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Integrating cuproptosis and immunosenescence: A novel therapeutic strategy in cancer treatment

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ABSTRACT

Recent advancements in our understanding of cell death mechanisms have progressed beyond traditional apoptosis to encompass various forms of regulated cell death, notably cuproptosis. This copper-dependent cell death occurs when copper interacts with lipoylated enzymes in the tricarboxylic acid cycle, leading to protein aggregation and subsequent cell death. Alongside this, immunosenescence the gradual decline in immune function due to aging has emerged as a significant factor in cancer progression and response to treatment. Innovative strategies that integrate cuproptosis and immunosenescence are showing considerable promise in cancer therapy. By leveraging the altered copper metabolism in cancer cells, cuproptosis can selectively induce cell death, effectively targeting and eliminating tumors. Simultaneously, addressing immunosenescence can rejuvenate the aging immune system, enhancing its capacity to identify and destroy cancer cells. This dual approach creates a synergistic effect, optimizing therapeutic efficacy by directly attacking tumor cells while revitalizing the immune response. Such integration bolsters the defense against cancer progression and recurrence and holds great potential for advancing cancer treatment modalities and improving patient outcomes. This paper delves into the interactions between cuproptosis and immunosenescence, emphasizing their implications for developing innovative cancer therapies.

1. Introduction

In recent years, our understanding of cell death mechanisms has significantly expanded, moving beyond classical apoptosis to include various forms of regulated cell death. This broader perspective encompasses several key processes: Necroptosis is regulated cell death characterized by cellular and organelle swelling, leading to membrane rupture and the release of intracellular components. Pyroptosis, originally described in immune cells during antimicrobial responses, is another controlled form of cell death that results in cell lysis and inflammation [1].

Autophagy-dependent cell death relies on the autophagic pathway and its components to mediate cell death under specific conditions [2]. Anoikis occurs when cells detach from their extracellular matrix, disrupting integrin signaling and leading to programmed cell death [3]. In contrast, Entosis involves the invasion of one living cell into another of the same type, requiring the actin cytoskeleton and energy expenditure [4], NETosis is a specialized form of cell death executed by neutrophils, which release neutrophil extracellular traps (NETs) that capture and eliminate pathogens [5]. Additionally, ferroptosis is an iron-dependent mechanism characterized by the accumulation of lipid peroxides, resulting in oxidative damage and membrane disruption. This process is distinct from apoptosis and is regulated by glutathione-dependent antioxidant defenses [6,7].

Lastly, cuproptosis is a copper-dependent form of cell death that occurs through the interaction of copper ions with lipoylated tricarboxylic acid cycle enzymes, leading to protein aggregation and subsequent cell death. This mechanism has significant implications in cancer biology, particularly regarding the altered copper metabolism of cancer cells [8].

In parallel, the gradual decline in immune function associated with aging, known as immunosenescence, has emerged as a significant factor influencing cancer progression and response to therapy. Innovative approaches focusing on the strategic manipulation of cancer treatment with cuproptosis and immunosenescence are proving to be promising. Cuproptosis can selectively induce cell death in cancer cells by leveraging their altered copper metabolism, effectively eradicating tumors. At the same time, targeting immunosenescence can rejuvenate the

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aging immune system, enhancing its capability to identify and attack cancer cells.

The interplay between these two processes offers significant advantages for cancer therapy. Combining the induction of cuproptosis, which directly kills cancer cells, with strategies to combat immunosenescence can create a synergistic effect, maximizing therapeutic efficacy. This dual approach not only targets tumor cells but also rejuvenates the immune system, offering a strong defense against cancer progression and recurrence. Consequently, integrating cancer treatment with cuproptosis and interventions against immunosenescence holds substantial promise for advancing cancer therapy and improving patient outcomes. This paper aims to explore the interplay between cuproptosis and immunosenescence in the context of cancer, highlighting their potential interactions and implications for treatment strategies.

2. Cuproptosis

Cuproptosis is a unique form of regulated cell death that occurs when excess copper ions disrupt mitochondrial function, resulting in the activation of specific cell death pathways. Cancer cells often exploit copper for their growth and survival, making them particularly susceptible to cuproptosis [9]. Understanding the mechanisms by which cuproptosis operates can reveal potential therapeutic targets. For instance, enhancing cuproptosis in tumor cells could provide a novel strategy for cancer treatment, especially in tumors characterized by high copper accumulation.

2.1. Mechanisms of cuproptosis and its consequences

2.1.1. Copper accumulation

The primary trigger for cuproptosis is the accumulation of copper ions within the cell. This can occur due to increased copper uptake, reduced efflux, or impaired cellular metabolism. Copper is a trace element essential to human physiology, playing a significant role in various signaling pathways and cancer-related biological processes. Additionally, elevated levels of copper can result in cell death; however, the precise mechanisms and specific types of cell death triggered by excess copper have historically been poorly understood [10,11]. Copper accumulation in cells arises from a variety of mechanisms, each playing a crucial role in regulating cellular copper levels and contributing to various pathological conditions. One primary source of copper is dietary intake; when copper-rich foods are consumed, the gastrointestinal tract absorbs it, leading to elevated copper levels in the bloodstream. This copper can then enter cells, influencing their function and health. Central to this process is the role of transport proteins. For example, CTR1 (Copper Transporter 1) is essential for facilitating the uptake of copper ions from the extracellular environment into the cytoplasm. When CTR1 is overexpressed or dysregulated, it can result in excessive copper accumulation within cells. Similarly, DMT1 (Divalent Metal Transporter 1) also participates in the transport of copper along with other divalent metals. This mechanism is particularly significant in conditions where iron levels are altered, highlighting the interconnectedness of metal transport in cells [12].

Copper can also enter cells through endocytosis, a process where it is internalized via receptor-mediated mechanisms. This pathway becomes especially relevant when copper is bound to proteins or nanoparticles, allowing for targeted uptake. Once inside the cell, copper is managed by specialized chaperones, such as ATOX1 (Antioxidant 1) and CCS (Copper chaperone for superoxide dismutase), which transport it to various cellular compartments, including the mitochondria and the nucleus. Any dysregulation in these chaperones can disrupt proper copper distribution, leading to cellular dysfunction and accumulation. Moreover, the body employs excretion mechanisms to maintain copper homeostasis. Transporters like ATP7A and ATP7B are critical for exporting copper from cells. ATP7A facilitates copper export in various tissues, while ATP7B plays a vital role in hepatic copper excretion. Mutations in these transporters can lead to serious conditions, such as Wilson's disease, which is characterized by harmful copper buildup in the body [13–15]. Cellular metabolism also influences copper handling. Conditions such as oxidative stress or mitochondrial dysfunction can alter how cells manage copper levels. For instance, oxidative stress may increase copper uptake or hinder its excretion, further contributing to accumulation. Environmental factors also play a significant role in copper accumulation. Exposure to contaminated water or industrial pollutants can elevate intracellular copper levels, particularly in tissues that struggle to detoxify heavy metals effectively. Additionally, inflammation can significantly disrupt copper homeostasis. During immune responses, copper levels may rise in macrophages and other immune cells, reflecting the body's attempts to combat infection or injury.

