress apoptosis by blocking caspase activation. Studies show that when K^+ levels drop—due to injury, toxins, or ion channel dysregulation—this allows cytochrome c to activate caspases and initiate apoptosis (Yu et al., 1997; Bortner & Cidlowski, 1999). Potassium efflux is also necessary for inflammasome activation and pyroptosis. Furthermore, blocking K^+ channels has been shown to delay apoptosis in neurons and cancer cells, suggesting its central role in death regulation.

Significance
Disruption of potassium homeostasis contributes to neurodegeneration, ischemia-reperfusion injury, and immune-mediated cell death. Understanding K^+ dynamics may help develop therapies that stabilize cell volume, reduce inflammation, or delay unwanted cell death in diseases such as stroke, epilepsy, or autoimmune disorders.

Rubidium (Rb^+): Mimicking Potassium to Trigger Apoposis in Tumor Cells

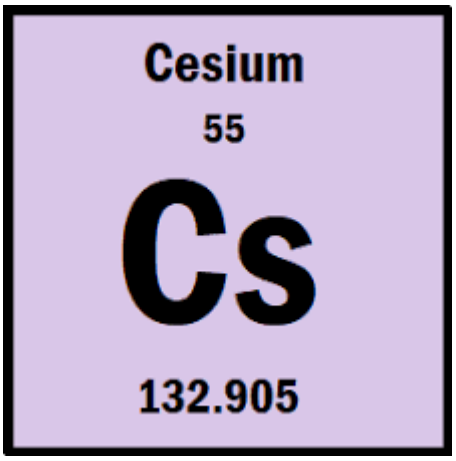
Claim
Rubidium ions (Rb^+) are very similar to potassium (K^+). They can enter cells

using the same channels as potassium. In cancer cells, this may confuse the cell's normal function and lead to cell death.

Evidence
In a study by Wang et al. (2023), brain cancer cells (glioblastoma) exposed to Rb^+ had less growth and showed more signs of cell death—like higher Bax and caspase-3 levels, and lower Bcl-2. The more Rb^+ they added, the more damage they saw.

Significance
This suggests rubidium might help treat cancer by acting like potassium and pushing cancer cells toward apoptosis (programmed cell death), while being safer for healthy cells.

Cesium (Cs^+): Neuroprotective Against Apoptosis, Yet Ionically Disruptive



Claim
Cesium (Cs^+), like rubidium, is similar to potassium. It can help brain cells survive when potassium is low, but too much can interfere with important cell signals.

Evidence
Yu et al. (2007) found that cesium helped keep brain cells (cerebellar neurons) alive by stopping cell death signals, especially when potassium was missing. It blocked enzymes like caspase-3 and kept mitochondria working. But other scientists also found that cesium can block potassium channels needed for immune system activity.(https://pubmed.ncbi.nlm.nih.gov/17804190/)

Significance
Cesium may be useful for brain protection in diseases, but it must be used carefully. High doses or long use could disrupt healthy cell signals and cause side effects.

Therapeutic Implications and Future Research

Claim
Targeted gaseous interventions could become foundational therapies — hydrogen for cell protection and helium for selective cell ablation — but clinical implementation requires deeper mechanistic understanding and safety profiling.

Evidence

Hydrogen in clinical studies
Trials in acute heart attack, stroke, neonatal hypoxia, and COVID-19 suggest H_2 reduces oxidative damage, inflammation, and apoptosis, leading to improved patient outcomes (Brenner et al., 2020; Nakamura et al., 2017).

Helium device development
Helium plasma instruments are emerging in interventional oncology and cardio-protection, but long-term safety and cell-type specificity are not yet fully addressed (Shashurin et al., 2017; Pagel et al., 2014).

Significance
To develop safe and effective gas-based therapies, future research must optimize dosage, timing, delivery (e.g., inhaled H_2, localized He plasma generators), and cell/tissue targeting while ensuring minimal off-target effects and toxicity.

Zinc

Claim: Zinc promotes tumour cell resistance to TNF-mediated cell death (1)

Explanations:

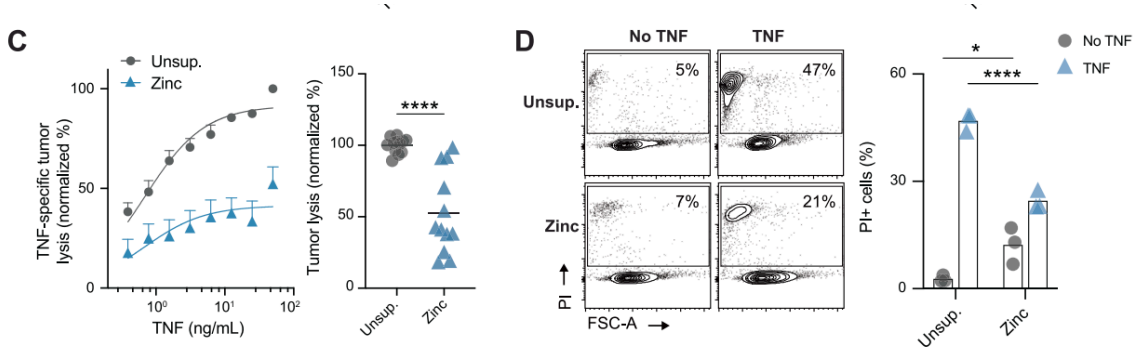
As CBFβ-deficient cells are resistant to TNF and exhibit transcriptional and post-transcriptional alterations in the homoeostasis of copper and zinc ions(1).

Researchers investigated whether exogenous supplementation of these ions would alter tumour cell sensitivity to TNF.

Metal toxicity is harmful but researches needed to determine the concentration of copper and zinc that would lead to increased intracellular ion levels. MC38 and E0771 cells both should be exposed to stop metal toxicity, and then selected concentrations at which tumour cell death was less than 10%, for use in subsequent assays. (1)

Next, to determine the effect of copper and zinc ion supplementation on tumour cell sensitivity to TNF, we treated MC38 and E0771 cells with TNF alone, or with serially diluted concentrations of each metal. (1) zinc supplementation led to a significant and substantial (>50%) dose-dependent decrease in the TNF sensitivity of both MC38 and E0771 cells (1)

The addition of zinc significantly decreased the sensitivity of both MC38 and E0771 to TNF-induced cell death, as measured by both TNF-specific lysis and total cell death. Together, these data confirmed that zinc can protect tumour cells from TNFmediated cell death. (Supplementary fig. CD)



Significance

This review is crucial for the development of future cancer immunotherapeutics that could deal with tumor immune evasions. demonstration of modulation of cellular zinc, achieved by supplementation or chelation, significantly altered tumour cell susceptibility to TNF by regulating the levels of inhibitors of apoptosis proteins. Consistent with this, treatment of tumour cells with a membrane-permeable zinc chelator had no impact on tumour cell viability alone, but significantly increased tumour cell lysis by CD8+ T cells in a TNF-dependent but performing-independent manner. These results underscore the crucial role of intracellular zinc in regulating tumour cell susceptibility to T cell-mediated killing, revealing a novel vulnerability in tumour cells that might be revolutionary in immunotherapy

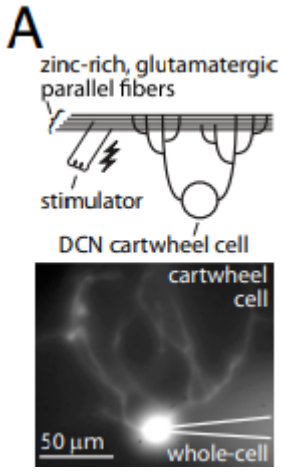
Zinc is causing neurotoxicity

Explanations:

Zn is not a form of free microelement in living organisms, because of that reason, most neuronal zinc is protein-bound. Previous studies have emphasized that, zinc toxicity causes variety of brain illnesses such as stroke, traumatic brain injury and seizures (2017, 2020) To be more detailed and certain, it is better to understand that there are several important postsynaptic receptors such as such as the voltage-gated calcium channels (VGCC), N-methyl-D-aspartate receptors (NMDAR), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPAR), that are both modulated by zinc and also permeable to zinc ions.

For example, Zinc ions play a significant role in modulating NMDA receptors, acting as both an inhibitor and a controlling function of receptors. Overall, NMDA receptors are important in brain functions, and neuroscience. When activated they act as an ion channel allowing calcium ions to flow into neurons, which is essential in improving and strengthening long term potentiation - synapses. The receptor and zinc ions are also interconnected with each other and zinc ions corelease with them at nanomolar concentrations.

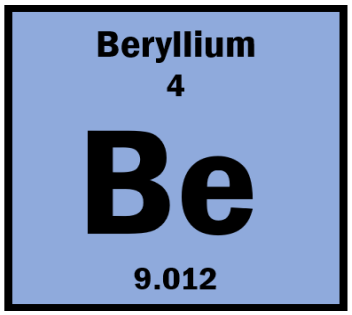
It is claimed that the excess release of free ionic zinc can not only regulate NMDA receptor expression but also causes several destructions, including calcium dysregulation, production of reactive oxygen species and excitotoxicity which lead to neural damage and cell death. (2015, 2017), (Fig.A) These examinations and scientific research play an essential role in different clinical situations like epilepsy and stroke. (2016)



Research gap and further work:

There is now evidence of mutations in NMDA receptors with altered zinc affinities that may have implications for neurodevelopment leading to a variety of developmental disorders including childhood epilepsy and cognitive deficits. (2016)

Beryllium



Beryllium

> Beryllium (Be) administered as Be nitrate caused experimental liver injury [29]. This was associated with a fall in hepatic reduced glutathione content and an increase in lipid peroxidation, interpreted as signs of oxidative stress. Overall, little scientific and clinical interest in Be intoxication and liver injury existed, providing insufficient insight on molecular aspects of Be liver injury [30,31,32,33,34]. Issues of Be were also not discussed in a recent excellent and comprehensive review article focusing on many HMs [9].

Toxicity effect behind Beryllium (Be) dust

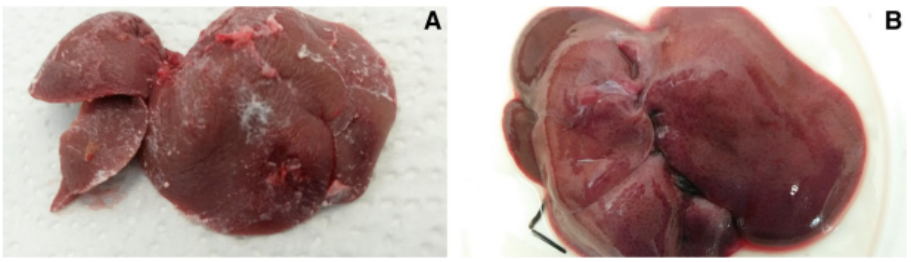


Fig. 1 Macroscopic changes on the liver of Be–Gly-exposed Wistar male rats: **a** deposition on the liver after a single intraperitoneal Be–Gly injection at the dose 4767 μmol kg^{-1} (body weight). **b** Control liver for comparison. To see these images in color, please, refer to the online copy of the article

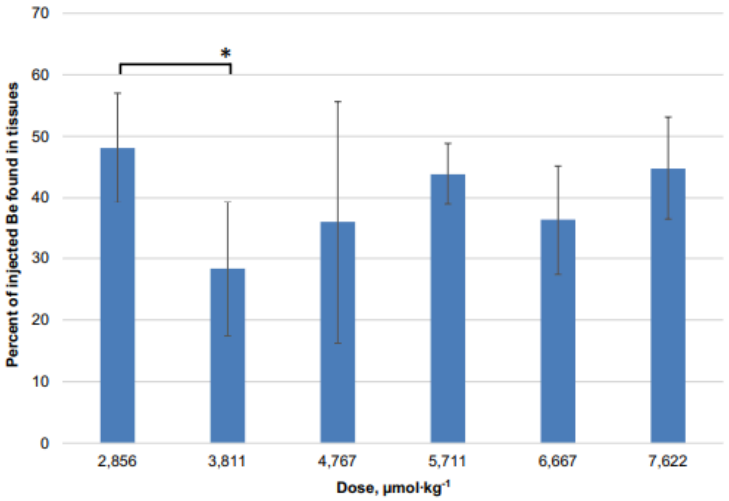


Fig. 2 Recovery of Be found in the tissues of Wistar male rats after the administration of 2856–7622 µmol kg^{-1} (body weight) Be–Gly composition (Day 1). Error bars represent inter-animal standard deviation ($n=3$). Recovery was calculated as a sum of Be amounts found in the analyzed tissue (Table 5). Statistical difference (one-way ANOVA, $p<0.05$) was found only for dose 3811 µmol kg^{-1} (body weight) in comparison to dose 2856 µmol kg^{-1} (body weight)

Claim: Development of chronic beryllium disease.

Beryllium: Be is famous to all with its gemstone forms, such as, aquamarine, emerald, beryl and chrysoberyl. Additionally it is a rare element. Be is found naturally and purifies element BE occurs as a fine gray powder (2004, 1922) Be‘s atomic number is 4 and it heads the Group IIA in periodic table with an element like, magnesium, calcium, strontium and radium. Be has a smallest ionic radius, r = 0.31 nm.

Beryllium has become a vital metal in several industries. However, recent Be-exposure in the workplace is a growing public health concern. Individuals exposed by Be are at risk to develop CBD (chronic beryllium disease). These individuals are mostly those who work with Be metal directly or partially (2009, 2004) Early studies that used skin patch testing showed that exposure to Be salts in normal control subjects resulted in immune sensitization to Be and potentially impaired lung function (2001), demonstrating that Be skin exposure can result in the induction of a Be-specific immune response.

Pathophysiology of CBD

High exposure to Be can lead to a cell mediated immune response where T-cells become sensitized to beryllium. Each exposure leads to an immune response including an activation of macrophages and CD4+ helper T-lymphocytes accumulation in the lungs. Every time this process proceeds, macrophages, CD+4 T-lymphocytes, and plasma cells aggregate to form noncaseating granulomas that evolve to cause fibrosis of the lung. (7)

Carbon (C)

Physicochemical Characteristics and Cellular Uptake

Elemental carbon in bulk forms (e.g., graphite, diamond) shows minimal biological reactivity. However, engineered carbon nanomaterials (CNMs)—including carbon nanotubes (CNTs), carbon dots (CDs), fullerenes (C_{60}), graphene derivatives, and carbon black nanoparticles (CBNs)—exhibit unique physicochemical properties such as high surface area, variable surface charge, and tunable functionalization. These features critically influence cellular uptake, biodistribution, and toxicity.

Cellular uptake mechanisms vary depending on particle morphology and surface chemistry. Macrophages internalize larger CNMs through phagocytosis or scavenger receptor-mediated uptake, while smaller particles such as CDs and fullerenes enter cells via clathrin- or caveolae-mediated endocytosis. Internalized CNMs typically localize in lysosomes, mitochondria, or cytosol, where they interact with subcellular structures and regulatory proteins .

Oxidative and Nitrosative Stress

A hallmark of CNM cytotoxicity is the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). CNMs can directly catalyze ROS formation via redox-active surface groups or indirectly by disrupting mitochondrial electron transport (Nel et al., 2006). For instance, exposure to multi-walled CNTs (MWCNTs) increases ROS in murine macrophages and skin fibroblasts, triggering oxidative damage cascades and leading to mitochondrial membrane depolarization .