This interplay between copper metabolism, immune function, and environmental influences underscores the complexity of copper homeostasis and its implications for health and disease [9,16]. Fig. 1 provides a comprehensive overview of the mechanisms involved in the accumulation of copper ions within the cell.

2.1.2. Influence of copper valence states on toxicity

The toxicity of copper also significantly varies with its oxidation states, primarily +1 (cuprous) and +2 (cupric). The +1 oxidation state is often considered more reactive and may generate reactive oxygen species (ROS) more readily than the +2 state. This increased reactivity can lead to heightened oxidative stress within cells, contributing to cellular damage and death. In contrast, the +2 state is more stable in biological systems and is typically involved in essential enzymatic functions, although excessive levels can also lead to toxicity [17,18]. Understanding the differential toxicity of these oxidation states is crucial for comprehending copper's role in cellular processes and its implications for various diseases, particularly cancer [19]. Further research into how the +1 and + 2 states influence cellular mechanisms may provide valuable insights for developing targeted therapies that manipulate copper metabolism for therapeutic benefit.

2.1.3. Mitochondrial dysfunction

Copper plays a crucial role in the function of various enzymes within the electron transport chain (ETC), particularly in cytochrome *c* oxidase (Complex IV). However, when copper levels become excessive, they can inhibit these enzymes, reducing ATP production and diminishing the energy supply for vital cellular processes. This disruption leads to decreased cellular respiration and energy shortages, posing serious risks to cell viability and function. Moreover, elevated copper levels can catalyze the production of reactive oxygen species (ROS) within mitochondria. This happens through Fenton-like reactions, where excess copper facilitates free radical formation [20,21]. The increased ROS can inflict damage on mitochondrial components, including lipids, proteins, and DNA, exacerbating mitochondrial dysfunction and potentially triggering programmed cell death, such as apoptosis or necrosis. For example, in neurodegenerative diseases like Alzheimer's, copper accumulation in neurons is associated with mitochondrial dysfunction. The resulting oxidative stress contributes to neuronal death, highlighting how copper overload can activate apoptotic pathways [21,22].

Copper accumulation also interferes with the dynamic processes of mitochondria, such as fission and fusion, which are essential for maintaining mitochondrial integrity. When copper toxicity disrupts these processes, it can lead to fragmented and dysfunctional mitochondria, compromising their ability to meet the energy demands of the cell. Additionally, mitochondria are critical regulators of programmed cell death. Excess copper can induce a phenomenon known as mitochondrial permeability transition, leading to the release of pro-apoptotic factors like cytochrome *c* into the cytosol. This release activates apoptotic pathways, contributing to cell death and tissue damage, particularly in organs that are more sensitive to copper toxicity, such as the liver and brain [22,23]. Furthermore, copper accumulation can disrupt calcium homeostasis within mitochondria. Mitochondria play a key role in

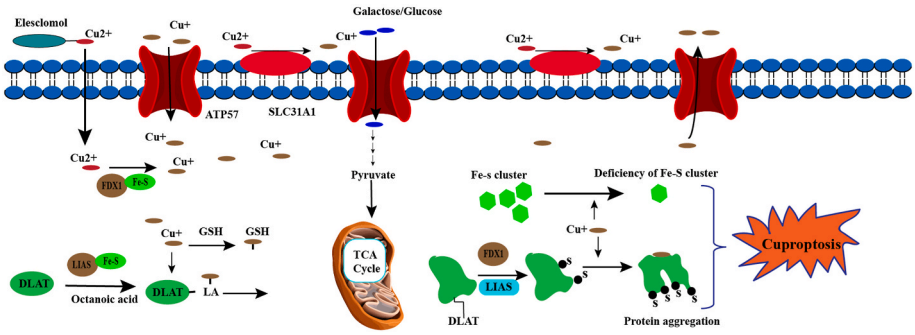

Fig. 1. Schematic model of cuproptosis illustrating the mechanism by which elesclomol binds extracellular copper (Cu^{2+}) and transports it into intracellular compartments. Increased Cu accumulation leads to cuproptosis primarily through FDX1-mediated mitochondrial proteotoxic stress. FDX1 (Ferredoxin 1) reduces Cu^{2+} to Cu^{+}, promoting the lipoylation and aggregation of mitochondrial enzymes like DLAT involved in the TCA cycle while destabilizing Fe–S cluster proteins. Additionally, Cu importers (e.g., SLC31A1) and exporters (e.g., ATP7B) regulate cuproptosis sensitivity by modulating intracellular Cu^{+} levels. The solid orange circles in the TCA cycle represent metabolites relevant to the lipoic acid pathway. Abbreviations: DLAT (dihydrolipoamide S-acetyltransferase), FDX1 (ferredoxin-1), Fe–S (iron-sulfur), LIAS (lipoic acid synthetase), TCA (tricarboxylic acid).

regulating intracellular calcium levels, which are vital for numerous cellular signaling pathways. Alterations in calcium levels can further aggravate mitochondrial dysfunction, impairing energy metabolism and increasing the susceptibility to cell death. Lastly, copper is involved in regulating mitochondrial biogenesis, a process influenced by factors like PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha). When copper levels are excessively high, this signaling pathway can be disrupted, resulting in impaired mitochondrial biogenesis and a reduction in mitochondrial mass, which deepens the energy deficits experienced by cells [24–27].

2.1.4. Activation of death pathways

The oxidative stress induced by copper accumulation can activate various cell death pathways. For example, it can lead to the opening of the mitochondrial permeability transition pore (mPTP), which results in the loss of mitochondrial membrane potential and the release of pro-apoptotic factors. Furthermore, copper accumulation can lead to apoptosis and necrosis. The accumulation of ROS caused by the accumulation of copper can trigger oxidative stress, damaging mitochondrial membranes and leading to the release of pro-apoptotic factors, such as cytochrome *c*, into the cytosol [28,29]. When cytochrome C is released into the cytosol, it binds to apoptotic protease-activating factor 1 (Apaf-1) and activates caspases, the key executioners of apoptosis [30,31]. This cascade leads to programmed cell death, which can be detrimental in tissues sensitive to copper toxicity. In addition to apoptosis, copper can induce necroptosis, a form of programmed necrosis characterized by cell swelling and membrane rupture. This pathway is often activated in response to severe cellular stress or damage. Research has shown that copper-induced oxidative stress can activate necroptotic pathways in various cell types, contributing to inflammation and tissue injury [32]. In conditions like acute kidney injury, excessive copper accumulation may lead to necroptotic cell death, exacerbating renal damage. Excess copper can disrupt calcium homeostasis, leading to calcium overload in cells. Elevated intracellular calcium levels can activate various proteases and lipases, contributing to apoptotic and necrotic cell death pathways. In cardiac cells, excessive copper can lead to calcium overload, contributing to cardiomyocyte death and heart dysfunction [27,33,34]. This effect underscores the importance of copper homeostasis in maintaining cardiac health.

2.1.5. Inhibition of proteasomal activity

Copper accumulation in cells can significantly disrupt various cellular processes, particularly through the inhibition of proteasomal activity. The proteasome is a crucial component of the ubiquitin-proteasome system (UPS), responsible for degrading ubiquitinated proteins. This system plays an essential role in maintaining protein homeostasis, regulating the cell cycle, and controlling apoptosis. When copper levels become excessive, they can lead to a marked decrease in proteasomal function, which has a range of negative consequences for cellular health. One primary mechanism by which excess copper impacts the proteasome is through direct binding to its components. This interaction can alter the structure and function of proteasomal proteins, disrupting their assembly and impairing the proteasome's ability to degrade proteins effectively [35–37]. Additionally, elevated copper levels can promote the elevation of ROS, which can damage both proteasomal subunits and regulatory proteins, further inhibiting proteasomal activity. Copper accumulation can also interfere with the ubiquitination process, which is critical for marking proteins for degradation. When the balance of this system is disrupted, proteins that should be degraded can accumulate, overwhelming the proteasome and reducing its efficiency. Furthermore, copper-induced dysregulation of calcium homeostasis can activate proteases and kinases that inhibit proteasomal function, exacerbating the accumulation of unwanted proteins. The inhibition of proteasomal activity has several significant consequences for cellular function. First, the accumulation of proteins that should be degraded can lead to cellular stress and dysfunction, particularly as misfolded or damaged proteins build up within the cell. This situation can disrupt normal cellular processes and contribute to disease progression [37–40].

Moreover, the proteasome plays an essential role in regulating the cell cycle by degrading cyclins and other proteins involved in cell division. When proteasomal activity is compromised, this regulation becomes dysfunctional, potentially leading to uncontrolled cell growth or inappropriate apoptosis. In addition, the proteasome is involved in apoptosis by degrading pro-survival proteins. When its activity is inhibited, cells may fail to undergo apoptosis, when necessary, which can contribute to tumor development or chronic diseases. This inhibition can also lead to the accumulation of inflammatory proteins, resulting in an exaggerated inflammatory response that can further damage tissues [41–43].

2.2. Role of cuproptosis in cancer

The link between copper and cancer has been recognized for over a century [44]. Studies have shown that elevated copper levels are present in the tumors and serum of both animal models and patients with various cancer types. This association has been documented across a range of cancers, including lung cancer, where increased copper has been noted in multiple studies [45,46] Similarly, breast cancer research has consistently revealed higher copper concentrations [47,48]. Moreover, gastrointestinal cancers have also shown significant copper accumulation [49–51], alongside thyroid [52], oral [53], gynecologic [54],

gallbladder [55], and prostate cancers [56]. This growing body of evidence highlights the potential role of copper in cancer biology and underscores the need for further research to understand its mechanisms and implications in tumor development and progression. Furthermore, several cuproptosis-related markers can be used to target cancer treatment.

In addition to their role in cell death, several markers associated with cuproptosis can be leveraged for cancer treatment. These markers provide valuable insights into the molecular mechanisms underlying copper-induced cell death and can be exploited to develop targeted therapies.

For instance, proteins such as FDX1, LIPT1 (Lipoyl (Octanoyl) Transferase 1), and DLAT (Dihydrolipoamide S-Acetyltransferase) are involved in the mitochondrial processes that regulate cellular metabolism and copper homeostasis. By understanding how these proteins interact and influence cell death, researchers can identify potential therapeutic targets to induce cell death in cancer cells [57]. Additionally, modulating the activity of copper transporters like SLC31A1 (Copper Transporter 1) can influence copper uptake in cancer cells, making them more susceptible to treatments that exploit copper-induced cytotoxicity. This approach not only targets cancer cells but also spares healthy tissues, reducing side effects and improving the overall efficacy of cancer treatment [57]. Furthermore, identifying and targeting metallothioneins (MTs), which bind to copper ions and regulate oxidative stress, can enhance the effectiveness of cancer therapies by preventing cancer cells from evading cell death. Combining these strategies with conventional treatments like chemotherapy and radiotherapy may provide a synergistic effect, ultimately leading to improved treatment outcomes for patients [58]. Numerous biomarkers have been pinpointed as promising candidates for inducing cuproptosis, which can aid in the treatment of cancer.

2.2.1. Cuproplasia

Copper accumulation can lead to a condition known as cuproplasia, which involves regulated cell growth and proliferation influenced by copper. This process is associated with various cellular functions, including redox signaling and mitochondrial respiration [44]. Pharmacologically, cuproplasia can be targeted by copper-selective chelators or metal ionophores, and manipulating proteins related to copper homeostasis may also affect it. Changes in the expression of specific copper-related proteins, such as CTR1 and ATPase7A, have been linked to cancer progression [59]. Studies have shown that overexpression of proteins including ATPase7B, CTR1, COX17, and ATOX1 occurs in prostate and breast cancers, with higher levels correlating to poorer patient outcomes [60]. Cuproplasia mechanisms include activation of receptor kinases essential for tumorigenesis, such as phosphoinositide-3-kinase and epidermal growth factor receptor [61,62]. Copper enhances the activity of kinases involved in signaling pathways critical to cancer development, and inhibiting copper uptake can suppress tumor growth in certain cancer models [63]. Additionally, copper levels can influence cancer susceptibility in specific contexts, such as KRAS-dependent colorectal cancer [64].

2.2.2. Cancer metastasis

Metastasis is the primary reason for the vast majority of deaths associated with cancer [65]. Metastasis is a complex, multistep process involving molecular and phenotypic changes that enable tumor cells to spread and establish colonies in distant organs [66]. This process, known as the invasion-metastasis cascade, is facilitated by cancer cells acquiring invasive and stem cell-like traits through epithelial-mesenchymal transition (EMT) [67]. EMT leads to the loss of epithelial characteristics and enhances the cells' ability to invade and migrate [65]. Copper (Cu) plays a crucial role in various metalloenzymes that are vital for cancer metastasis. It activates enzymes that promote cell proliferation and metabolism, such as lysyl oxidase (LOX), matrix metalloproteinase (MMP-9), and SOD1, which remodels the ECM, creating environments conducive to metastasis [68–70]. LOX acts as an oncogene in several cancer types, facilitating tumor spread by activating focal adhesion kinase and recruiting precursor cells to metastatic sites [71]. Additionally, the loss of copper-dependent enzymes like superoxide dismutase 3 (SOD3) can lead to oxidative stress, further supporting tumor progression. SOD3 appears to have protective effects against tumor metastasis, and its restoration can inhibit tumor cell spread [72]. Copper-binding proteins, such as MEMO1 and COMMD1, also influence cancer cell migration and invasion. MEMO1 enhances cell movement by modifying the cytoskeleton, while COMMD1 inhibits pathways that promote tumor growth [73]. Furthermore, the Cu-binding glycoprotein SPARC is implicated in promoting tumor invasion through its effects on cell-matrix interactions [74]. Studies have identified ATOX1 as essential for cell migration and metastasis in breast cancer, further underscoring the significant role of copper in cancer progression [75,76].