Functionalized MWCNTs, especially those with amine or acid modifications, show enhanced ROS production due to increased reactivity and surface charge. Excessive ROS promotes lipid peroxidation, DNA fragmentation, and protein carbonylation, setting the stage for multiple death pathways .

Apoptotic and Necrotic Pathways

Carbon nanomaterials activate mitochondria-dependent apoptosis via the intrinsic pathway. This involves oxidative stress-mediated damage to the

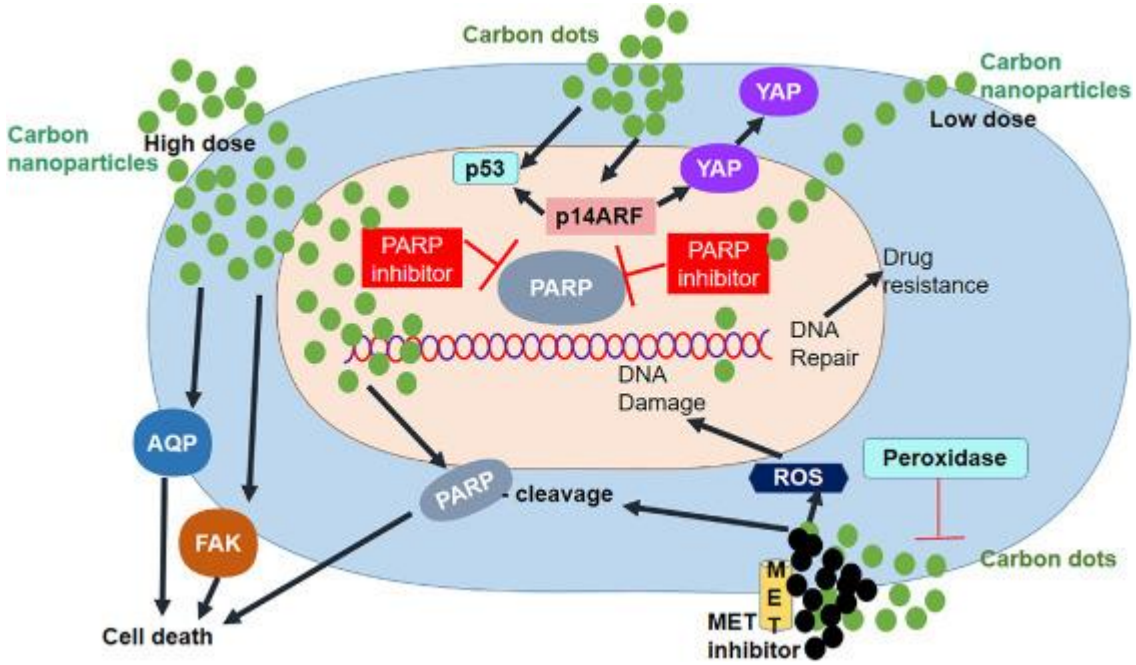
mitochondrial outer membrane, followed by cytochrome c release, caspase-9 and caspase-3 activation, and nuclear fragmentation .

In vivo studies have demonstrated that MWCNTs trigger apoptosis in gill and liver cells of aquatic models (e.g., Oryzias latipes), with increased expression of pro-apoptotic markers such as p53, Bax, and caspases . Similarly, primary macrophages from leech hemolymph showed dose- and time-dependent apoptosis upon MWCNT exposure .

Autophagy

Necrotic cell death has also been observed, particularly at high CNM concentrations or in particles with high aspect ratios. This form of death is typically associated with membrane rupture, ATP depletion, and uncontrolled ion influx—outcomes of physical damage from needle-like CNTs or of catastrophic mitochondrial failure. Autophagy represents a double-edged response to CNMs. Moderate exposure may activate protective autophagy that facilitates degradation of internalized particles and damaged organelles . However, chronic or high-dose exposure disrupts autophagic flux, resulting in autophagosome accumulation and autophagy-associated cell death.

Furthermore, the interplay between ROS, ER stress, and lysosomal dysfunction can amplify autophagy-related cytotoxicity. Some CNMs also interfere with mTOR and AMPK signaling pathways, further modifying the autophagic balance.



Silicon (Si)

Physicochemical Characteristics and Cellular Uptake

Silicon is a group 14 metalloid element commonly encountered in biological systems in the form of silicic acid or amorphous silica (SiO_2). While bulk silicon dioxide is biologically inert, engineered silica nanoparticles (SiNPs) have unique physicochemical characteristics including high surface area, tunable porosity, surface charge, and size-dependent reactivity. Cellular uptake of SiNPs typically occurs via clathrin-mediated or caveolae-dependent endocytosis. Once internalized, SiNPs accumulate in lysosomes, mitochondria, and the cytosol, where they can interfere with normal cellular processes .

Oxidative and Inflammatory Stress

SiNPs are potent inducers of oxidative stress. Their surface silanol groups can catalyze the formation of reactive oxygen species (ROS), including hydroxyl radicals and hydrogen peroxide. ROS-mediated lipid peroxidation, protein oxidation, and DNA strand breaks have been observed in various cell types. Inflammatory responses are also triggered by crystalline and amorphous SiO_2, involving lysosomal destabilization, NLRP3 inflammasome activation, and proinflammatory cytokine release, notably IL-1β and TNF-α .

Apoptotic, Necrotic, and Autophagic Pathways

Apoptosis: SiNP-induced ROS generation leads to mitochondrial outer membrane permeabilization (MOMP), cytochrome c release, caspase-9 and caspase-3 activation, and classical apoptotic morphology in a wide range of mammalian cells.

Necrosis

High doses of crystalline silica cause direct membrane rupture, ATP depletion, and necrotic death, particularly in macrophages and pulmonary epithelial cells

Autophagy

SiNPs activate autophagic flux in various cell types. While initially cytoprotective, prolonged or excessive autophagy leads to

autophagy-associated cell death, characterized by LC3-II accumulation and lysosomal overload.

Titanium (Ti)

Physicochemical Characteristics and Cellular Uptake

Titanium is widely used in the form of titanium dioxide (TiO_2), a white, photoactive compound notable for its chemical stability, low solubility, and optical properties. TiO_2 exists in several crystalline phases — anatase, rutile, and brookite — each with different levels of biological reactivity. Nano-sized TiO_2 particles (TiO_2 NPs), particularly anatase forms under 100 nm, are commonly incorporated into sunscreens, food additives, and biomedical coatings due to their biocompatibility and UV-reflecting capacity.

Upon exposure to cells, TiO_2 NPs enter via endocytosis (clathrin- and caveolin-mediated pathways) and accumulate primarily in the cytosol, lysosomes, and mitochondria. Surface charge, crystalline structure, and photoactivation status greatly influence cellular internalization and biological reactivity.

Oxidative, Genotoxic, and Inflammatory Stress

Oxidative Stress: TiO_2 NPs generate high levels of reactive oxygen species (ROS), particularly when photoactivated by ultraviolet (UV) light. These ROS include hydroxyl radicals (•OH), superoxide anions ($O_2^{\bullet -}$), and singlet oxygen ($^1O_2$), which cause lipid peroxidation, protein denaturation, and DNA strand breaks. Mitochondria are especially vulnerable, with dysfunction leading to ATP depletion and release of pro-apoptotic signals.

Genotoxic Stress: Exposure to TiO_2 NPs is associated with chromosomal aberrations, micronuclei formation, and DNA double-strand breaks, especially in epithelial and immune cells. The DNA damage is enhanced under light exposure due to photo-induced oxidative bursts.

Inflammatory Stress: TiO_2 NPs stimulate immune cells, particularly macrophages, to release inflammatory cytokines such as IL-6 and TNF-α. This is mediated via oxidative stress and NF-κB signaling. Long-term inflammation is associated with granuloma formation and fibrotic remodeling in lung and skin tissues..

Apoptotic, Autophagic, and Pyroptotic Pathways

Apoptosis

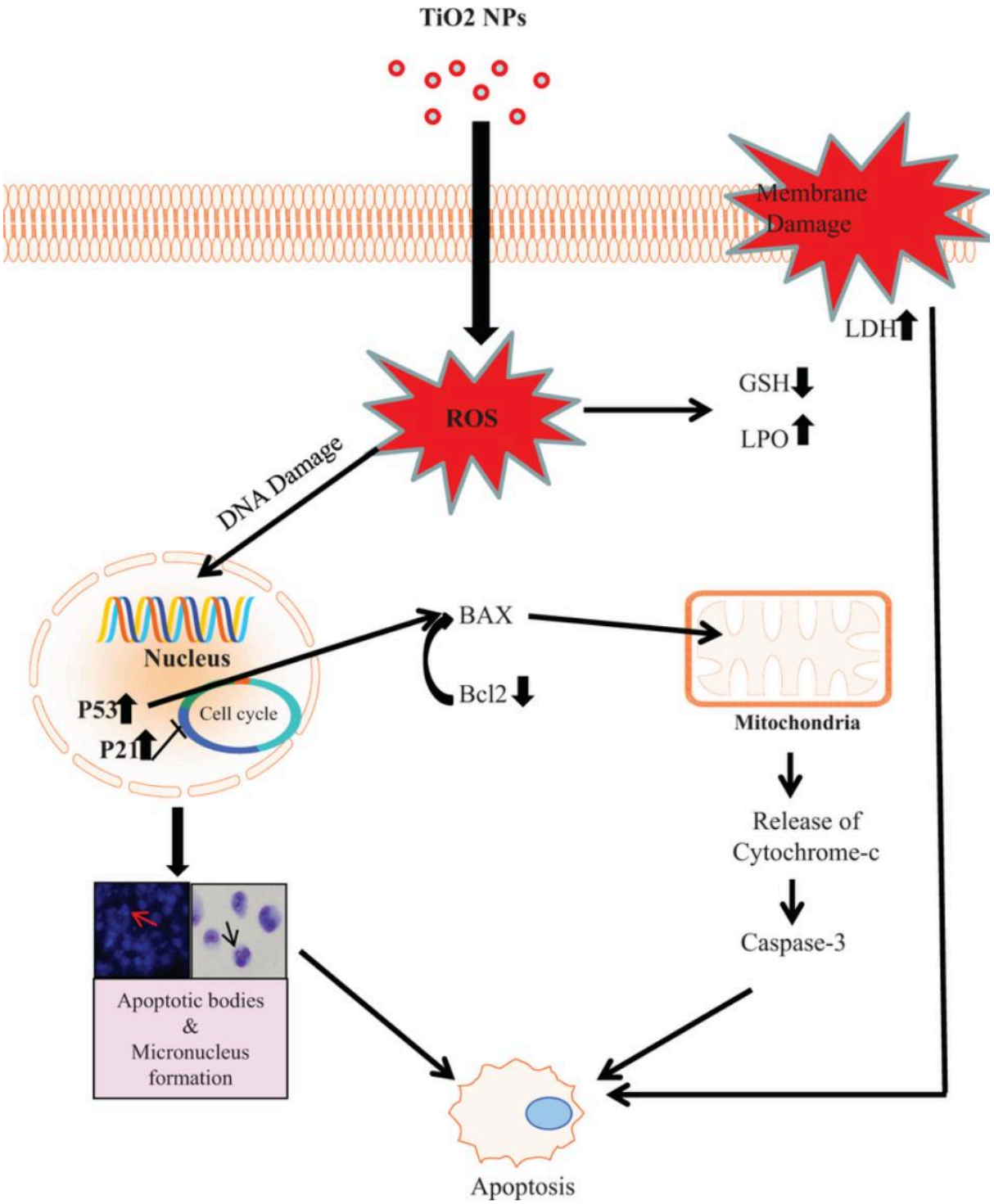
TiO_2 NPs induce mitochondria-mediated apoptosis, triggered by ROS accumulation and mitochondrial membrane depolarization. This process involves cytochrome c release, caspase-9 and caspase-3 activation, and nuclear condensation . This is a common response in epithelial cells, fibroblasts, and macrophages.

Autophagy

Sublethal TiO_2 exposure activates autophagic flux, indicated by upregulated LC3-II levels and autophagosome formation. While autophagy initially serves as a protective mechanism to eliminate damaged organelles and internalized particles, persistent exposure may overload lysosomal capacity, resulting in autophagy-associated cell death.

Proptosis

Recent studies indicate that TiO_2 NPs can activate the NLRP3 inflammasome in macrophages. This leads to caspase-1 activation, IL-1β secretion, and membrane pore formation, hallmarks of pyroptotic inflammatory death. This is particularly relevant for dermal and pulmonary exposure models.



Germanium (Ge)

Physicochemical Characteristics and Cellular Uptake

Germanium (Ge), a group 14 metalloid, exists in both organic and inorganic forms, with distinct biological properties. While organic germanium

compounds such as Ge-132 (carboxyethylgermanium sesquioxide) were initially proposed as therapeutic agents for cancer and immune modulation, inorganic forms like germanium dioxide (GeO_2) have been associated with cellular toxicity. Germanium is not an essential element for humans or plants, and its physiological role remains undefined .

Cellular uptake of germanium compounds is influenced by their solubility and oxidation state. GeO_2, being water-soluble under acidic conditions, enters cells primarily through passive diffusion or endocytosis. Accumulation is most commonly observed in the cytoplasm, mitochondria, and to a lesser extent, the nucleus, where germanium interferes with redox signaling, electron transport, and enzyme activity.

Cellular Stress Induced by Germanium

Mitochondrial Stress: Inorganic germanium disrupts mitochondrial membrane potential, leading to impaired oxidative phosphorylation, ATP depletion, and cytochrome c release into the cytosol. This mitochondrial dysfunction is a primary trigger of apoptotic cascades.

Oxidative Stress: Germanium exposure promotes ROS generation, including superoxide anions ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\bullet OH$). This results in lipid peroxidation, DNA strand breaks, and oxidative modification of proteins, particularly within liver and kidney cells.

Lysosomal Stress: Studies have reported lysosomal membrane permeabilization (LMP) following germanium accumulation. This results in the cytoplasmic release of acid hydrolases and cathepsins, promoting additional damage to cytosolic proteins and organelles. Lysosomal leakage may act synergistically with mitochondrial stress to initiate cell death pathways.