2.2.3. Tumor angiogenesis

Angiogenesis, the formation of new blood vessels, involves the growth of capillaries from existing vessels. This process is crucial for supplying the increasing demands for nutrients and oxygen in tumor tissues, which supports tumor growth and progression [77]. Angiogenesis includes several coordinated actions, such as the proliferation and migration of endothelial cells, the formation of vascular lumens, and the establishment of vascular networks. The balance between pro-angiogenic and anti-angiogenic signals regulates this process [78]. Pro-angiogenic growth factors like fibroblast growth factors (FGFs), vascular endothelial growth factor (VEGF), and placental growth factor (PLGF) promote angiogenesis, while factors such as endostatin and angiostatin inhibit it [79]. Copper (Cu) acts as a cofactor in several pro-angiogenic molecules, enhancing angiogenesis by activating growth factors like basic FGF, VEGF, and angiogenin [80,81]. Research has shown that copper plays a significant role in promoting angiogenesis across various cancers [82]. It activates multiple pro-angiogenic factors directly, including TNF-α, IL-6, and hypoxia-inducible factor-1 (HIF-1α) [81,83]. Additionally, copper stabilizes nuclear HIF-1, increasing the expression of angiogenic genes [84]. Copper also fosters the proliferation and mobility of endothelial cells, crucial early steps in tumor angiogenesis [85]. It enhances ECM remodeling by promoting FGF-1 release and lysyl oxidase (LOX) activity [86]. The ATP7A protein contributes to VEGFR2 signaling and angiogenesis by preventing the degradation of VEGFR2, indicating an interplay between copper metabolism and autophagy [87]. Moreover, superoxide dismutase 1 (SOD1) enhances endothelial function and VEGF production, promoting angiogenesis and tumor development. Copper deficiency impairs SOD1 activity and reduces angiogenesis [88,89]. The role of AOC3 in angiogenesis also involves the infiltration of M2 macrophages driven by IL-1β [90]. Additionally, ATOX1, a transcription factor for NADPH oxidase, may modulate angiogenesis, promoting inflammatory neovascularization [91].

2.2.4. Chemoresistance

One of the mechanisms contributing to cancer resistance to platinum-based drugs involves impaired drug uptake, which leads to reduced levels of these drugs inside cancer cells, along with increased efflux. This dual effect hinders the effectiveness of treatments such as cisplatin, oxaliplatin, and carboplatin [92]. Research has unveiled that copper transport mechanisms may play a significant role in this resistance [93]. Studies have shown that the transporters responsible for maintaining copper homeostasis also facilitate the movement of platinum drugs. For example, the copper transporter CTR1 has been identified as a key player in the uptake of cisplatin and its analogs. Additionally, the ATP7A and ATP7B proteins are crucial for the efflux of cisplatin from cells [94,95]. Evidence suggests that CTR1, along with ATOX1 and copper exporters such as ATP7A and ATP7B, is involved in the transport of cisplatin (cDDP), highlighting the interconnectedness of

copper homeostasis and platinum-based cancer therapies [96,97]. These findings point to a compelling relationship between copper transport systems and the efficacy of platinum drugs. By targeting these copper transport mechanisms, there is potential to enhance the effectiveness of platinum-based chemotherapy in cancer treatment. This approach could help overcome drug resistance and improve therapeutic outcomes for patients undergoing treatment with platinum compounds.

2.2.5. Immune evasion

Copper significantly influences the expression of programmed death ligand 1 (PD-L1), a transmembrane protein frequently overexpressed in specific cancer cells. This overexpression enables cancer cells to evade detection and attack by the immune system, allowing them to withstand antitumor therapies. Specifically, elevated copper levels enhance PD-L1 expression, thereby promoting immune evasion in tumors. Research indicates that copper chelation can enhance the ubiquitin-mediated degradation of PD-L1, increasing tumor-infiltrating $CD8^+$ T cells and natural killer (NK) cells, which are crucial for effective immune responses against tumors [98]. By modulating PD-L1 levels, copper impacts the immune environment of tumors, which may affect the efficacy of immune therapies. The interaction between PD-L1 and its receptor, PD-1, found on lymphocytes, is critical as it suppresses the activity of cytotoxic T cells, which are responsible for killing cancer cells [99]. In neuroblastoma cells, an increase in copper due to elevated expression of CTR1 (a copper transporter) activates signaling pathways such as STAT and EGFR, leading to heightened levels of PD-L1 [98]. Interestingly, the use of the copper chelator TEPA has been shown to improve survival rates in mouse models by reducing PD-L1 expression in neuroblastoma xenografts, which in turn increases the presence of tumor-infiltrating T cells. Checkpoint inhibitors that target the PD-L1/PD-1 pathway is currently utilized in clinical settings for the treatment of cancers such as lung cancer and melanoma [100]. Given the role of copper in regulating PD-L1 expression, it would be valuable to explore whether copper chelation could enhance the effectiveness of these immunotherapies. This approach could open new avenues for improving treatment outcomes in patients with various forms of cancer.

3. Immunosenescence

The progressive deterioration in immune system performance that comes with aging is known as immunosenescence [101]. Numerous alterations in both innate and adaptive immune responses are the manifestation of this phenomena, which has many noteworthy consequences. The general health of older persons may be jeopardized because they frequently have a diminished capacity to react appropriately to illnesses and vaccines [102,103]. Immunosenescence is marked by a reduction in both the number and functionality of immune cells, including T cells, B cells, and natural killer (NK) cells. This decline impairs the immune system's ability to recognize and eliminate cancer cells, facilitating tumor growth and metastasis. Factors contributing to immunosenescence include chronic inflammation, oxidative stress, and alterations in the bone marrow microenvironment. As cancer often develops in older individuals, understanding the mechanisms of immunosenescence is crucial for developing effective immunotherapies [104,105].

3.1. Mechanisms of immunosenescence

3.1.1. T cell dysfunction

Although the total number of T cells in humans remains relatively stable throughout life, significant age-related changes occur in T cell composition, particularly in the balance between naïve and memory T cell subsets. After puberty, the production of functional naïve T cells declines due to thymic involution, leading to increased proliferation of existing naïve T cells and their eventual transformation into virtual memory cells [106,107]. While the proportion of memory T cells rises during early life and remains steady in adulthood, it begins to show signs of senescence around age 65 [108]. In humans, memory T cells can be categorized into two main types: central memory T cells (TCM), which are primarily found in secondary lymphoid tissues, and effector memory T cells (TEM), which circulate in various peripheral regions. TCM cells are mostly $CD4^+$ T cells, while TEM cells are predominantly $CD8^+$ T cells [109,110].

A significant change associated with aging is the loss of the co-stimulatory molecule CD28, leading to an accumulation of highly differentiated CD28-TEM cells, primarily within the $CD8^+$ population. These cells exhibit reduced proliferation, shorter telomeres, a limited T cell receptor repertoire, and increased cytotoxic activity. The loss of CD28 is linked to a greater vulnerability to infections and a diminished immune response to vaccinations in older individuals. Despite this, $CD28^-$ T cells are not inactive and may contribute to tissue immunity and control of cytomegalovirus (CMV) infection [111–113]. Memory T cells formed in youth are believed to remain effective over decades, while those generated in older age exhibit significant impairments. The ability to mount protective immune responses relies on a diverse T cell repertoire, which decreases in older adults due to thymic involution. However, persistent infections like CMV may also alter T cell dynamics, leading to a contraction of naïve $CD4^+$ T cells in CMV-positive individuals, while naïve $CD8^+$ T cells remain unaffected [114,115].

Research indicates that the decline in naïve $CD8^+$ T cell numbers is likely due to the increased development of virtual memory T cells rather than thymic aging [116]. Additionally, newly identified innate/memory-like $CD8^+$ T cells may play a role in immunity. Aging also impacts T cell polyfunctionality, with older individuals displaying enhanced polyfunctionality in $CD8^+$ effector memory T cells, while central memory T cells show declines. Knowledge comes from studies of circulating T cells, which represent only a small portion of the total T cell pool. Limited research on age-related changes in specific T cell subsets and the effects of CMV infection further complicate our understanding of T cell aging [117–119]. Understanding these dynamics is crucial for developing effective immunotherapies for older adults.

3.1.2. B cell alterations

The diminished ability to generate protective antibody responses in older individuals is largely due to significant changes in B cell compartment composition and the reduced functional responsiveness of peripheral B cells [120,121]. Consequently, the diverse, youthful peripheral B cell repertoire becomes more limited, lacking naïve cells that can respond to new antigens. Age-related shifts in peripheral B cell composition stem from both prolonged B cell survival and decreased generation in the bone marrow [122,123]. This reduction in B cell production is attributed to factors such as lower frequencies of B cell progenitors, diminished proliferative capacity, decreased interleukin-7 (IL-7) production, and impaired V-DJ rearrangement [124,125]. The latter is influenced not by reduced expression of recombination-activating genes but by changes in the E2A-encoded proteins that bind the immunoglobulin heavy chain promoter [126]. Additionally, age-related defects in hematopoietic stem cells (HSCs) negatively impact B lymphopoiesis, including issues with telomere maintenance, epigenetic modifications, and a shift from lymphoid to myeloid lineage potential [127]. In the peripheral system, the survival of memory B cells, homeostatic proliferation, and clonal expansion contribute to the restricted repertoire and weakened antibody responses observed in aging [128,129]. Furthermore, intrinsic defects in aged B cells include reduced class switch recombination (CSR), lower expression of activation-induced cytidine deaminase (AID) and E47, and decreased activation signaling [130]. Germinal centers (GCs) also show a reduction in number and size [131]. Collaborative studies on immunoglobulin genes from GC B cells revealed age-related changes in hypermutation patterns, although these did not suggest alterations in the mechanisms of somatic hypermutation itself. Instead, changes appear linked to founder cell effects or selection processes, with notable tissue-specific differences in Ig gene selection [132].

Efforts to reverse the immunosenescent phenotype in B cells have involved modifying gene expression. Research also demonstrated that restoring E47 expression in aged splenic B cells can improve age-related defects, enhancing AID expression and CSR alongside B cell immune responses [133–135].

3.1.3. NK cell changes

An important line of defense for human health, NK cells are vital parts of the innate immune system. Infections, cancer, inflammatory disorders, and an increasing buildup of aging cells as people age are all associated with dysfunctional NK cell activity [136]. Studies generally show that older persons have a higher total NK cell count, even if the total number of NK progenitors in bone marrow and peripheral blood does not seem to be impacted by age [137,138]. But this increase is accompanied by a decrease in their capacity for cytotoxicity and proliferation [139]. In particular, the population of CD56 dim NK cells tends to increase while the percentage of immature CD56 bright NK cells tends to decrease. More than 90 % of NK cells are CD56 dim NK cells, which are mostly cytotoxic and have an important immunomodulatory function [140,141]. Additionally, NK cell activation receptors such as NKp30, NKp46, and DNAM1 have altered expression with aging, which may impair their ability to perform immunological surveillance [142,143]. As NK cell function declines with age, the NK cells from younger donors show a higher capacity for growth in response to IL-2 stimulation than those from older donors [141]. Moreover, pro-inflammatory cytokine levels like IL-1, IL-4, IL-6, IL-8, IL-10, and TNF-α rise while indicators of NK cell activity like perforin, granzyme, and cytokine release (including IFN-α and IFN-γ) fall [144,145]. Additionally, the frequency of T cell precursors among CD34+Lin-cells decreases with increasing donor age, whereas the frequency of NK/T cell precursors tends to increase, suggesting a change in the lymphoid differentiation potential from T cells to NK/T cells. Notably, at the age of 60, the numbers of both NK and NKT cells rise noticeably [146,147].

3.1.4. Additional changes in immune cells

Dendritic cells are crucial for coordinating immune responses and maintaining tolerance, but their functions such as antigen presentation and interferon production decline with age. Similarly, neutrophils exhibit reduced phagocytic ability, while the effects of aging on macrophage phagocytosis and antigen presentation remain unclear [148,149]. Age-related changes in tissue-specific macrophages and neutrophils may contribute to chronic low-grade inflammation, leading to immunosuppressive disorders and diseases like cancer. In aged tumor-bearing mice, there is an increase in myeloid-derived suppressor cells (MDSCs), which impair immune responses, hinder tumor clearance, and disrupt metabolic homeostasis [149,150].

MDSCs can be recruited to local areas by chemokines and cytokines secreted by senescent cells, facilitating immune evasion and tumor metastasis. Research indicates that MDSC accumulation may arise from pathological processes or pregnancy. Furthermore, MDSCs can promote immunosenescence and induce detrimental bystander effects in host tissues through the secretion of TGF-β and IL-10 [151]. Changes in the extracellular matrix (ECM) in the aging tumor microenvironment (TME) may also contribute to metastasis in elderly patients [101]. Understanding these senescence-related immune cell changes is vital for cancer research (Fig. 2).

3.1.5. Chronic inflammation

Diseases are caused by the degenerative aging of organs, which raises inflammation levels and makes healing challenging due to the impacts of cellular senescence, immunosenescence, and chronic inflammation [152]. The relationship between immunosenescence and chronic inflammation, often referred to as inflammaging, highlights a significant aspect of aging. Inflammaging describes the persistent low-grade inflammatory state prevalent in older adults, characterized by elevated levels of pro-inflammatory markers that diminish the immune system's capacity to respond effectively to both new and previously encountered antigens [153]. This chronic inflammation is linked to various age-related diseases, including atherosclerosis, cardiovascular issues,