Death Pathways Induced by Germanium

Apoptosis

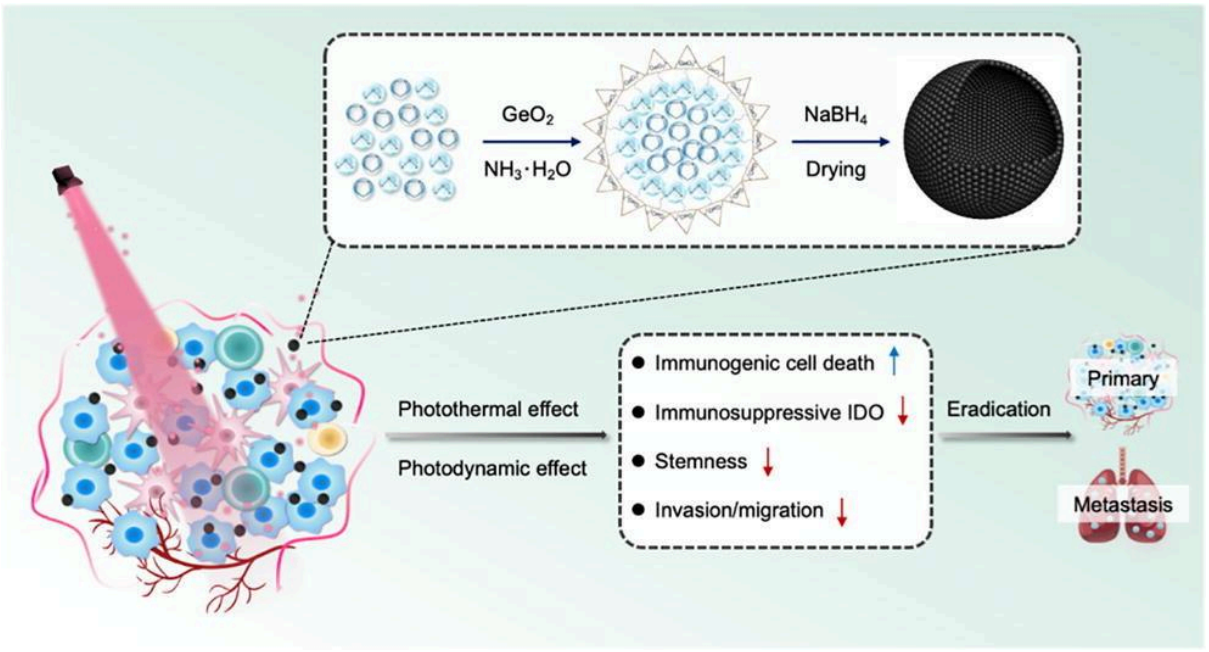
The primary mode of cell death following germanium exposure is intrinsic (mitochondrial) apoptosis. ROS accumulation leads to Bax translocation to the mitochondrial membrane, mitochondrial outer membrane permeabilization (MOMP), and cytochrome c release, followed by activation of caspase-9 and caspase-3. Morphologically, this is associated with cell shrinkage, chromatin condensation, and nuclear fragmentation.

Necrosis

At higher concentrations or during chronic exposure, especially with GeO_2, cells undergo necrotic death. This form of death is characterized by plasma membrane rupture, organelle swelling, and uncontrolled ion leakage, often observed in renal and hepatic tissues. Necrosis appears to be a consequence of irreversible energy failure due to mitochondrial collapse.

Autophagy and Other Pathways

Current evidence does not consistently support the involvement of autophagic or pyroptotic pathways in germanium-induced cytotoxicity. Some studies suggest that sub-lethal doses may transiently activate autophagic flux, but this response is likely cytoprotective and does not contribute to direct cell death.



Zirconium (Zr)

Physicochemical Characteristics and Cellular Uptake

Zirconium (Zr) is a group 4 transition metal commonly used in ceramics, nuclear reactors, medical implants, and dental materials, primarily due to its chemical stability, corrosion resistance, and low allergenicity. The most biologically relevant forms include zirconyl salts (e.g., $ZrOCl_2 \cdot 8H_2O$) and zirconium dioxide (ZrO_2), a crystalline, poorly soluble oxide.

In biological systems, soluble zirconium salts can be taken up by cells via endocytosis or through membrane perturbation, especially at high

concentrations. Once internalized, Zr tends to accumulate in lysosomes, the cytoplasm, and occasionally the nucleus, where it binds to phosphate groups, interfering with nucleic acids, membrane phospholipids, and enzyme substrates.

Death Pathways Induced by Zirconium

Apoptosis

The most well-documented response to Zr exposure is mitochondrial (intrinsic) apoptosis. Oxidative and lysosomal stress lead to Bax upregulation, mitochondrial outer membrane permeabilization, and cytochrome c release, followed by caspase-9 and caspase-3 activation. Morphologically, this is accompanied by cell shrinkage, nuclear condensation, and fragmentation.

Necrosis

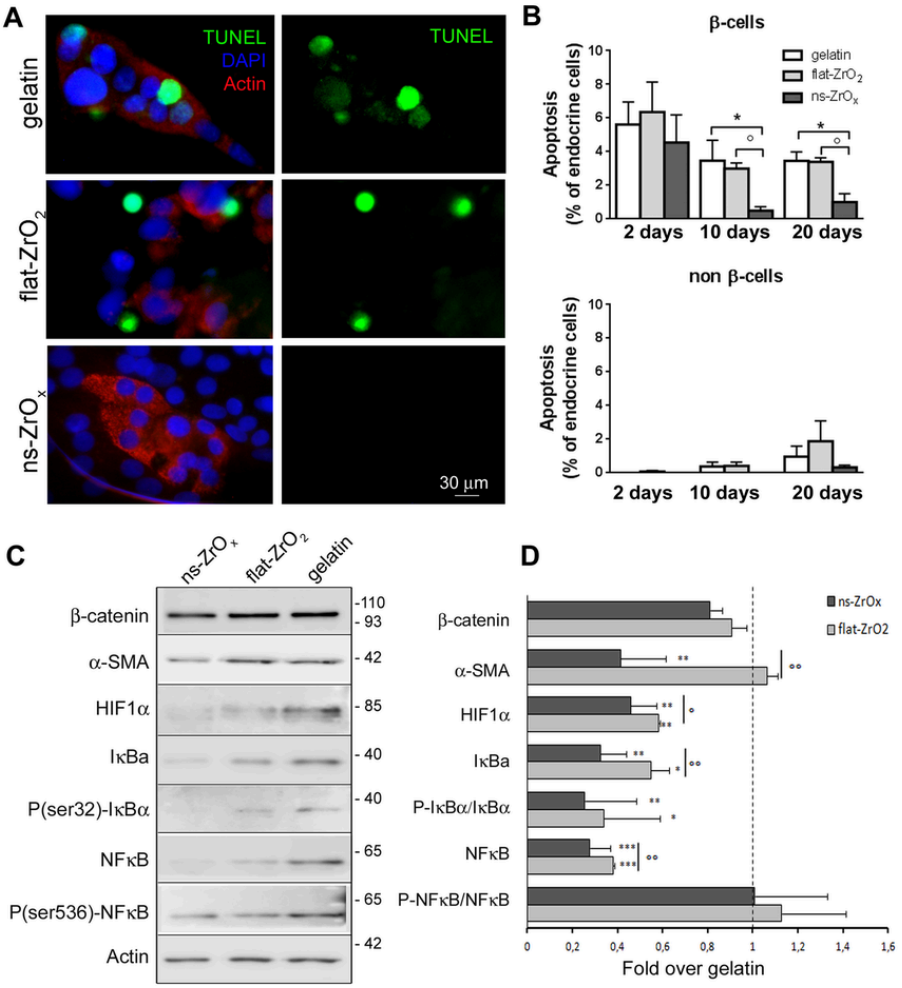
At high concentrations or following chronic exposure, Zr salts cause non-programmed necrosis, marked by cellular swelling, membrane rupture, and ATP depletion. This has been reported particularly in renal tubular cells, hepatocytes, and splenocytes .

Autophagy

Evidence suggests that Zr exposure can trigger autophagic vacuole formation and LC3-II upregulation, possibly as a compensatory mechanism to remove damaged organelles. However, when autophagic capacity is overwhelmed, this response may lead to autophagy-associated cell death, though the role remains unclear.

Inflammation-Linked Immunotoxicity

Zr-induced lysosomal destabilization in macrophages and dendritic cells can provoke chronic inflammation, immunosuppression, and cell exhaustion, especially in the spleen and lymphoid tissues.



Tin (Sn)

Physicochemical Characteristics and Cellular Uptake

Tin (Sn), a post-transition metal from group 14, exists in multiple oxidation states, primarily Sn^{2+} and Sn^{4+}, and in both inorganic and organotin forms. Among them, organotin compounds, such as tributyltin (TBT) and triphenyltin (TPT), are of particular biological concern due to their lipophilicity, membrane permeability, and high toxicity.

Inorganic tin compounds typically enter cells through divalent metal transporters (e.g., DMT1), while organotins diffuse across lipid membranes owing to their hydrophobic nature. Once internalized, tin accumulates in the cytoplasm, mitochondria, endoplasmic reticulum, and nucleus, where it interacts with sulfhydryl groups, membrane lipids, and nuclear receptors, disrupting essential cellular functions.

Death Pathways Induced by Tin

Apoptosis

Tin compounds are potent inducers of apoptosis. Organotins activate both the intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Mitochondrial membrane depolarization, cytochrome c release, and activation of caspase-9 and caspase-3 are observed. Simultaneously, upregulation of Fas/FasL triggers caspase-8-dependent apoptosis, especially in lymphocytes and hepatocytes.

Necrosis

At higher concentrations, tin compounds cause massive ATP depletion, cell swelling, and plasma membrane rupture, consistent with oncosis-like necrosis. This has been especially documented in renal and hepatic tissues exposed to tributyltin.

Autophagy

Some studies report autophagic vacuole formation and increased LC3-II expression following organotin exposure. While early autophagy may serve a cytoprotective role, excessive or prolonged activation appears to shift toward autophagy-associated cell death.

Immunotoxicity and Lymphocyte Depletion

Organotins impair immune function, especially in T-lymphocytes, by promoting apoptosis, reducing cytokine production, and altering thymic architecture, leading to immunosuppression.

Lead (Pb)

Physicochemical Characteristics and Cellular Uptake

Lead (Pb), a heavy metal in group 14 of the periodic table, is toxic even at low concentrations and has no known beneficial biological role. It primarily exists in the divalent form (Pb^{2+}) under physiological conditions. Due to its ionic radius and charge, Pb^{2+} readily mimics calcium (Ca^{2+}) and iron (Fe^{2+}), entering cells via voltage-gated calcium channels and divalent metal transporters (e.g., DMT1).

After cellular entry, lead accumulates in the cytoplasm, nucleus, and especially mitochondria, where it binds to sulfhydryl (-SH), carboxyl (-COOH), and phosphate groups, disrupting enzyme function, membrane integrity, and genomic architecture. Pb also replaces zinc and calcium in metalloproteins, leading to altered protein conformation and impaired biological activity.

Death Pathways Induced by Lead

Apoptosis: Lead induces apoptotic cell death through both intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Mitochondrial swelling, loss of membrane potential, and cytochrome c release are followed by activation of caspase-9 and caspase-3. Pb also upregulates p53, increases Bax/Bcl-2 ratios, and initiates DNA fragmentation, particularly in hepatocytes and astrocytes.

Necrosis

At higher concentrations, Pb causes rapid ATP depletion, plasma membrane rupture, and cell swelling, resulting in necrotic cell death. This is prominent in renal and hepatic cells, where Pb overload causes mitochondrial failure and ionic imbalance.

Autophagy

Lead exposure activates autophagic flux in several cell types, including astrocytes and renal epithelial cells. Although initially cytoprotective, excessive autophagy leads to autophagy-associated cell death, characterized by accumulation of autophagosomes, LC3-II upregulation, and p62 degradation.

Developmental Toxicity and Embryonic Cell Death

Pb disrupts cell proliferation, alters epigenetic regulation (e.g., DNA methylation), and impairs mitotic spindle function in embryonic stem cells. These effects contribute to teratogenic outcomes, embryonic apoptosis, and long-term developmental defects.

Hafnium (Hf)

Physicochemical Characteristics and Cellular Uptake

Hafnium (Hf), a transition metal in group 4, is chemically similar to zirconium due to nearly identical ionic radii and shared tetravalent states (Hf^{4+}). Elemental hafnium is poorly soluble and biologically inert under most environmental and physiological conditions. However, its oxide form — hafnium dioxide (HfO_2) — has emerged as a nanomaterial of interest in fields such as radiotherapy enhancement, nanomedicine, and semiconductor technology.

HfO_2 nanoparticles (Hf-NPs) enter cells primarily via clathrin-mediated endocytosis, caveolae-dependent pathways, or macropinocytosis, depending on particle size, surface charge, and coating. Once internalized, Hf-NPs localize in lysosomes, the cytosol, and sometimes perinuclear compartments, where they may interfere with organelle function and cellular redox state.

Death Pathways Induced by Hafnium

Apoptosis

Hf-NPs trigger intrinsic (mitochondria-dependent) apoptosis, especially when combined with radiation. This includes cytochrome c release, caspase-9 and caspase-3 activation, DNA fragmentation, and nuclear condensation. Tumor cells exposed to Hf-NPs during irradiation exhibit high levels of Annexin V positivity and cleaved PARP, consistent with apoptotic profiles.

Radiation-Sensitized Necrosis

In settings of excessive ROS and depleted antioxidant capacity, especially during radiotherapy, Hf-NPs promote necrotic cell death. This involves plasma membrane rupture, organelle swelling, and ATP depletion — features of secondary necrosis that follow oxidative collapse.

Rutherfordium (Rf)

Physicochemical Characteristics and Cellular Availability

Rutherfordium (Rf), atomic number 104, is a synthetic transactinide and a member of group 4 in the periodic table. It has no naturally occurring isotopes and is produced exclusively in particle accelerators via nuclear fusion reactions. All known isotopes of Rf are extremely unstable, with half-lives ranging from milliseconds to a few seconds . Due to its short half-life, no

compound of Rutherfordium has ever been isolated in quantities sufficient for biological testing.

Rf is predicted to exhibit a +4 oxidation state, similar to Hf^{4+} and Zr^{4+}, and to form analogous oxides or halides. However, these chemical properties are inferred from relativistic quantum chemistry and chromatographic behavior, not from direct experimentation. Due to its rarity and radioactivity, Rf is not accessible for biochemical incorporation, toxicology screening, or in vivo experimentation.

Hypothetical Death Pathways Induced by Rutherfordium

Apoptosis (Predicted)

DNA double-strand breaks and oxidative lesions caused by ionizing radiation can activate p53, promote Bax translocation, and initiate caspase-9 and caspase-3-dependent apoptosis. This has been observed with other alpha emitters, and could be extrapolated hypothetically to Rf decay scenarios.

Necrosis (Predicted)

High-dose alpha radiation in close cellular proximity may overwhelm DNA repair and antioxidant defenses, leading to membrane rupture, organelle swelling, and unregulated necrotic cell death — particularly if decay products accumulate locally.

Flerovium (Fl)

Physicochemical Characteristics and Biological Inaccessibility

Flerovium (Fl), atomic number 114, is a synthetic superheavy element belonging to group 14 of the periodic table. All of its known isotopes are extremely short-lived, with half-lives ranging from a few milliseconds to a few seconds. Due to its rapid radioactive decay and minuscule production yields—often on the order of single atoms—Flerovium has never been incorporated into any biological or biochemical study.

Chemically, Flerovium is predicted to behave differently from its lighter congeners (e.g., lead and tin), possibly exhibiting noble-gas-like or weakly metallic characteristics due to relativistic stabilization of its outer electron shell. The theoretical +2 and +4 oxidation states are proposed, but no stable Fl compounds have ever been isolated. Thus, its biological availability is considered virtually nonexistent.

Hypothetical Death Pathways Induced by Flerovium

Apoptosis

Radiation-induced DNA damage and oxidative stress could hypothetically activate mitochondrial apoptosis pathways, including p53 activation, mitochondrial outer membrane permeabilization, cytochrome c release, and caspase-9/-3 activation.

Necrosis

If radiation exposure were too intense or sudden for the cell to initiate repair, energy collapse and membrane rupture could lead to necrosis. Swelling, ion leakage, and ATP depletion would characterize this form of cell death.

No autophagy or pyroptosis reported: There is no evidence, experimental or theoretical, to suggest Fl would trigger autophagy or inflammasome-mediated pyroptosis, as no molecular pathways are known or expected to be engaged by such a transient element.