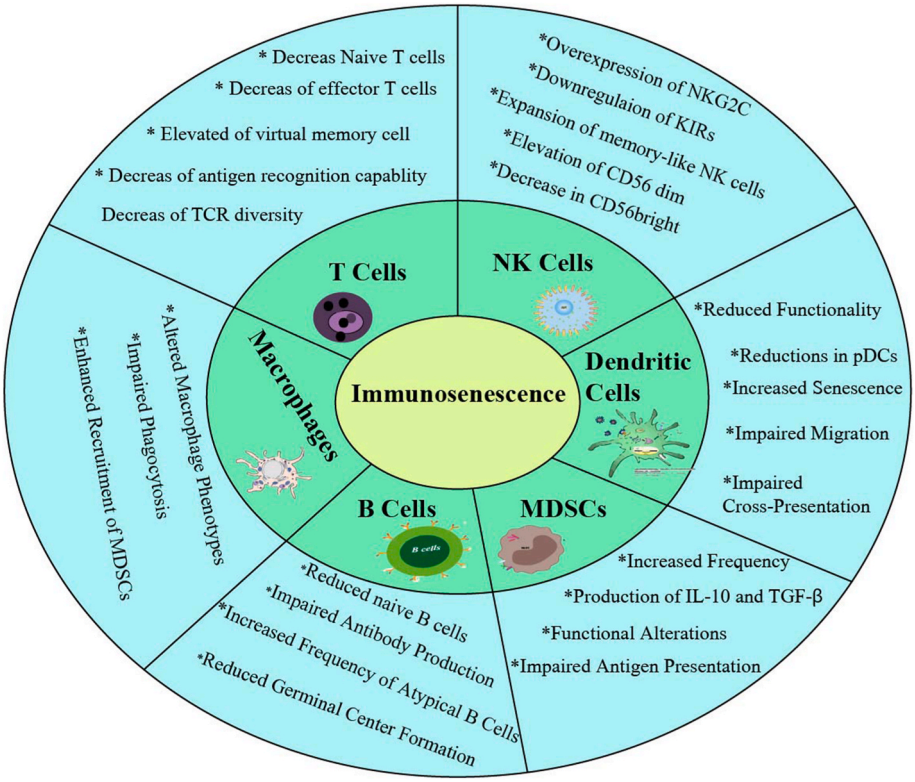

Fig. 2. Immunosenescence-related alterations in different immune cell subsets.

type 2 diabetes, and neurodegenerative disorders, suggesting a common inflammatory pathway across these conditions [154,155]. Immunosenescence and inflammaging are interconnected; factors contributing to chronic inflammation can induce immunosenescence, while age-related immune decline can perpetuate inflammation. Key pro-inflammatory cytokines, like IL-6, play a pivotal role in this cycle, being associated with several age-related health issues and contributing to functional decline and increased mortality [156].

Moreover, the process of inflammaging is not solely rooted in the immune system. It is influenced by several factors, including cellular senescence and the senescence-associated secretory phenotype (SASP), microbiome imbalances, innate immune memory, and metabolic changes driven by mitochondria. For instance, disturbances in gut microbiota can lead to increased pro-inflammatory mediators, while trained innate immunity, resulting from epigenetic changes, can create a state of chronic activation in the immune system [157,158]. This state may enhance responses to infections but can also lead to harmful hyperactivation, contributing to persistent inflammation.

3.2. Impact of immunosenescence on cancer progression

The immune system serves as the body's primary defense against foreign agents and cancer cells. Successful immunotherapy, such as checkpoint inhibitors, can lead to durable tumor responses in certain cancer patients. Chimeric antigen receptor (CAR)-T-cell therapy, which involves engineering T-cells to target tumor antigens, has shown effectiveness in hematological cancers but has been less successful in solid tumors [159]. Research has investigated the potential of CDK4/6 inhibitors in breast cancer models, demonstrating that these inhibitors not only induce cell cycle arrest in tumor cells but also enhance the cytotoxic elimination of these cells by T cells through the activation of endogenous retroviral elements. Notably, CDK4/6 inhibition does not hinder T-cell expansion; rather, it improves the efficacy of PD-1 inhibition. Additionally, PD-L1 stability is affected by the Cullin 3-SPOP E3 ligase, which regulates its degradation through cyclin D-CDK4 activity [160,161]. T-regulatory cells, which express higher levels of CDK6, are more responsive to CDK4/6 inhibition, promoting the activation of cytotoxic $CD8^+$ T cells against cancer cells. These findings indicate that combining CDK4/6 inhibitors with PD-L1 blockade could enhance the effectiveness of immunotherapy in cancer patients [162].

CDK4/6 inhibition may act as a protective mechanism, but senescence also plays a role in B-cell malignancies. B-cells from older bone marrow show increased levels of p16 and p19, indicating that cell cycle arrest and senescence may help prevent leukemia as individuals age. [134]. However, research on Eμ-Myc transgenic mice reveals a "stemness" signature in senescent B-cell lymphomas associated with enhanced Wnt signaling [163].

Chemotherapy studies using models that manipulate senescence pathways show that previously senescent cells can exit cell cycle arrest and proliferate, bolstered by increased Wnt signaling, which enhances their tumor initiation potential. Interestingly, inducing senescence in acute lymphoblastic and acute myeloid leukemia models can convert non-stem leukemia cells into self-renewing stem cells. These findings suggest a surprising connection between senescence and cancer stemness, prompting further exploration into whether non-neoplastic cells possess similar stem-like properties and how senescence might activate this potential [163].

3.3. Challenges in immunotherapy

Aging is a major risk factor for cancer, yet patients over 75 make up less than 10 % of clinical trial participants, limiting care for this demographic [164,165]. While new cancer treatments targeting the elderly are emerging, immunotherapy results vary between age groups due to differences in tumor types, stages, and comorbidities. In non-small cell lung cancer patients, immunosenescence may affect the efficacy of antibody treatments, especially immune checkpoint blockade (ICB) [166]. According to preclinical research, older mouse models respond less well to ICB than younger ones, indicating that age has a substantial influence on treatment results for a variety of tumor types and physiological states [167]. Even though aging is a significant risk factor for cancer, little is known about how ICB therapy is affected by age, and the microenvironment of the elderly is frequently disregarded [168]. According to Kugel et al.'s study, older patients fared better with anti-PD-1 treatment than younger ones [168]. Anti-PD-1 and PD-L1 therapies have been demonstrated to be safely tolerated by the elderly, with efficacy and toxicity profiles comparable to those of younger patients. According to a meta-analysis, anti-PD-1 medications work well for both groups, although older patients have mortality risks that are on par with or even lower than those of control groups without experiencing higher levels of toxicity [143,169,170]. However, elderly patients were more likely to experience severe adverse consequences. In specific investigations, anti-CTLA-4 and anti-PD-1 therapy proved helpful in older melanoma models, but anti-PD-L1 had no benefit in aged patients. Furthermore, compared to younger animals, older mice with oral cancer showed faster tumor shrinkage after anti-PD-L1 treatment. Significantly, it was discovered that the TME of elderly mice and patients with triple-negative breast cancer had decreased interferon signaling and antigen presentation [171,172]. This underscores the intricate relationship among age, immune response, and therapy effectiveness. Optimizing immunotherapy for older cancer patients requires more research on these dynamics.

4. Interplay between cuproptosis and immunosenescence in cancer

The interplay between cuproptosis and immunosenescence presents a complex relationship that may significantly influence cancer outcomes. Understanding this interaction is crucial for developing effective therapeutic strategies, especially in aging populations where both processes are prevalent. On one hand, the induction of cuproptosis in cancer cells can lead to profound changes in the TME. When cancer cells undergo cuproptosis, they may release a variety of signals, including damage-associated molecular patterns (DAMPs) and inflammatory cytokines. These signals can attract immune cells to the tumor site, potentially enhancing immune cell infiltration and activation. For instance, dying tumor cells can stimulate dendritic cells and macrophages, which play key roles in initiating and regulating immune responses. However, the effects of these signals can vary widely depending on the specific context. In some cases, they may promote a robust immune response, while in others, they might trigger immunosuppressive pathways that inhibit effective tumor targeting by immune cells [173].

Conversely, immunosenescence may significantly affect how immune cells respond to therapies that induce cuproptosis. As individuals age, their immune systems undergo numerous changes, including a decline in the functionality of T cells and B cells. These aging immune cells may exhibit impaired recognition and response to tumor antigens released during cuproptosis [27]. This diminished responsiveness can reduce the overall efficacy of treatments designed to exploit cuproptosis as a therapeutic strategy. Aging immune cells struggle to proliferate and mount effective responses when faced with new challenges, including the antigens associated with dying tumor cells.

Additionally, the chronic inflammatory state often observed in immunosenescence, known as inflammaging, may further complicate the relationship between cuproptosis and immune responses [16,174]. This persistent low-grade inflammation can influence copper metabolism and homeostasis, potentially altering the availability of copper within the TME. For instance, elevated levels of pro-inflammatory cytokines may affect the expression of copper transporters, leading to altered copper accumulation in both immune and tumor cells. Such changes could modulate the susceptibility of cancer cells to cuproptosis, either by enhancing their vulnerability or by promoting adaptive

mechanisms that allow them to survive despite copper-induced stress [27].

Moreover, the interplay between cuproptosis and immunosenescence highlights the need for a more nuanced understanding of how age-related changes in the immune system can affect cancer treatment outcomes. As researchers continue to investigate these interactions, it will be essential to consider not only the direct effects of cuproptosis on tumor cells but also the broader implications for immune function and tumor-immune interactions.

5. Manipulating cuproptosis and immunosenescence to improve cancer therapy

Manipulating cuproptosis and immunosenescence to enhance cancer therapy involves employing a range of strategies to selectively enhance or inhibit these biological processes. By understanding the mechanisms underlying cuproptosis, the copper-induced programmed cell death, and immunosenescence, the age-related decline in immune function, researchers and clinicians can develop innovative therapeutic approaches. Here are some key strategies being explored to leverage cuproptosis and immunosenescence for improved cancer treatment.

5.1. Manipulating cuproptosis

To effectively manipulate cuproptosis, targeting copper homeostasis is crucial. Copper homeostasis refers to the regulation of copper levels in the body, which is vital for numerous cellular functions, including enzyme activity, mitochondrial respiration, and antioxidant protection. Imbalances in copper can adversely affect the central nervous system, liver function, lipid metabolism, and chemotherapy resistance [175]. The body primarily stores copper in muscle and bone, with smaller amounts in the liver and blood. Dietary copper is absorbed as Cu^{2+}, then reduced to Cu^{+} by digestive tract enzymes. Cu^{+} is transported into cells via CTR1 and associated with the copper chaperone protein Atox1, allowing its entry into hepatocytes through ATP7B within the Golgi complex, where it helps form ceruloplasmin [176]. The distribution of CTR1 is dynamic; elevated extracellular copper levels trigger its endocytosis, while lower levels restore its expression. Excess copper is excreted into bile by ATP7B, and ATP7A helps mobilize copper from liver stores to maintain balance [177]. Both copper deficiency and excess can be toxic, leading to conditions such as oxidative stress. Menkes disease, a genetic disorder caused by mutations in the ATP7A gene, results in severe copper deficiency [178]. Fig. 3 illustrates the mechanism for copper targeting and its potential application in cancer therapy.

5.1.1. Copper ionophores

One effective strategy involves using copper ionophores, which are compounds designed to facilitate the entry of copper ions into cells. Certain copper ionophores have demonstrated potential in this regard because of their inherent selectivity in causing cancer cells to undergo cuproptosis more preferentially than healthy cells [179]. Various classes of copper ionophores have been investigated as potential anticancer agents to induce cuproptosis. These include compounds such as flavonoids, 8-hydroxyquinolines (HQs), dithiocarbamates, and bis (thiosemicarbazone) ligands [44,180–182]. Among the most recognized dithiocarbamates used as anticancer ionophores are pyrrolidine dithiocarbamate and diethyldithiocarbamate (DTC), which is the active metabolite of the well-known drug disulfiram (DSF) [183,184]. Research has demonstrated that DSF works well against a range of cancer cell types [185–187]. Since the active form of DSF is the copper complex of DTC, it is noteworthy that the anticancer effects of DSF are much increased when combined with copper. The intracellular copper accumulation that DSF promotes seems to be directly related to the toxicity that is associated with DSF [188]. Additionally, the Cu-DSF mixture has been investigated as a complementary treatment to well-known chemotherapeutic drugs such as doxorubicin, gemcitabine, temozolomide, and cisplatin [189]. Furthermore, targeting chloride channel-3 (ClC-3), a member of the chloride channel superfamily, is one suggested mechanism for Cu-DSF's selective activity on cancer cells. Cu-DSF has been found to induce apoptosis by activating ClC-3, which is overexpressed in cancer cells compared to normal cells [190].

5.1.2. Copper transporter

Copper transporters play essential roles in maintaining copper homeostasis within cells, which is critical for various cellular functions. Among these, SLC31A1 (CTR1) is the primary copper uptake transporter located on the plasma membrane, facilitating the influx of copper ions (Cu^{2+}) into cells. In contrast, SLC31A2 (CTR2), while also involved in copper uptake, has a less clearly defined role compared to CTR1. By targeting and inhibiting CTR1 and, to a lesser extent, CTR2, researchers can effectively reduce copper levels in cancer cells. This reduction in

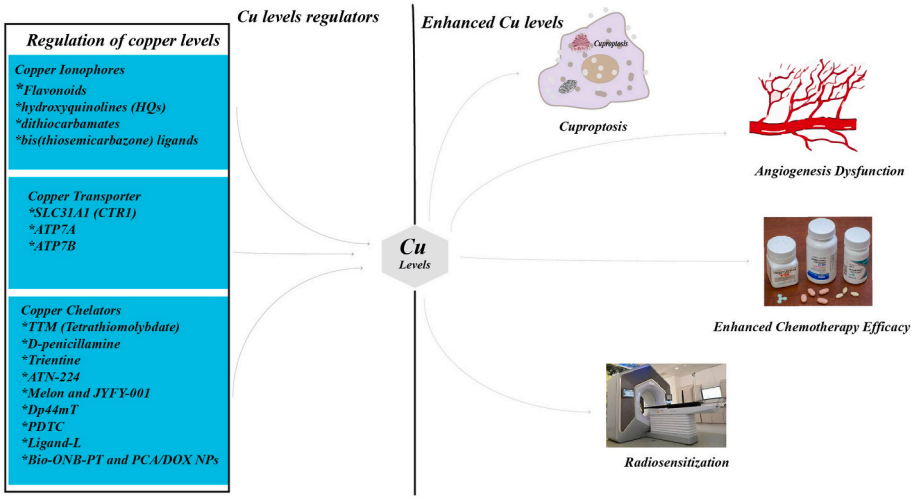

Fig. 3. Mechanisms of copper targeting and its potential applications in cancer therapy. Copper ionophores, transporters, and chelators play crucial roles in regulating cellular copper levels. Elevated copper concentrations can influence various biological processes, including promoting tumor growth and angiogenesis. Additionally, high copper levels can induce cell death through mechanisms such as cuproptosis, apoptosis via reactive oxygen species (ROS) elevation, and pyroptosis by activating inflammasomes and caspase-1. Furthermore, modulating copper levels can enhance treatment efficacy by sensitizing cancer cells to chemotherapy and radiotherapy, primarily by increasing oxidative stress and inhibiting DNA repair mechanisms.