Germanium (Ge)

Physicochemical Characteristics and Cellular Uptake

Germanium (Ge), a group 14 metalloid, exists in both organic and inorganic forms, with distinct biological properties. While organic germanium compounds such as Ge-132 (carboxyethylgermanium sesquioxide) were initially proposed as therapeutic agents for cancer and immune modulation, inorganic forms like germanium dioxide (GeO_2) have been associated with cellular toxicity. Germanium is not an essential element for humans or plants, and its physiological role remains undefined (Ishihara, 2003).

Cellular uptake of germanium compounds is influenced by their solubility and oxidation state. GeO_2, being water-soluble under acidic conditions, enters cells primarily through passive diffusion or endocytosis. Accumulation is most commonly observed in the cytoplasm, mitochondria, and to a lesser extent, the nucleus, where germanium interferes with redox signaling, electron transport, and enzyme activity (Jang, 2004).

Cellular Stress Induced by Germanium

Mitochondrial Stress: Inorganic germanium disrupts mitochondrial membrane potential (Δψm), leading to impaired oxidative phosphorylation, ATP depletion, and cytochrome c release into the cytosol. This mitochondrial dysfunction is a primary trigger of apoptotic cascades (Jang, 2004).

Oxidative Stress: Germanium exposure promotes ROS generation, including superoxide anions ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH). This results in lipid peroxidation, DNA strand breaks, and oxidative modification of proteins, particularly within liver and kidney cells (Takahashi, 1998).

Lysosomal Stress: Studies have reported lysosomal membrane permeabilization (LMP) following germanium accumulation. This results in the cytoplasmic release of acid hydrolases and cathepsins, promoting additional damage to cytosolic proteins and organelles (Matsumura, 2001). Lysosomal leakage may act synergistically with mitochondrial stress to initiate cell death pathways.

Redox Imbalance: Germanium interferes with glutathione metabolism and NADPH-dependent antioxidant systems, exacerbating oxidative stress and compromising cellular defenses (Ishihara, 2003).

Death Pathways Induced by Germanium

Apoptosis: The primary mode of cell death following germanium exposure is intrinsic (mitochondrial) apoptosis. ROS accumulation leads to Bax translocation to the mitochondrial membrane, mitochondrial outer membrane permeabilization (MOMP), and cytochrome c release, followed by activation of caspase-9 and caspase-3 (Jang, 2004). Morphologically, this is associated with cell shrinkage, chromatin condensation, and nuclear fragmentation.

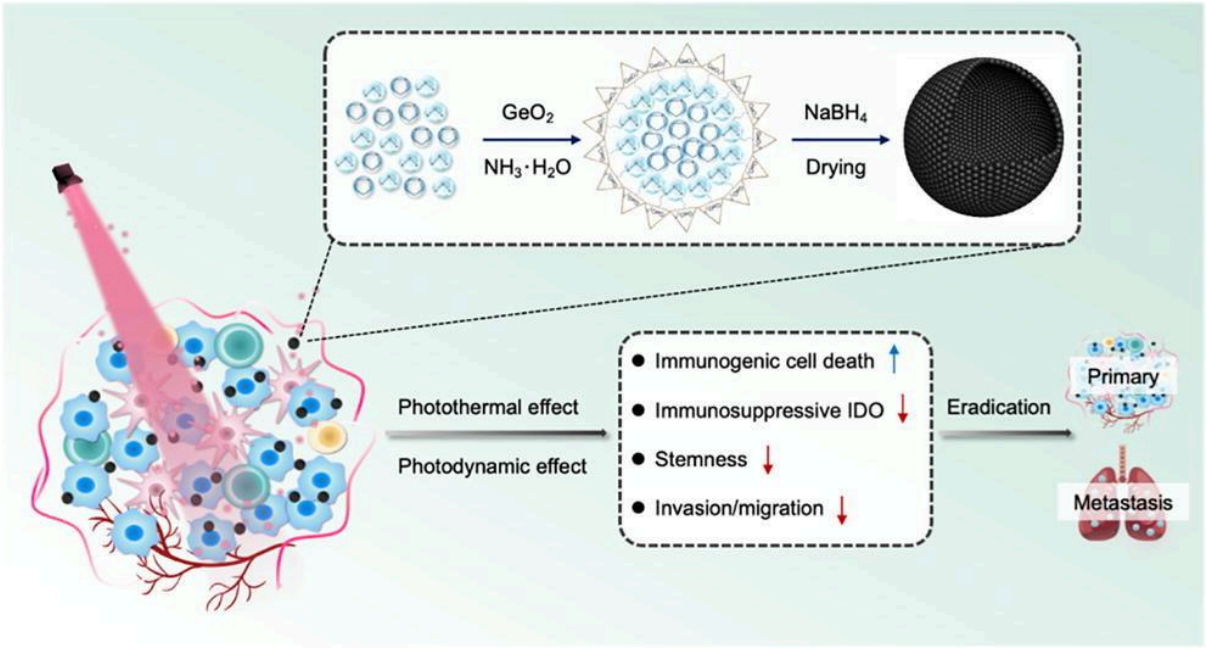
Necrosis: At higher concentrations or during chronic exposure, especially with GeO_2, cells undergo necrotic death. This form of death is characterized by plasma membrane rupture, organelle swelling, and uncontrolled ion leakage, often observed in renal and hepatic tissues (Ishihara, 2003). Necrosis appears to be a consequence of irreversible energy failure due to mitochondrial collapse.

Autophagy and Other Pathways: Current evidence does not consistently support the involvement of autophagic or pyroptotic pathways in germanium-induced cytotoxicity. Some studies suggest that sub-lethal doses

may transiently activate autophagic flux, but this response is likely cytoprotective and does not contribute to direct cell death (Takahashi, 1998).

Modulating Factors in Germanium Toxicity

The toxicity of germanium depends on its chemical form, dose, and duration of exposure. Organic germanium compounds such as Ge-132 were once considered non-toxic at therapeutic doses, but chronic use led to tissue accumulation and renal failure in clinical reports. Inorganic forms like GeO_2 exhibit higher cytotoxicity, particularly under chronic or repeated exposure, which leads to mitochondrial degeneration, tubular necrosis, and immune suppression (Matsumura, 2001). Co-exposure with other redox-active metals or antioxidant depletion may exacerbate cellular injury.



Supporting Studies

Multiple studies conducted in the late 1990s and early 2000s demonstrated germanium's cytotoxic potential in both in vitro and in vivo systems. Ishihara (2003) showed that GeO_2 leads to mitochondrial swelling and decreased cell viability in renal epithelial cells. Takahashi (1998) confirmed that germanium compounds induce ROS-mediated DNA fragmentation and chromatin damage. Jang (2004) further demonstrated cytochrome c release and apoptotic markers in hepatic and neuronal cell models exposed to inorganic Ge. Matsumura (2001) provided evidence for lysosomal leakage and additive stress from combined mitochondrial–lysosomal impairment.

Despite initial therapeutic interest, especially in alternative medicine, germanium compounds were later linked to nephrotoxicity, neurotoxicity, and immunosuppression, resulting in regulatory bans in multiple countries for use in dietary supplements.

Nitrogen

Abstract

Nitric oxide (NO) is a small gas molecule that plays a very important role in the human body. In low concentrations, it works like a messenger and helps regulate blood vessels, immune system, and brain signals. But when NO is produced too much, especially during inflammation or other diseases, it becomes toxic and can damage cells. This happens through many molecular processes like oxidative stress, DNA damage, mitochondrial problems, and finally, cell death. In this paper I focus on how NO causes cell death and explain the mechanisms behind it. Also, I talk a little about how NO can be used in medicine and therapy if it is delivered in the right way and in the right amount [1, 3].

Introduction

Nitric oxide is a very small and simple molecule, but it does many important things in our body. It can go through cell membranes and help with many normal functions like relaxing blood vessels, helping neurons talk to each other, and controlling immune responses [3, 4]. At very low levels, NO is helpful and healthy. But if its concentration becomes high, it changes from being helpful to harmful. Too much NO can be dangerous and can start processes that lead to cell damage or even death [2, 5]. This is important in many diseases like stroke, inflammation, and brain disorders. Because of that, scientists are studying NO a lot to understand when it helps and when it harms. Also, researchers want to use NO in treatments, but they need to control how and where it is released in the body [1, 5].

Methods and Materials

For this research to be concluded, many different scientific articles and reviews about NO and how it affects cells were read.The main idea was to understand the main ways NO is produced in the body and what happens when there is too much of it. The three main enzymes that make NO are nNOS (neuronal), eNOS (endothelial), and iNOS (inducible). nNOS and eNOS produce small amounts of NO in normal conditions responding to calcium

signals, but iNOS can make large amounts during inflammation, independently of calcium levels. I also looked into how NO interacts with other molecules like superoxide and forms a very dangerous molecule called peroxynitrite. This causes oxidative stress and damages cell parts like mitochondria, DNA, and proteins. Resources that explain both the helpful and harmful actions of NO and some additional studies that talk about using NO in therapy were included [1, 3].

Results

It is clear that NO has both good and bad sides, depending on how much of it is made. In small amounts, it helps the body function. But at high levels, it becomes toxic. The biggest problem comes when NO reacts with superoxide and makes peroxynitrite. This molecule causes damage inside the cell by breaking DNA, changing proteins, and hurting mitochondria. Mitochondria make energy (ATP), and when they don't work well, the cell starts to die. In addition, when DNA gets damaged, a repair enzyme called PARP becomes active. However if PARP works too much, it uses up all the cell's energy and NAD^+, and this can lead to cell death, especially by necrosis. What's also important is that NO activates p53 protein, which can stop cell growth or start apoptosis, depending on how bad the damage is. Another alternative way NO causes problems is by changing proteins with something called S-nitrosylation, which can stop some proteins from working properly. All these things together show that too much NO can lead to either apoptosis or necrosis. Still, if we can control how much NO is released and where,it can be used in medicine, like for treating lung diseases or maybe cancer. Scientists are working on NO donors and delivery systems that give NO slowly and only to the right tissues, which is a very promising area of research.

Phosphate

Abstract

Phosphates are important for life, but only in certain amounts, since it can harm cells and cause diseases. In this work, look at how different types of phosphorus — black phosphorus (BP), red phosphorus, and inorganic phosphate — affect cells and cause cell death. We found that BP's toxicity depends on particle size and thickness, leading to oxidative stress and

membrane damage. Red phosphorus, when exposed to visible light, creates reactive oxygen species that damage membranes and kill bacteria. High levels of inorganic phosphate cause endothelial cells to die through a mitochondrial pathway involving reactive oxygen and caspase activation. These findings help us understand how phosphates can be toxic and linked to diseases with phosphate imbalance.

Introduction

Phosphorus is an important element in biology, involved in metabolism, energy transfer, and cell structure [1–3]. But high levels of phosphate can be harmful, causing oxidative stress and cell death [4]. For example, people with chronic kidney disease often have too much phosphate in their blood, which is linked to faster artery disease and damage to blood vessel cells [5]. New phosphorus-based materials like layered black phosphorus (BP) and red phosphorus are being studied for medical and environmental uses. However, we still don't fully understand how safe they are and how toxic they might be [2, 6]. In this work, we bring together studies on how BP's toxicity depends on particle size, how red phosphorus kills bacteria using light, and how inorganic phosphates affect blood vessel cells. This helps us better understand how different forms of phosphorus can cause cell death and related effects.

Materials and Methods

Black phosphorus (BP) was divided by size and thickness. Size checked by electron microscopy and light scattering, concentration by spectrophotometer [4]. Red phosphorus powder tested under visible light [6]. Sodium phosphate added to cells at nearly 2.5 mM to mimic high phosphate [5]. Used human kidney (293T), mouse fibroblasts (NIH 3T3), and human/bovine endothelial cells. Cells grown in standard conditions. Cell viability measured by impedance without dyes [4]. Apoptosis tested by flow cytometry. ROS measured with fluorescent dye. Mitochondria tested with TMRE dye. Phosphate transport blocked by PFA; antioxidants reduced ROS. Caspase activity blocked by Z-VAD-FMK. Cell shape checked by microscopy. Stats by ANOVA, $p < 0.05$.

Results

Layered black phosphorus (BP) showed clear dose-dependent toxicity in cell cultures. Larger and thicker BP particles caused stronger harmful effects, mainly by increasing production of reactive oxygen species (ROS) inside the cells. This led to damage of the cell membranes and decreased cell survival. Among tested cells, human embryonic kidney cells (293T) were most sensitive to BP, followed by mouse fibroblasts (NIH 3T3) and human corneal epithelial

cells (HCoEpiC). The results suggest that physical properties of BP particles strongly affect their cytotoxicity. Red phosphorus powder activated by visible light generated high levels of reactive oxygen species that oxidized bacterial membrane proteins of Escherichia coli. This damage reduced bacterial respiration and caused cell death. The photocatalytic effect of red phosphorus was stable and repeated over several cycles without losing activity, indicating potential for environmental or antibacterial applications. High concentrations of inorganic phosphate (nearly 2.5 mM), close to levels seen in hyperphosphatemia, caused apoptosis in human (EAhy926) and bovine (GM-7373) endothelial cells. This effect was stronger when calcium concentration was elevated. Apoptosis was accompanied by increased ROS production, loss of mitochondrial membrane potential, and activation of caspase enzymes. Morphologically, apoptotic cells showed shrinkage, membrane blebbing, and loss of adhesion to the substrate. Using phosphonoformic acid (PFA) to block phosphate transport into cells, or antioxidants to reduce ROS, completely prevented cell death, demonstrating that phosphate uptake and oxidative stress are critical for cytotoxicity. Inhibiting caspases with Z-VAD-FMK also stopped apoptosis, confirming caspase-dependent cell death pathways.

Vanadium

Abstract

Vanadium is metal with many biological effects. In plants high vanadium causes oxidative stress and programmed cell death (PCD) because of more reactive oxygen species (ROS) [2]. In medicine vanadium compounds show selective toxicity to cancer cells of lung and pancreas by activating apoptosis, necroptosis and mitotic catastrophe [1,3]. This review collects data about vanadium effect on cell death in plants and human cancer cells and talks about main mechanisms and possible therapy use of vanadium complexes.

Introduction

Vanadium is a biologically active metal. In high doses it causes toxic effects, mostly in plants. It mostly collects in the roots of rice and causes oxidative stress because of more ROS [2]. This damages cell membranes and starts programmed cell death (PCD), this protects plants from stress. Also vanadium is interesting in medicine as a possible anti-cancer drug. Vanadium compounds, special organic complexes, show selective toxicity to cancer cells like A549 (lung) and PANC-1 (pancreas) [1,3]. Vanadium causes not only

classic apoptosis but also mixed cell death, connected with oxidative stress, mitotic catastrophe and necroptosis. This makes vanadium valid for fighting cancer cells resistant to apoptosis.

Materials and Methods
In experiments used vanadyl sulfate (V+4), sodium metavanadate (V+5) and vanadium complexes with organic ligands [1,3]. In plants (rice) measured growth, biomass, ROS and antioxidant enzymes at different vanadium levels [2]. In cell lines A549 (lung cancer), PANC-1 (pancreas cancer) and normal pancreas cells studied vanadium effect on cell viability, ROS, apoptosis, cell cycle and autophagy. Methods were flow cytometry, fluorescence tests and western blot [1–3].

Results
In rice experiments vanadium more than 35 mg/l very reduces plant growth and biomass, especially roots. Vanadium collects mostly in roots. Vanadium increases antioxidant enzymes activity and hydrogen peroxide (H2O2) level, this shows oxidative stress. Stress damage cell membranes and start programmed cell death (PCD) with vacuolization and chromatin condensation. This shows the toxic effect of vanadium on plant cells.

In A549 cancer cells vanadium compounds cause a big increase of ROS — 12 to 14 times more than control at 100 μM after 48 hours. But usual apoptosis markers like caspase activity and proteins Bcl-2, Bax, FasL did not change. This shows classic apoptosis no start. Vanadium with valence V(+4) causes more ROS than V(+5), so valence is important.

In PANC-1 pancreatic cancer cells vanadium complexes with phenanthroline and quinoline ligands show strong selective toxicity. They reduce cancer cell viability but normal pancreas cells (hTERT-HPNE) are less affected. Studies show vanadium complexes stop autophagy at toxic doses, so cells survive worse. Also vanadium causes cell cycle stop in G2/M phase and lead to mitotic catastrophe — wrong cell division and cell death. At higher doses vanadium causes a mix of apoptosis and necroptosis. This helps to kill cancer cells that resist apoptosis. ROS increase is important to start this cell death.

Antimony

Abstract
Antimony (Sb) is a metal that can harm many tissues like the liver and brain.

This review shows Sb causes cell death by different ways: DNA damage and delayed apoptosis, oxidative stress and mitochondrial damage, and nerve cell death by autophagy and apoptosis linked to blocking Akt/mTOR signaling. These results show how ROS and mitochondria are important in Sb toxicity and help find ways to protect cells.

Introduction

Antimony is a natural metal found in the environment and used in industry and medicine. Sb exposure can hurt the liver, lungs, heart, and brain [1,3]. Past studies found Sb damages DNA and causes apoptosis in many cells [2]. But scientists don't fully understand how Sb kills cells, especially nerve cells. New studies show Sb causes oxidative stress and mitochondrial problems in liver cells, and triggers autophagy in nerve cells by blocking Akt/mTOR pathway [1,3]. This review joins all data to explain how Sb causes cell death.

Materials and Methods

$SbCl_3$ and Sb tartrate to treat cells were used as main resources.Moreover, antioxidants like N-acetylcysteine and inhibitors of autophagy. Cells used: CHO-K1 (hamster), BES-6 (human lung), HF (human fibroblast), rat liver cells, and PC12 nerve cells. Cells were grown in normal conditions (DMEM with 10% serum, 37°C, 5% CO_2). Sb was added in different amounts (10–200 μM) for 4 hours. After treatment, cells were checked immediately or after growing in fresh medium for some hours. DNA damage was measured by counting micronuclei, apoptosis by TUNEL test, ROS by special dyes, mitochondrial health by JC-1 dye, autophagy by LC3-II and p62 levels, and protein signals by western blot. Antioxidants were used to see if ROS caused damage.

Results

$SbCl_3$ caused DNA damage (micronuclei) in all tested cells after 4 hours at higher doses. Fibroblasts were most sensitive, lung cells medium, hamster cells least. Apoptosis was not seen right after but appeared after 16 hours, showing delayed cell death. Calcium balance was also disturbed, which may help cell death start. In liver cells, Sb caused more ROS and lipid damage, and mitochondria lost membrane potential. Antioxidants helped protect cells, but low glutathione made damage worse. In nerve cells, Sb causes autophagy and apoptosis depending on dose. It lowered Akt and mTOR activity. Activating Akt or using antioxidants lowered cell death. This shows Sb causes nerve cell death by blocking Akt/mTOR and increasing ROS.

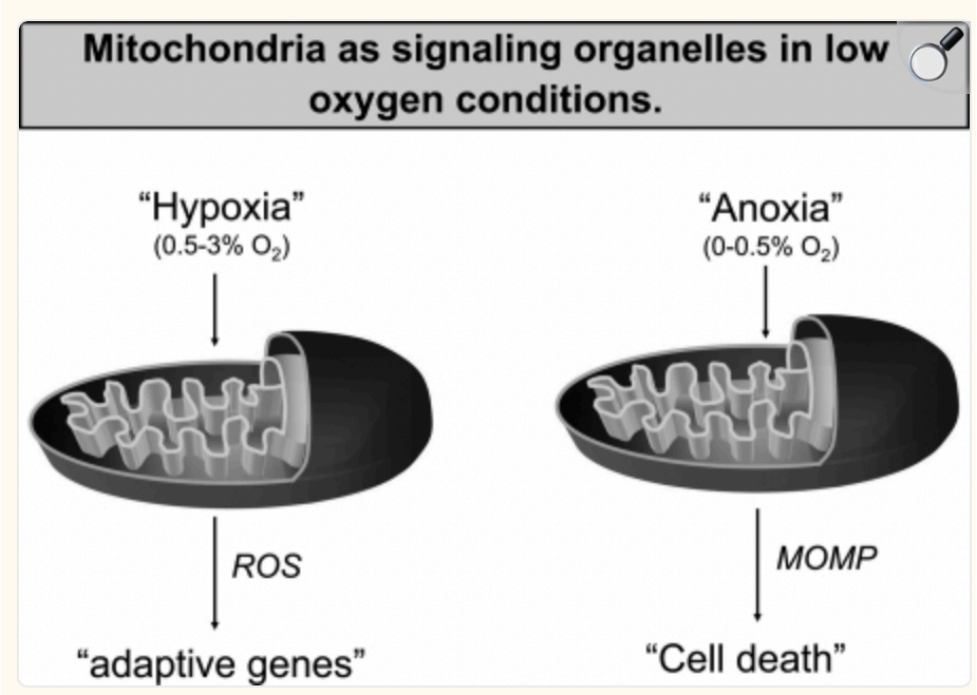
Element	Symbol	N	Group	Period	Block	Category	Electron Config. (Abbr.)	Oxidation States	Natural State	Radioactive
Oxygen	O	8	16	2	p	Nonmetal	[He] $2s^2$ $2p^4$	-2, -1, 0, +1, +2	Gas	No
Sulfur	S	16	16	3	p	Nonmetal	[Ne] $3s^2$ $3p^4$	-2, +2, +4, +6	Solid	No
Chromium	Cr	24	6	4	d	Transition metal	[Ar] $3d^5$ $4s^1$	+2, +3, +6	Solid	No
Selenium	Se	34	16	4	p	Metalloid	[Ar] $3d^{10}$ $4s^2$ $4p^4$	-2, +2, +4, +6	Solid	No
Molybdenum	Mo	42	6	5	d	Transition metal	[Kr] $4d^5$ $5s^1$	+2, +3, +4, +5, +6	Solid	No
Tellurium	Te	52	16	5	p	Metalloid	[Kr] $4d^{10}$ $5s^2$ $5p^4$	-2, +2, +4, +6	Solid	No
Tungsten	W	74	6	6	d	Transition metal	[Xe] $4f^{14}$ $5d^4$ $6s^2$	+2, +3, +4, +5, +6	Solid	No
Polonium	Po	84	16	6	p	Metalloid (Radioactive)	[Xe] $4f^{14}$ $5d^{10}$ $6s^2$ $6p^4$	-2, +2, +4, +6	Solid	Yes
Seaborgium	Sg	106	6	7	d	Transition metal (synthetic)	[Rn] $5f^{14}$ $6d^4$ $7s^2$	+6 (predicted)	Synthetic	Yes
Livermorium	Lv	116	16	7	p	Post-transition (synthetic)	[Rn] $5f^{14}$ $6d^{10}$ $7s^2$ $7p^4$	-2, +2, +4 (predicted)	Synthetic	Yes

Oxygen

Introduction

Mitochondria can initiate cell death or activate genes that promote cell survival in response to low oxygen. The BCL-2 family of proteins regulate cell death in response to anoxia (0–0.5% O2). By contrast, under hypoxia (0.5–3% O2), mitochondrial oxidative stress activates hypoxia-inducible factors (HIFs) to promote cell survival. In fact, oxygen plays a crucial role in a difference of cellular processes, such as sterol and fatty acid synthesis, and it is necessary for oxidative phosphorylation. Thus, it is not surprising that changes in oxygen availability can have drastic effects on the function of a cell. Several studies indicate that low-oxygen conditions can induce apoptosis. This occurs when oxygen levels decrease to at, or below, 0.5% (anoxia). When oxygen levels are 0.5–3% (hypoxia), cells do not undergo apoptosis. Instead, hypoxia activates a variety of cellular events that ultimately lead to cell survival.

Pathophysiological conditions where the oxygen concentration is insufficient to sustain cellular homeostasis are frequently linked to hypoxia. However, embryonic stem cells live at low oxygen and it is important for both embryonic and fetal development. Hypoxia can vary in intensity from mild to severe and can be present in acute and chronic forms. The cellular response to oxygen deprivation is governed mainly by a group of oxygen-sensitive transcription factors, named hypoxia-inducible factors (HIF-1α, HIF-2α/EPAS, and HIF-3α). In normoxia, HIF-1α and HIF-2α are polyubiquitinated and targeted for proteasomal degradation. Rather they are stabilized at low oxygen concentration. Once stabilized, dimerize with HIF-1β, which is constitutively expressed, and regulate the transcription of more than 100 genes (e. g. glycolytic enzymes and survival factors) required to cope with low oxygen tensions.



Oxidative stress is a condition where our bodies' oxidative systems are out of standard balance, leading to various human diseases,like aging, carcinogenesis, and degenerative illnesses. Numerous researches found that oxidative stress plays a pivotal role in the pathogenesis of human disease by promoting cell death, including apoptosis, necroptosis, pyroptosis, ferroptosis or by disrupting pro-survival signals like autophagy and unfolded protein response

Sulfur

Sulfur Form	Mechanism	Cell Outcome
Nano-sulfur / Trisulfides	Mitochondrial stress & apoptosis	Cancer cell death
H_2S	Mitochondrial inhibition / signaling	Apoptosis or ferroptosis regulation

Sulfur deprivation	Disrupted antioxidant synthesis	ROS increase, organelle dysfunction, cell death
Elemental sulfur	Biological defense accumulation	Local cell death in plant defense

The dominant form of sulfur (S) in terrestrial and aquatic habitats is usually the sulfate anion (SO_4) , the most oxidized form of S. Animals do not have the enzymatic machinery needed for reducing SO_4 to sulfide (S-2) , which is required to synthesize most S-containing compounds. Plants and microbes have specific transporters that efficiently import SO_4) into cells, where it is activated and then reduced to S-2 for incorporation into S-containing amino acids and other molecules, such as S-adenosylmethionine (SAM), GSH, FeS clusters, thio nucleosides, sulfolipids, vitamins, and enzyme cofactors, such as CoA (CoA), molybdopterin, thiamine, or biotin. However, most organisms have a low capacity to store S and thus have developed diverse acclimation strategies that optimize S use and balance the rate of S metabolism with S availability. These processes allow organisms to remain viable even when S is severely limiting to growth.

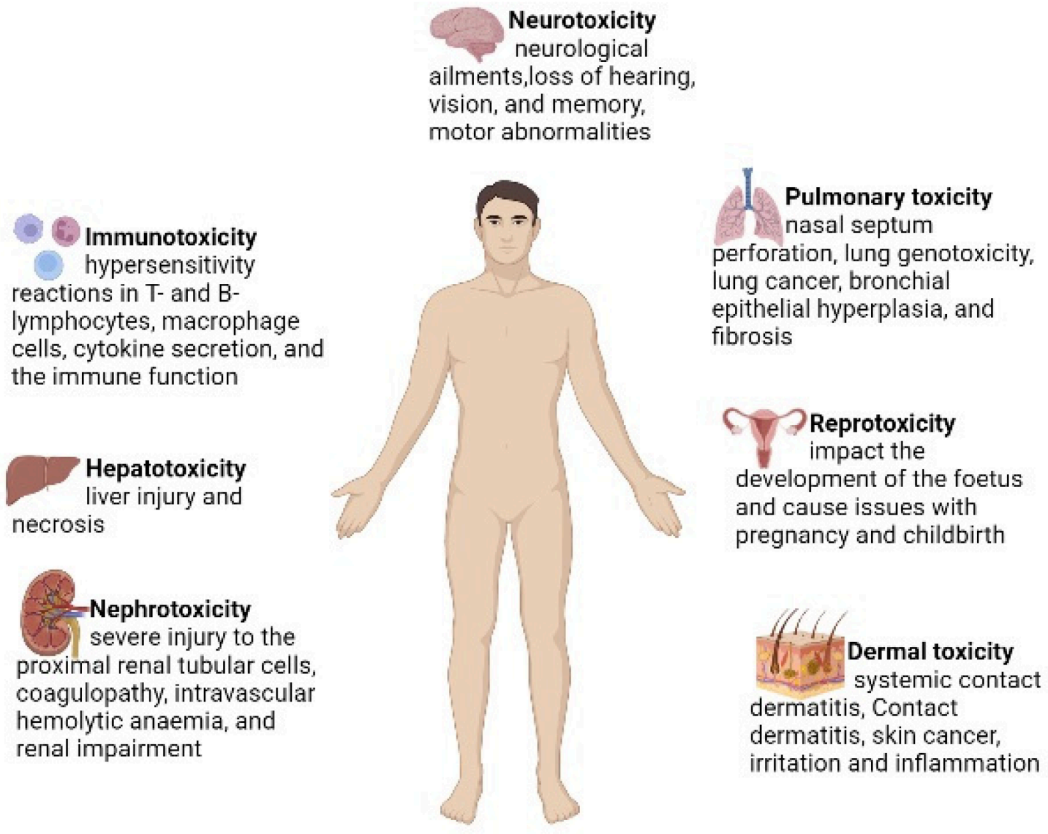
Hydrogen sulfide (H_2S) has become somewhat of a wonder molecule in the past 25 years due to the discovery of its malleable cell- and tissue-specific production lending control over its numerous physiological functions.1 Generation of H_2S occurs primarily via the breakdown of the sulfur-containing amino acids cysteine and/or homocysteine by the enzymes cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfotransferase (3-MST) or through non-enzymatic catalysis coordinated by iron and vitamin B6.2 H_2S imparts its bioactivity as a regulator of redox status and mitochondrial bioenergetics while serving as substrate for protein sulfhydration (aka persulfidation) of thiol (–SH) groups to hydropersulfides (–SS(n)H) that impact protein structure, function, and/or stability.3

Elemental S is well documented in certain specialized prokaryotes, but has rarely been detected in eukaryotes. Elemental S was first identified in this laboratory as a novel phytoalexin in the xylem of resistant genotypes of Theobroma cacao, after infection by the vascular, fungal pathogen Verticillium dahliae. In the current work, this phenomenon is demonstrated in a resistant line of tomato, Lycopersicon esculentum, in response to V. dahliae. A novel gas chromatography-mass spectroscopy method using isotope dilution

analysis with S internal standard was developed to identify unambiguously and quantify S in samples of excised xylem. Accumulation of S in vascular tissue was more rapid and much greater in the disease-resistant than in the disease-susceptible line.

Chromium

Cr (VI) is a well-known toxic agent, and its toxicity highly depends on the oxidation states and ionic species. Cr (VI) has higher solubility and reactivity as compared to Cr (III). It can easily cross the plasma membrane and enter the cell compartment through several cell surface receptor phosphate transporters and anion transporters. Cr (VI) is more hazardous due to its higher oxidative state and solubility. Cr (VI) has a negative impact on human health, which is responsible for the damage of several organs, including the lungs, liver and kidneys. The lethal effects of Cr (VI) are listed in Figure 2.



Several studies have shown that Cr (VI) can cause cancer and damage to multiple organs, including the liver, heart, and kidneys. According to Gumbleton and Nicholls (1988), Cr (VI) causes damage to the kidneys in rats after they get a shot of Cr (VI) under the skin. When Cr (VI) is given by mouth,

Bagchi et al. found that it causes lipid peroxidation in the mitochondria and microsomes of the liver and raises the levels of lipid metabolites in the urine. Cr (VI) can also cause chromosomal abnormalities, DNA strand breaks, and cancer of the lungs.

The reduction of Cr (VI) is considered a detoxification process when it occurs at a distance from the nucleus and other cell organelles or outside the cell. If Cr (VI) reduction occurs within the cell, it induces oxidative-mediated toxicity and damages cell organelles, and mutation in the DNA takes place . In case Cr (VI) is converted into Cr (III) outside the cell, the reduced Cr (III) and other intermediate components are unable to transport into the cell compartment and hence a toxic effect is not observed. Cr (VI) passes through the cell membrane and enters the intracellular space and is subsequently reduced to Cr (III). During the reduction process, ROS are generated, which causes cell toxicity. Studies suggest that Cr (VI) toxicity is mainly due to an increase in ROS production, which is produced by the Fenton reaction. The generation of ROS in different cell lineages and their lethal impacts

Table 1. Showing the changes to occur upon Cr treatment on Oxidative stress markers and how they are altered in lungs, liver, and kidneys in different animal models and cell lines.

Organ	**Concentration and compound type**	**Time of exposure**	**Biological models or Cell line**	**Oxidative Stress marker changes**	**Refer ence**
Lungs	Potassium dichromate 2,4,6 mg/kg	35 days	Wistar Rats	MDA, GSH levels increase. SOD levels decrease.	[9]
Empty Cell	Potassium dichromate 700 ppm	3 weeks, 10 days	Wistar Rats	CAT, GPx, and SOD levels decrease.	[13]

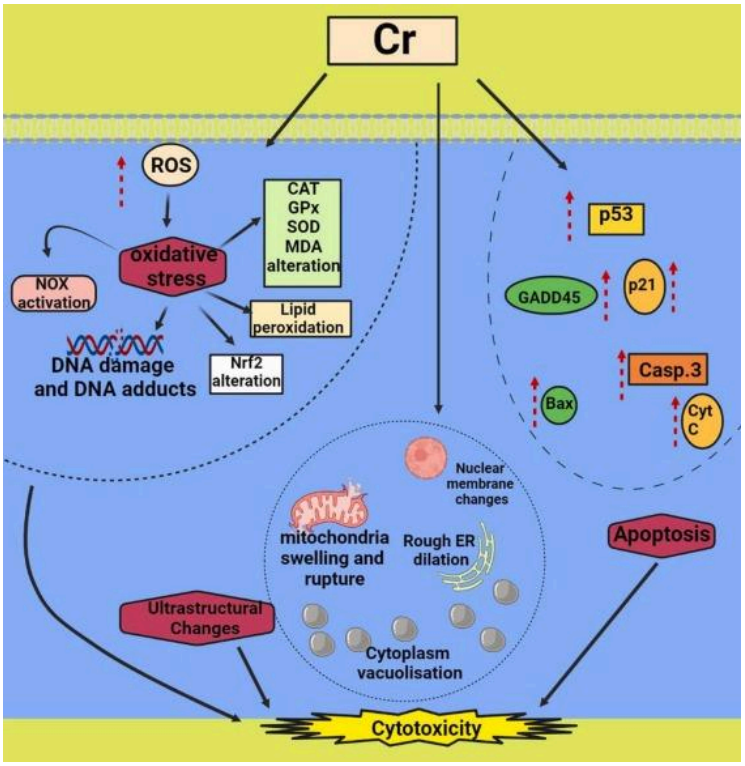
Empty Cell	Potassium dichromate 10 μM	24 h	LEC (Cell lines).	Thioredoxins alterations.	[26]
Empty Cell	Sodium dichromate dihydrate 2 μM	48 h	B2B (Cell Lines).	GPx and SOD levels decrease.	[27]
Empty Cell	Sodium chromate 25,50 μM	3 h	B2B (Cell Lines).	Trx and Prx undergo oxidation. Irreversible TrxR inhibition	[53]
Liver	Potassium dichromate 2.5, 5.0, 7.5, and 10 mg/kg	5 days	SD rats	MDA, SOD, and CAT levels increased.	[10]
Empty Cell	Chromium chloride 1, 2.5, 5 or 10 10 mg/l	96 h	*Carassius auratus*	SOD, CAT, and GST levels decreased.	[54]
Empty Cell	Potassium dichromate 127 mg/kg	12 h	Rats	GR, GSH, CAT, GST, SOD, GPX levels decrease.	[16]
Empty Cell	Potassium dichromate 20 mg Cr/kg	12 h	Swiss albino mice	SOD and CAT levels decrease.	[19]
Empty Cell	Potassium dichromate 0, 25, 50, 100, 200, and 400 μg/ L	4 weeks	*Mugil cephalus*	Rise in GSH levels. Decrease in GST and SOD levels.	[55]
Empty Cell	Potassium dichromate 93.95 mg/L, 187.9 mg/L, 281.85 mg/L	96 h	*Cyprinus carpio*	Rise in SOD and GPx levels. Decrease in CAT levels.	[56]

Kidney	Potassium dichromate 2.5, 5.0, 7.5, and 10 mg/kg body wt. per day	5 days	SD rats	Rise in MDA, SOD, CAT levels	[10]
Empty Cell	$CrCl_3 \cdot 6H_2O$ and Potassium dichromate 10.0 mg/L	96 h	*Carassius auratus L*	Rise in SOD levels. Decrease in GST and CAT levels.	[57]
Empty Cell	Sodium dichromate 0 mg/L, 21.42 mg/L, 42.85 mg/L and 85.7 mg/L	96 h	*Carassius auratus*	Rise in GPx activity.	[88]
Empty Cell	Potassium dichromate 93.95 mg/L, 187.9 mg/L, 281.85 mg/L	96 h	*Cyprinus carpio*	Rise in SOD, GPx activity. Decrease in CAT activity.	[56]
Empty Cell	Potassium dichromate 0.01, 0.1, 1 and 5 mg/L	14 days	*Aristichthys nobilis*	A rise in GST activity	[59]
Empty Cell	Potassium dichromate 67 mg/kg body wt.	21 days	Wistar rats	Rise in MDA ad SOD levels. A decline in GPX and CAT levels.	[60]

A study on lung tissue upon Cr (VI) exposure showed an increase in the p53 expression levels, which showed that Cr-induced apoptosis was dependent on p53 expression. A study on A549 cell lines, when exposed to Cr, showed a

rise in Bax and cytochrome C Levels as well. The caspase-3 (cleaved) expression levels were also seen to rise upon similar exposure significantly. Furthermore, an elevation was seen in the levels of p53 in Cr exposed cells

Lung fibroblasts of humans, when treated with Cr (VI), showed down-regulation in the levels of BCL-W and BCL-XL. A rise was seen in the level of Bcl-2-like protein 2 (Bcl-2). Bcl-Xs levels also showed significant elevation. An upregulation was also seen in growth arrest and DNA damage (GADD45) and p21 expression level



Cr(VI) reduction occurs both inside and outside the cell. Due to its weak membrane permeability, the final metabolite Cr(III) is normally retained in the same place it was produced. For example, intracellular Cr(VI) reduction leads to a massive intracellular accumulation of Cr(III) ranging from 10- to 20-fold after 3 h up to about 100-fold after 24 h of exposure. High levels of Cr(III) in cells react with DNA, which is the principle mechanism underlying Cr(VI) genotoxicity. In contrast, Cr(III) generated from extracellular reduction cannot enter the cell and poses little or no toxic and carcinogenic activity, rendering the extracellular reduction process as a detoxification mechanism.

After Cr enters into the biological system, Cr (VI) is reduced to Cr (III) and releases free radicals into the system. The released free radicals are highly

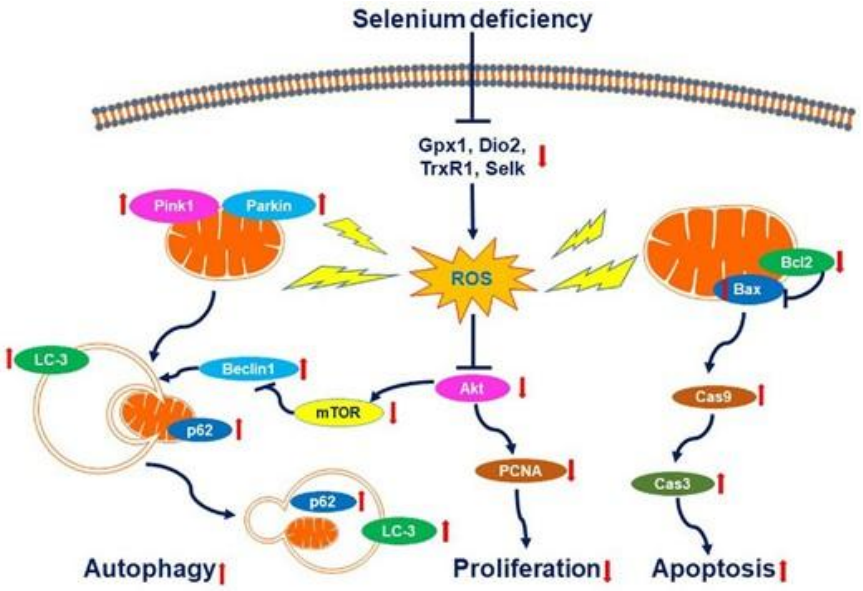
reactive and interact with various macromolecules. Antioxidants play an important role in balancing the reactive oxygen species (ROS) levels in biological systems. Many studies have reported toxic potentials of Cr in aquatic organisms. Cr is reported to induce histological changes in fish gills. Hematological studies in Cr exposed fish have revealed thrombocytopenia, anemic, leukopenia conditions, erythrocytosis, and leukocytosis. Cr inhibits ion-transporting ATPases in gills, kidney, and intestinal tissues. Cr (VI) has also been reported to alter antioxidant and associated enzymes including superoxide dismutase (SOD), catalase (CAT) and glutathione reductase.

Selenium

Selenium (Se) is an essential trace mineral for humans and animals, but high concentrations of Se induce apoptosis and oxidative effects. Although cell apoptosis has been evidenced as a critical mechanism mediating the anticancer activity of Se, the underlying molecular mechanisms remain elusive.

Se deficiency weakened the activity of antioxidant enzymes and increased the accumulation of oxidation products in the liver. Se deficiency also led to excessive fission of the mitochondria and downregulated the expression of the Mfn2 and Opa1 genes in the calf liver. Mitochondrial damage-induced apoptosis by increasing the expression of pro-apoptotic genes such as CytC, Cas3, Cas9, fas, and Cas8, leading to a decrease in energy metabolism. Se deficiency also triggered the expression of inflammatory-related factors such as IL-1β, IL-6, TNF-α, and NF-κB. Taken together, the results suggest that Se deficiency causes oxidative stress, triggers an inflammatory response, disrupts mitochondrial dynamic balance, and then induces apoptosis, eventually leading to calf liver damage. These findings might provide valuable clues for elucidating the mechanism of Se deficiency-induced injury in domestic animals

Some endemic diseases, including Keshan disease and Kashin-Beck disease, have been linked directly to selenium deficiency. There is growing evidence that pregnancy-related illnesses are associated with maternal selenium deficiency. According to Xu et al., the risk of preeclampsia (PE) is inversely correlated with blood selenium levels, and the incidence of PE is considerably decreased by selenium supplementation.



Numerous studies have demonstrated that selenium plays a crucial regulatory role in the health, survival, and proliferation of neural stem and progenitor cells, as well as its anti-aging qualities. But since the majority of this information comes from rodent models, it's unclear how it affects human hippocampus progenitor cells.

Iodine

Introduction

Cell necrosis and apoptosis are differentially regulated during goitre development and iodine-induced involution, with important implications for thyroid health and broader iodine-related disorders. Additionally, molecular iodine can induce a unique form of apoptosis in certain cancer cells, such as human breast carcinoma, via a caspase-independent, mitochondria-mediated pathway.

Abstract

Cell death during goitre development and iodine-induced involution is regulated differently: necrosis dominates in goitre due to oxidative stress, while apoptosis increases during iodine-induced involution. Molecular iodine also induces caspase-independent, mitochondria-mediated apoptosis in human breast cancer cells through thiol depletion, Bax activation, and AIF

nuclear translocation. These findings highlight distinct cell death mechanisms in thyroid disease and reveal iodine's potential as a selective anticancer agent.

Iodine deprivation and cell death

Iodine deprivation can cause cell death, particularly through its impact on thyroid hormone synthesis and cellular metabolism. Iodine is essential for producing thyroid hormones (T3 and T4), which regulate cellular oxidation, protein synthesis, and overall metabolism. When iodine intake is insufficient, thyroid hormone production decreases, leading to hypothyroidism and impaired cellular functions in various tissues, including the brain, muscle, heart, and liver [1].

In the developing brain, iodine deficiency during critical periods (such as mid-second trimester of pregnancy) causes reduced thyroid hormone availability, leading to impaired neurogenesis processes like cellular proliferation, differentiation, migration, and selective cell death. This can result in cellular hypoplasia (reduced cell number) and abnormal brain development, which may include increased apoptosis (programmed cell death) and irreversible brain damage [1].

Moreover, iodine in molecular form (I_2) has been shown to induce caspase-independent apoptosis in certain cells, such as human breast carcinoma cells, by disrupting mitochondrial membrane potential and oxidative phosphorylation, leading to a rapid form of cell death termed "iodoptosis" when used in clinical iodine preparations like povidone-iodine (PVP-I) [3]. This indicates that iodine can directly cause cell death under certain conditions.

In summary, iodine deprivation primarily causes cell death indirectly by impairing thyroid hormone production, which is critical for cell survival and development, especially in the brain. Additionally, iodine in certain molecular forms can directly induce apoptosis in some cell types[1][2].

During iodine deficiency, several key cellular processes are impaired primarily due to insufficient thyroid hormone synthesis:

Cellular proliferation, differentiation, migration, and selective cell death are disrupted, especially during neurogenesis in fetal and early brain development, leading to impaired brain structure and function [2].

thyroid hormone synthesis is reduced because iodine is essential for producing thyroxine (T4) and triiodothyronine (T3), which regulate cellular oxidation, protein synthesis, and metabolism[1][2].

Metabolic processes regulated by thyroid hormones are affected, including calorigenesis, thermoregulation, nitrogen retention, glycogenolysis, glucose absorption, lipolysis, and glucose uptake by adipocytes [2].

Compensatory mechanisms in the thyroid gland occur, such as increased thyroid-stimulating hormone (TSH) secretion, leading to thyroid hypertrophy (goiter) and altered iodine uptake dynamics, which reflect cellular stress in thyroid follicular cells [1].

Impaired development and function of multiple tissues including muscle, heart, liver, kidney, and particularly the developing brain, due to inadequate hormone supply [1][2].

In summary, iodine deficiency impairs fundamental cellular processes related to growth, differentiation, metabolism, and survival, largely through reduced thyroid hormone availability and its downstream effects on cellular function and organ development [1][2].

During the development of goitre, thyroid cells predominantly die through necrosis, a form of accidental cell death caused by oxidative damage and insufficient antioxidant protection. This process results in cell swelling and membrane rupture. Conversely, when iodine treatment triggers the shrinkage of the goitre, the thyroid cells mainly undergo apoptosis, a controlled and programmed form of cell death that facilitates the safe removal of excess cells. The balance between these two types of cell death is influenced by the thyroid's oxidative environment and iodine metabolism. Deficiency in antioxidants like vitamin E worsens necrosis but does not affect apoptosis, highlighting their separate regulatory mechanisms. Additionally, blocking thyroid hormone synthesis with methimazole inhibits apoptosis during involution, indicating hormonal control over this process. These findings reveal that necrosis and apoptosis are distinctly regulated during thyroid enlargement and regression, with important consequences for thyroid health and disease [3].

Conclusion

Necrosis dominates during goitre development due to oxidative stress, while apoptosis is the main mechanism during iodine-induced involution of the

thyroid.Iodine deficiency leads to severe developmental, cognitive, and reproductive consequences, preventable through iodized salt.Molecular iodine can trigger caspase-independent, mitochondria-mediated apoptosis in breast carcinoma cells, highlighting a potential therapeutic mechanism for cancer that is distinct from classical apoptosis pathways.

He (Helium)

Depending on how it is used, helium can affect both cytotoxic and cytoprotective pathways, making it a powerful regulator of cell death. The gathered research examines two main areas: helium as a gaseous agent in ischemia conditioning, where it exhibits tissue-protective properties, and helium employed as a cold atmospheric plasma (CAP) for therapeutic applications, especially against cancer.

The biomedical applications of helium reveal an amusing dependence on its physicochemical form. Helium-based cold atmospheric plasma demonstrates significant cytotoxic activity against cancer cells through the production of reactive oxygen intermediates. These species cause substantial mitochondrial membrane damage and trigger apoptotic cell death via caspase enzyme activation.

What is really exciting is how well this works when combined with other treatments. Scientists have found that pairing helium plasma with heat therapy or low-dose radiation creates a kind of one-two punch that's especially effective against lymphoma and lung cancer cells. The cancer cells just can't handle the combined stress, and their viability drops dramatically. The best part? Healthy cells, like the endothelial cells that line our blood vessels, seem to shrug off the treatment with minimal damage.

However, when helium is administered as a conventional gas rather than plasma, it produces dramatically different biological effects.When doctors give helium before or after events like heart attacks or strokes (what researchers call ischemia-reperfusion injury), it actually protects cells from dying. Studies in lab animals show that helium activates cellular survival pathways, particularly something called the RISK pathway, and influences proteins like caveolin-1 to help cells weather the storm.

Transcriptomic analysis revealed that helium exposure fundamentally altered cellular gene expression patterns, promoting pro-survival genetic programs

while simultaneously downregulating inflammatory cascades and apoptotic signaling pathways.

Scientists are still figuring out exactly how this works, but they think the location of those reactive oxygen species matters a lot. ROS outside the cell seem to be particularly good at triggering the death signals in cancer cells. Meanwhile, researchers are developing sophisticated ways to measure exactly how much "biological dose" of helium plasma to use, treating it almost like a form of precision radiation therapy that doesn't actually use ionizing radiation.

Indeed, helium demonstrates remarkable therapeutic plasticity, functioning as both a cytotoxic agent against neoplastic cells and a cytoprotective intervention for normal tissues. This binary capability positions helium-based therapies as versatile tools spanning oncological interventions and perioperative organ preservation strategies.

Ne (Neon)

Neon has an effect on cell death through two main biomedical channels: cold atmospheric plasma (CAP) technologies and high-energy radiation of neon ions. In both cases, the main mechanisms are reactive oxygen species (ROS), DNA damage, and programmed cell death pathways — the most important being apoptosis and pyroptosis.

Neon-controlled plasma jets have strong cytotoxic and virucidal effects. Studies using microplasma jets and inkjet devices have shown that neon plasma causes oxidative stress, which leads to the death of tumor cells and significant inactivation of coronaviruses. These effects are especially strong in direct contact (conductive exposure), when intracellular ROS production reaches its maximum. It is important to note that the virucidal activity of neon plasma correlates with a 3,000-fold decrease in viral load. However, although neon plasma was highly effective in killing tumor cells, its ability to induce immunogenic cell death (ICD), which is crucial for long-term antitumor immunity, was weaker than that of argon-based systems such as kINPen.

On the ionizing radiation side, neon-ion beams (used in particle therapy and radiobiology) show high linear energy transfer (LET) characteristics, producing dense ionization tracks that cause complex DNA damage. These beams are significantly more lethal to cells than lower-LET radiation like X-rays. Several

studies examined the effects of neon-ion beams on both tumor and normal cells, showing they induce a combination of apoptosis, chromatin breaks, and, in some contexts, mutagenesis. The degree of cell death and biological damage was shown to depend on factors like oxygen availability, intratumoral heterogeneity, and LET magnitude. Comparison with other ions (helium, carbon, oxygen) has shown that neon is one of the most biologically effective, especially in conditions of tumor hypoxia, where it retains a strong cytotoxic potential.

Notably, one study demonstrated that cold plasma, including neon plasma, can also cause pyroptosis, a highly inflammatory form of programmed cell death, through activation of ROS-induced GSDME.

Ar (Argon)

The organ performs many different functions when it comes to controlling cell death. For example, it can kill cancer cells and protect neurons at the same time. Plasma argon is often used in cold atmospheric plasma (CAP) and plasma-activated media (PAM) technologies, which have been proven to be very effective in fighting cancer. Resulting in the formation of reactive oxygen species (ROS) by the usage of CAP ot PAM argon, these types result in DNA damage, mitochondrial dysfunction, and caspase-dependent apoptosis. Only cancerous cells, like osteosarcoma and lung cancer, are harmed by these oxidative processes, healthy stem cells are unaffected.In addition, argon plasma treatment can cause immunogenic cell death (CD), which allows the immune system to better detect tumors by reducing immune system-suppressing signals such as CD47.

At the molecular level, argon-triggered oxidative stress can destabilize tumor-supporting proteins. For instance, cleavage of the chaperone protein HSP90, which is vital for many oncoproteins, has been identified as a key step in argon-induced tumor cell death. This effect makes argon an effective tool in cancer treatment, especially when combined with its capacity to stimulate inflammatory and apoptotic cell death pathways like pyroptosis.

Beyond plasma, ionized argon beams used in radiation therapy exhibit high linear energy transfer (LET), allowing them to inflict complex and irreparable DNA double-strand breaks.According to research, the ability of these rays to generate short DNA fragments is a defining characteristic of their therapeutic

effectiveness. In addition, the therapeutic area is expanded due to the side effects of radiation from heavy argon ions, which lead to the fact that even nearby cells that have not been exposed to radiation experience stress reactions or die as a result of the release of signaling molecules by irradiated cells.

In contrast to its antitumor role in oncology, argon also exhibits neuroprotective properties when used as a gas in pretreatment protocols.When argon is inhaled before hypoxic or ischemic injury, experimental data show that it activates pathways mediated by Toll-like receptors (TLRs), in particular TLR2 and TLR4, which reduce oxidative damage and apoptosis signaling in neuronal tissues. This mechanism supports the survival of healthy cells in adverse environmental conditions and also highlights argon's potential in neuroregeneration and intensive care.

In summary, argon demonstrates powerful context-dependent effects on cell death. As a plasma or ion beam, it efficiently eradicates cancer cells through oxidative and DNA-damaging mechanisms while also enabling immune engagement. Conversely, as an inert gas, argon can shield neurons from damage through anti-apoptotic and anti-inflammatory pathways. This dual functionality makes argon a promising and adaptable tool in both cancer therapy and regenerative medicine.

Fe (Iron)

Ferroptosis is a special type of programmed cell death that differs from other types such as apoptosis (programmed cell death) and necrosis (pathological cell death). Its key feature is its dependence on iron and the process of lipid peroxidation, which make up cell membranes.During ferroptosis, there is an accumulation of reactive oxygen species (ROS), extremely active molecules that damage cellular structures.It is increasingly recognized as a central mechanism for the development of various human diseases, including cancer, neurodegeneration, ischemic reperfusion injury, and reproductive function disorders.

Ferroptosis is based on a violation of iron homeostasis.The Fenton reaction, catalyzed by an excess of intracellular iron, especially in the mitochondria, leads to the formation of hydroxyl radicals that affect polyunsaturated fatty acids in cell membranes.If protective systems such as glutathione peroxidase

4 (GPS 4) do not regulate lipid peroxidation, this leads to irreversible cell damage and death.According to several studies, ferroptosis has therapeutic potential because it can be controlled using iron chelators, antioxidant systems, and important metabolic regulators.

According to recent studies, ferroptosis and autophagy are closely related.Autophagic degradation of ferritin, or ferritinophagy, releases free iron and makes cells more vulnerable to ferroptosis death.According to other studies, ferroptosis is not an independent process, but rather is associated with larger mechanisms of controlled cell death, such as cu proptosis (copper-mediated death), in which copper and iron play a crucial role as executioners.

Mitochondria play a central role in the progression of ferroptosis.Under oxidative stress, the accumulation of iron in the mitochondria increases the production of ROS and lipid peroxidation.This contributes to tissue damage in conditions such as neurodegeneration, and is also associated with pregnancy complications such as repeated miscarriage, when ferroptosis disrupts placental homeostasis.

Although ferroptosis is harmful in degenerative diseases and certain inflammatory conditions, it can be used as a powerful therapeutic agent for cancer.Cancer cells, due to their high iron requirements and metabolic reprogramming, are particularly vulnerable to the effects of ferroptosis triggers.Targeting ferroptosis in tumors offers a new approach, especially for the treatment of therapy-resistant cancers.

In parallel, ionizing radiation, especially from heavy charged particles, can have a synergistic effect on the ferroptosis pathways.Radiation causes the formation of short DNA fragments, which potentially enhances death from ferroptosis.This suggests that the combination of radiation therapy with ferroptosis inducers may enhance therapeutic efficacy.

Thus, ferroptosis is a double-edged sword in biology.Its regulation is closely related to iron metabolism, mitochondrial function, and oxidative stress.On the one hand, it promotes cell damage in neurological and reproductive disorders, and on the other, it offers promising therapeutic strategies for destroying cancer cells.Understanding and combating varroatosis may open up new possibilities for precision medicine for a wide range of diseases.

Kr (Krypton)

No effect on cell death

Ru (Ruthenium)

Ruthenium complexes immediately became the subject of research as powerful antitumor agents capable of causing various forms of regulated cell death in tumor cells using a variety of cellular targets. The complexes have demonstrated selective cytotoxicity to many cancer cells based on the destruction of mitochondria, the formation of reactive oxygen species, DNA damage, receptor-mediated death and apoptosis, while they return to normal cells.

Several groups have found that ruthenium II radical complexes can provide apoptosis directed at mitochondria. These complexes accumulate in mitochondria, causing membrane depolarization, release of cytochrome c, and activation of cascades of caspases. Other groups have shown that specific ruthenium ligands stimulate the release of reactive oxygen species that have allowed for apoptosis signals that are protected from above by an oxidative lever, especially in lung, breast, and prostate cancer models.

In addition to classical apoptosis, ruthenium compounds are capable of inducing necroptosis, a specific form of programmed necrosis. Experimental data confirm this fact by demonstrating damage to mitochondria without activation of caspases, which indicates a non-apoptotic but strictly regulated mechanism of cell death. Some ruthenium-containing complexes also affect the cell cycle, leading to its arrest, genomic instability and damage to nuclear DNA, thereby preventing tumor proliferation.

It is important to emphasize that the structural versatility of ruthenium determines the variety of mechanisms of action of these compounds. Thus, some ruthenium complexes are capable of destroying death receptors on the plasma membrane, directly triggering the process of external apoptosis. Other ruthenium complexes affect DNA, either by blocking its replication or by disrupting its functioning mechanisms, which leads to cell cycle arrest in the G2/M phase and subsequent cell death. For example, the well-known KP1019 complex damages DNA in yeast organisms, which indicates its preserved cytotoxic mechanisms of action.

Recent studies have revealed dual-acting ruthenium compounds with both antitumor and antiviral properties, which makes them very promising for therapeutic purposes. By adding particular ligands, such as dithiocarbamates, hydroxyquinoline, or terpyridine derivatives, these compounds can be improved, allowing for more precise control over their biological activity and exposure selectivity.Because they can trigger numerous cell death pathways, such as mitochondrial apoptosis, necroptosis, and receptor-mediated mechanisms, ruthenium-based compounds are therefore extremely promising antitumor agents.Their capacity to damage DNA, induce selective oxidative stress, and interfere with the cell cycle provides a multimodal strategy for tumor removal that may find use in precision medicine and combination therapy.

Xe (Xenon)

Xenon has powerful cytoprotective properties, especially known for its neuroprotective, anti-apoptotic and anti-inflammatory effects, especially known for its neuroprotective, anti-apoptotic and anti-inflammatory effects.Instead of causing cell death, xenon appears to constantly act as a cell survival enhancer by modulating signaling pathways to prevent or delay apoptosis in various disease and injury models, especially in the brain, heart, and kidneys. It constantly acts as a cell survival enhancer by modulating the signal.

Mechanistic xenon mediates the effects by modulating cellular stress responses, including interfering with signaling cascades of apoptosis and enhancing protective autophagy.In several neuron models, xenon has been shown to protect against hypoxia, ischemia, and excitotoxicity by acting through pathways including NMDA receptor antagonism, PI3K/Akt signaling, and regulation of autophagy.Exposure to xenon increased autophagy in case of neuronal damage caused by seizures, which contributed to cell survival under stress.

The scientists named xenon's ability to reduce mitochondrial dysfunction and activation of caspases, key mediators of apoptotic cell death.Early administration of xenon in models of myocardial infarction and kidney transplantation significantly reduced apoptosis, oxidative stress, and chronic inflammation.Xenon demonstrated protective effects in explosion-induced traumatic brain injury and in models of perinatal hypoxic-ischemic brain injury,

where it preserved tissue integrity and reduced damage to the nervous system when administered in a timely manner.

The anti-apoptotic properties of xenon extend not only to the nervous system.It has shown an advantage in cardiac ischemia by reducing cell death and inflammatory markers, as well as preserving the kidneys during transplantation by preventing damage caused by ischemia and chronic nephropathy.

In some cases, xenon has been studied along with other gases such as argon.Combined or comparative studies have shown that although both gases have protective properties, xenon often has a stronger anti-apoptotic effect, possibly due to its more selective interaction with ion channels and intracellular signaling molecules.

What is the main way that xenon promotes survival by modulating cell death, particularly in situations of ischemic, excitotoxic, or inflammatory stress?Because it inhibits apoptosis, enhances autophagy, and stabilizes mitochondria, xenon is a promising therapeutic agent for neuroprotection, organ preservation, and injury recovery in neonatal medicine, transplantation, and intensive care.

Os (Osmium)

Osmium-based compounds represent a promising and diverse class of antitumor agents capable of causing various forms of regulated cell death in tumor cells through mechanisms including mitochondrial destruction, production of reactive oxygen species (ROS), metabolic disorders, and calcium imbalance.These compounds often exhibit high selectivity against cancer cells and have a universal structure that allows precise regulation of their biological activity.

The main mechanism of action of osmium complexes is apoptosis directed at mitochondria.Several studies have shown that osmium (II) and osmium(VI) complexes accumulate in mitochondria, where they initiate ROS production, cause depolarization of mitochondrial membranes, activate caspases, and lead to apoptotic cell death.In colon cancer models, osmium compounds disrupt energy metabolism and oxidative balance, increasing the sensitivity of cancer cells to programmed death.

Which osmium(VI) nitride complexes go beyond classical apoptosis and induce oncosis, a form of necrotic cell death characterized by cell swelling and loss of membrane integrity, as well as reactions similar to autophagy?These effects are especially relevant in models of glioblastoma and hypoxic tumors, where osmium complexes were effective even in therapy-resistant cancer stem cells and in conditions of low oxygen content.

Osmium compounds can disrupt cellular calcium homeostasis, as is observed in benzimidazole-containing osmium(II) complexes.This violation of the intracellular Ca2+ level leads to stress of the endoplasmic reticulum and promotes cell death.

Another complex, such as osmium perox compounds, has demonstrated photoactivatable cytotoxicity, allowing the killing of hypoxic tumor cells under the influence of light, a promising photodynamic therapy strategy.

In addition, osmium complexes can cause cell cycle arrest, DNA damage, and decreased cell proliferation without significantly affecting healthy cells.The researchers talked about the ability to overcome multidrug resistance and affect tumor cells, which increases their therapeutic significance.

How do osmium-based compounds exert a strong antitumor effect by activating numerous cell death pathways, including mitochondrial-mediated apoptosis, oxidative damage caused by ROS, calcium imbalance, and metabolic disorders?Their chemical composition can be changed, and they selectively affect tumor cells, as well as compatibility with light-activated, The same applies to traditional treatment methods, which makes osmium complexes very attractive candidates for a new generation of antitumor treatment.Osmium complexes make very attractive candidates for a new generation of antitumor treatment.

Rn (Radon)

Radon, a naturally occurring radioactive gas, has a complex effect on cells, determining whether they will survive or die.Although radon is known as a risk factor for lung cancer, it also affects the functioning of mitochondria (cell power plants), disrupts the process of cell self-destruction (apoptosis), causes oxidative stress and damages DNA, especially in bronchial cells, which are the main target in lung cancer caused by radon.

Studies have shown that prolonged exposure to radon can disrupt the normal functioning of cells, suppressing apoptosis and triggering protective reactions to stress.In particular, cells exposed to radon are less likely to self-destruct, especially if their mitochondrial DNA is damaged.This allows damaged cells to survive and multiply, increasing the risk of developing cancer.

One of the key mechanisms is mitophagy, the process by which damaged mitochondria are destroyed.Although it may be a defense mechanism, the constant oxidative stress caused by radon, It can lead to the degradation of mitochondria and the transition of cells into a state conducive to the development of cancer.

Research has also linked radon exposure to certain genetic changes that increase the risk of cancer.The analysis showed that the radiation from radon is distributed unevenly in the tissues, which leads to local damage and contributes to the development of cancer.

In general, radon affects cell death in different ways.While short-term exposure can lead to cell death, long-term exposure tends to suppress apoptosis, allowing damaged cells to survive and contributing to the development of cancer.This dual nature makes radon a dangerous carcinogen with long-term consequences.

Hs (Hassium)

No effect on cell death

Og (Oganesson)

No effect on cell death

Co (Cobaltum)

Cobalt and its compounds are toxic to cells and can cause their death in various ways, including apoptosis, necrosis, and other processes. The main causes of cobalt toxicity are related to oxidative stress, damage to

mitochondria and DNA, as well as disruption of cellular signaling pathways. How strongly cobalt affects cells depends on its shape, concentration, exposure time, and cell type.

For example, cobalt (Co^{2+}) ions can cause apoptosis (programmed cell death) in various cells by activating caspases, disrupting mitochondria, and causing DNA fragmentation. For example, in snail cells, cobalt activates RNA interference through Dicer, which promotes the transmission of apoptosis signals.

In addition to apoptosis, cobalt, especially in high concentrations, can lead to necrosis. Experiments on myotubes and neurons show that excessive exposure to cobalt causes depletion of ATP reserves, cell swelling and rupture of cell membranes, which are signs of necrotic death. Cobalt-induced necrosis is often accompanied by significant oxidative damage and impaired cellular homeostasis.

In models of drug-resistant glioblastoma, cobalt chloride-induced hypoxia activates autophagy-dependent apoptosis by suppressing the PI3K-Akt-mTOR pathway. This indicates that cobalt may increase the sensitivity of cancer cells to death by affecting the systems responsible for stress and nutrient sensitivity.

In addition, cobalt nanoparticles can cause cell death, resembling ferroptosis, with lipid peroxidation and impaired iron metabolism. These effects can be mitigated with antioxidants such as alpha lipoic acid.

Cobalt also has genotoxic and neurotoxic potential. In brain tissues, it disrupts the structure and function of neurons, which is associated with markers of toxicity and potential neurodegenerative consequences. Exposure to cobalt in organotypic cultures leads to apoptotic degeneration and loss of sensory cells, which highlights the risks associated with exposure to cobalt in the environment and in production.

Despite its toxicity, some cobalt compounds exhibit anti-cancer properties. For example, cobalt(II) diphenyl azodi oxide complexes are capable of selectively destroying liver cancer cells, which indicates the possibility of their use in therapy. Cobalt has a dual nature: in large doses it is poisonous, but in certain forms and concentrations it can be useful, especially in the fight against cancer.

Further research is needed for the safe use of cobalt in medicine and industry, as well as to minimize its harmful effects on humans and the environment. It is important to develop methods of protection against cobalt in production and in the environment, as well as to look for ways to treat poisoning. In addition, the long-term health effects of cobalt exposure, including the risk of developing neurodegenerative diseases and cancer, should be studied.

Ni (Niccolum)

Nickel and its compounds have a pronounced toxic effect on cells, causing various types of cell death, including apoptosis, necrosis, and disruption of the endoplasmic reticulum (ER) due to stress. The main mechanisms of this toxicity are related to oxidative stress, DNA damage, mitochondrial malfunction, inflammatory processes, and cell cycle arrest. The degree of these effects depends on the shape of the nickel (ions, vapors, or nanoparticles), concentration, duration of exposure, and cell type.

Apoptosis is one of the key ways by which nickel induces cell death. Studies have shown that exposure to nickel chloride ($NiCl_2$) causes apoptosis in liver, kidney, fibroblast, monocyte, and osteoblast cells. This process is often accompanied by cell cycle arrest in the G2/M phase, activation of caspases, and increased formation of reactive oxygen species (ROS), which indicates the important role of oxidative stress.

For example, nickel ions released from corroding cardiovascular stents can cause apoptosis in monocytes, potentially contributing to vascular remodeling and chronic inflammation. Similarly, NIH/3T3 fibroblasts exposed to nickel vapors used in the refining process showed DNA fragmentation and apoptosis caused by ROS, which highlights the occupational risks associated with exposure to nickel in industry.

In addition to apoptosis, nickel also causes ER stress, especially in kidney and liver cells. This is manifested in the activation of unfolded protein (UPR) response pathways such as PERK, IRE1, and ATF6. Disruption of cellular homeostasis, for example, under the influence of nickel nanoparticles, triggers a cascade of stress reactions leading to cell death.

While apoptosis is the main mechanism, nickel can also cause other forms of cell death, such as necrosis and impaired autophagy. The sensitivity of cells to

nickel varies, as demonstrated by the different reactions of osteoblasts affected by osteoarthritis and healthy cells.

The toxic effects of nickel are based on oxidative stress, DNA damage, inflammation, ER stress, and mitochondrial dysfunction. These results highlight the importance of understanding nickel's toxicity both from the point of view of industrial and biomedical health risks, and from the point of view of studying its selective cytotoxicity as a potential tool for targeted therapy.

Rh (Rhodium)

Rhodium complexes exhibit pronounced anti-cancer activity, destroying cancer cells in various ways, including triggering programmed cell death (apoptosis), damaging genetic material, and creating oxidative stress. These compounds, characterized by a variety of structures, effectively inhibit tumor growth both in cell cultures and in living organisms. Rhodium-containing drugs are particularly promising for fighting cancer characterized by disorders in the DNA repair system, since they selectively destroy such cells without affecting healthy ones. In addition, they are able to affect cancer stem cells, which are often resistant to standard therapy. Preclinical studies confirm the ability of these compounds to reduce the size of tumors and slow the progression of the disease with minimal side effects, making them promising candidates for the development of new anti-cancer drugs.

Pd (Palladium)

Palladium (Pd) and its compounds, including Pd(II) complexes and palladium nanoparticles, have shown notable cytotoxic effects against cancer cells by triggering apoptosis, interfering with autophagy, generating oxidative stress, and disrupting key cellular signaling pathways. These effects are highly dependent on the chemical form of palladium, its dose, and the biological context, such as cell type and cancer model.

A prominent mechanism of palladium-induced cell death is ROS-dependent apoptosis. Pd(II) complexes and palladium nanoparticles significantly increase reactive oxygen species (ROS), which lead to mitochondrial damage, DNA fragmentation, and caspase activation. For example, Pd(II) complexes in

melanoma and colorectal cells caused genotoxic effects and ROS-mediated apoptosis, establishing oxidative stress as a key factor in Pd toxicity.

Palladium compounds also block autophagy, which increases their pro-apoptotic activity, according to several studies. This was particularly noticeable in colorectal cancer cells, where Pd(II) complexes enhanced apoptotic signaling and inhibited cellular repair mechanisms by interfering with several survival pathways, including the PI3K/Akt/mTOR axis.

Some palladium N-heterocyclic carbene (NHC) complexes showed great sensitivity for cancer cells while avoiding harm to healthy cells. Due to their strong in vitro cytotoxicity, these chiral Pd complexes are promising candidates for targeted chemotherapy with little side effects.

Palladium has also been studied as a component of nanoplatforms for the diagnosis and treatment of cancer. Pd nanoparticles combine imaging and therapy to provide theranostic properties. But even so, despite these advantages, studies have also revealed that palladium nanoparticles can exert toxic effects on normal cells, including fibroblasts and lung epithelial cells, raising concerns about long-term biocompatibility.

Further supporting its antitumor profile, Pd(II) complexes have shown strong efficacy against non-small cell lung cancer (NSCLC) cells, where they induced significant cell death. In some models, the activity of Pd complexes was comparable or even superior to that of related platinum compounds.

In summary, palladium-based agents induce cancer cell death primarily through ROS-driven apoptosis, autophagy inhibition, and disruption of survival signaling pathways. While some forms of palladium display promising anticancer selectivity and therapeutic potential, concerns regarding off-target toxicity and nanoparticle safety underscore the need for further research. Nevertheless, palladium remains a highly versatile element with strong potential in the development of next-generation anticancer therapies and theranostic tools.

Ir (Iridium)

Iridium compounds demonstrate great potential as anti-cancer drugs. They are able to destroy cancer cells using various mechanisms of programmed

cell death, such as apoptosis, autophagy, pyroptosis, ferroptosis, paraptosis and immunogenic death.

The main mechanism of action of iridium(III) complexes is associated with apoptosis triggered in mitochondria. Many of these compounds accumulate in the mitochondria, disrupting their function and leading to cell death. Some iridium compounds also affect the endoplasmic reticulum, causing stress and enhancing apoptosis.

In addition, some iridium complexes cause cell death through autophagy by blocking the important PI3K/AKT/mTOR signaling pathway necessary for cell survival. This effect is particularly noticeable in melanoma studies, where autophagy plays a key role in the destruction of cells under the influence of iridium.

Iridium may be a useful cancer treatment, according to recent research, particularly for tumors that are resistant to traditional treatments. It can trigger the immune system to fight cancer cells and cause pyroptosis, ferroptosis, and paraptosis, among other types of cell death.

When light activates iridium, it becomes more cytotoxic and radiation therapy is more effective. Iridium compounds are a promising candidate for the creation of novel anticancer medications because their structures can be altered to enhance cytotoxicity and cell uptake.

Pt (Platinum)

Platinum-based drugs continue to play a key role in cancer treatment.Their antitumor effect is based on DNA damage, generation of reactive oxygen species (ROS), and disruption of cellular signaling pathways.Modern platinum preparations, such as low molecular weight complexes and nanoparticles, act in a more diverse way, including autophagy mechanisms, regulation of oxidative stress, and effects on mitochondria.ROS formation plays an important role in platinum cytotoxicity.Some new platinum complexes cause a sharp increase in ROS levels inside cells, which leads to suppression of antioxidant protection, organelle damage, and rapid cell death.This "ROS storm" not only causes mitochondrial dysfunction and DNA damage, but also activates stress-related signaling pathways, making cancer cells more vulnerable.In addition, platinum complexes affect the redox balance and signal transmission in cells."Studies show that platinum compounds, acting on the

MAPK pathway and redox homeostasis, can selectively destroy colorectal and breast cancer cells.One platinum(II) complex has shown selective toxicity to breast cancer cells without damaging healthy ones.Platinum compounds are capable of causing various forms of cell death, including autophagy (for example, the Mono-Pt complex in ovarian cancer cells), which distinguishes them from cisplatin and opens up new therapeutic possibilities.Platinum nanoparticles (PTNP) exhibit a dual effect: some are cytotoxic to leukemic cells, while others protect cells from oxidative stress."The analysis of the transcriptome and the immune system demonstrates that platinum significantly affects the activity of genes and the level of inflammatory markers.These changes are closely related to both direct toxic effects on cells and the modulation of the immune response.Some platinum nanoparticles have virtually no effect on immunity, while others cause severe inflammation and death of certain types of blood cells, such as monocytes and leukemic cells. An important task in platinum-based therapy is to overcome the resistance of tumors to drugs. To do this, combinations of platinum preparations with taxanes are being studied, and platinum complexes are being developed that affect certain cell organelles. This approach makes it possible to bypass traditional resistance mechanisms.For example, exposure to organelles such as mitochondria or lysosomes contributes to the accumulation of drugs in these structures, which increases the effectiveness of treatment and reduces side effects.Ultimately, the antitumor effect of platinum compounds is realized through various mechanisms of cell death, mainly apoptosis and autophagy, through the formation of reactive oxygen species (ROS), damage to organelles and regulation of these processes.Despite the fact that nanoparticles and targeted delivery systems make it possible to more accurately direct drugs to tumors, maintaining a balance between toxicity to cancer cells and safety for healthy tissues remains a research priority.In conclusion, platinum remains one of the most versatile and promising elements in modern oncology.

Mt (Meitnerium)

No effect on cell death

Ds (Darmstadtium)

No effect on cell death

Conclusion:

The analysis presented in this paper affirms that chemical elements significantly influence the mechanisms governing cell cycle regulation and cell death. Essential elements like zinc and copper are integral to maintaining cellular integrity and supporting proliferative processes, whereas toxic elements such as cadmium and arsenic disrupt homeostasis, promoting oxidative stress and apoptosis. The complex interplay between elemental concentration, cellular context, and molecular targets highlights the need for further experimental and clinical research.

A deeper understanding of how individual elements affect cell fate could enhance our ability to predict toxicological risks, develop targeted cancer treatments, and optimize nutritional and environmental guidelines. This study contributes to the growing recognition of elemental biology as a crucial dimension of cellular regulation.

Declaration of generative AI and AI-assisted technologies in the writing process:

During the preparation of this section the authors used Humata AI and Future House in order of deep analysis of chosen research works and references.Also,GPT-4 was used for meticulous explanation of the given figures.After using this tools,the authors reviewed and edited the content as needed and take full responsibility for the content in published article.

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