copper availability disrupts the function of copper-dependent enzymes, which are crucial for tumor growth and survival. For instance, many cancer cells rely on copper for the activity of cytochrome *c* oxidase, an enzyme integral to mitochondrial respiration. Lowering copper levels can impair ATP production, leading to increased oxidative stress and ultimately triggering apoptotic pathways [191]. ATP7A and ATP7B are copper-transporting ATPases that help regulate copper distribution and excretion in the body. Inhibiting these transporters can lead to copper accumulation in cells, which can be toxic and promote cell death. In particular, ATP7A (Menkes protein) is crucial for copper export from cells, while ATP7B (Wilson's disease protein) is specifically involved in copper excretion from the liver. By inhibiting these transporters, it is possible to disrupt normal copper homeostasis, leading to copper overload and increased cell death in tumors [192].

The coordinated inhibition of copper transporters can serve as a strategic approach to suppress tumor growth. For example, copper chelators such as tetrathiomolybdate (TTM) can inhibit copper uptake by blocking CTR1 and effectively chelating copper, reducing its availability for cancer cells. This has shown promise in various cancer models, leading to decreased tumor growth and enhanced sensitivity to chemotherapy [193,194]. Techniques such as RNA interference (RNAi) can be employed to selectively knock down the expression of copper transporters like CTR1 and ATP7A in cancer cells, leading to reduced copper levels and increased cell death [195,196]. Combining copper transporter inhibitors with existing chemotherapeutics could enhance treatment efficacy. For instance, using copper chelators alongside drugs like cisplatin may increase the cytotoxic effects on tumor cells by exploiting the altered copper metabolism. Inhibiting copper transporters such as CTR1, ATP7A, and ATP7B presents a promising strategy for suppressing tumor growth by disrupting copper homeostasis.

5.1.3. Copper chelators

Copper chelators have emerged as important tools in cancer treatment due to their ability to disrupt copper homeostasis in tumor cells. By binding to copper ions and reducing their availability, these agents can induce oxidative stress, inhibit angiogenesis, serve as a vital source of nutrients and oxygen, and promote apoptosis in cancer cells. Here is a discussion of various copper chelators and their potential impact on cancer treatment:

TTM is one of the most studied copper chelators in oncology. It effectively reduces copper levels in the body and has shown promise in preclinical and clinical studies for various cancers, including breast and prostate cancer. TTM's ability to inhibit angiogenesis by reducing the levels of copper-dependent angiogenic factors, such as VEGF, enhances its therapeutic potential [197]. D-penicillamine is another copper chelator that has been utilized in cancer therapy, particularly in combination with oxaliplatin. This combination aims to enhance the efficacy of oxaliplatin by mitigating the effects of copper in promoting tumor growth. D-penicillamine can also be used alone to lower copper levels, which has been shown to increase the sensitivity of certain cancer cells to chemotherapy [198]. Trientine is similar to D-penicillamine and is used to treat Wilson's disease. Its potential in cancer therapy lies in its ability to lower copper levels, thereby potentially enhancing the effectiveness of conventional cancer treatments. Studies have indicated that trientine can induce apoptosis in cancer cells by disrupting copper-dependent processes [199]. TEPA (Tetraethylthiuram disulfide) is another chelator that has been explored for its anticancer properties. It can induce oxidative stress and apoptosis in cancer cells, making it a candidate for further investigation in cancer therapy [200]. ATN-224 is a novel copper chelator that has shown potential in preclinical models. It works by inducing copper depletion, which can lead to increased tumor cell death and reduced tumor growth [201]. Melon and JYFY-001 are less common copper chelators but have been investigated for their anticancer effects. Their mechanisms are still being explored, but preliminary studies suggest they may have the potential to disrupt copper metabolism in cancer [202,203].

Dp44mT is a potent copper chelator that has demonstrated significant anticancer activity. It induces apoptosis and inhibits tumor growth by disrupting copper-dependent signaling pathways. Its effectiveness in various cancer models highlights its potential as a therapeutic agent [204]. PDTC (Pyrrolidine dithiocarbamate) is known for its ability to chelate copper and has been studied for its anti-inflammatory and antioxidant properties. In cancer therapy, it may enhance the effects of other treatments by reducing copper levels [205]. Ligand-L and Curcumin are natural compounds that also exhibit copper-chelating properties. Curcumin, derived from turmeric, has garnered attention for its anti-inflammatory and anticancer effects, and its ability to chelate copper may contribute to its therapeutic benefits [206,207].

Bio-ONB-PT and PCA/DOX NPs are newer formulations that incorporate copper chelation into their therapeutic strategies. These agents aim to enhance the delivery and efficacy of traditional chemotherapeutics by targeting copper metabolism in cancer cells [208,209].

Overall, the impact of copper chelators in cancer treatment is multifaceted. By reducing copper availability, these agents can disrupt essential processes in cancer cells, inhibit tumor growth, and enhance the efficacy of existing therapies. As research continues to explore the mechanisms and combinations of these chelators, they may play an increasingly important role in the development of effective cancer treatments.

5.2. Strategies for manipulating immunosenescence in cancer therapy

5.2.1. Senolytic therapy

Senolytics are being developed to target and eliminate senescent cells (SnCs) as a strategy for treating age-related diseases. A primary challenge in this approach is the inherent resistance of SnCs to apoptosis, which limits the effectiveness of many cytotoxic drugs. Senolytic strategies aim to disrupt Senescent Cell Anti-Apoptotic Pathways (SCAPs) by inhibiting proteins that contribute to this resistance [210]. The combination of Dasatinib (a tyrosine kinase inhibitor) and Quercetin (a plant-derived flavonoid) has shown significant effectiveness in clinical trials, as it can target a wider range of senescent cell types than either drug alone. This combination has been particularly noted for its impact in conditions like idiopathic pulmonary fibrosis, diabetes, Alzheimer's disease, and chronic kidney disease [211–213].

Another notable senolytic, Navitoclax (ABT-263), targets BCL-2 family proteins and has been effective in eliminating senescent cells in various studies, including those related to osteoarthritis and neurodegenerative diseases. However, its effectiveness is limited to certain cell types [214–216]. Therefore, there is a need to discover new senolytic agents that can more broadly target senescent cells associated with age-related diseases.

Several senolytic agents have emerged as promising strategies for addressing age-related diseases, including Fisetin, HSP90 inhibitors, and P53/MDM2 inhibitors. Fisetin, a flavonoid present in various fruits and vegetables like strawberries and apples, has demonstrated the ability to eliminate senescent cells. Research suggests that Fisetin can reduce inflammation and enhance cognitive function, making it a potential therapeutic option for neurodegenerative disorders associated with aging [217]. HSP90 inhibitors target the heat shock protein 90, which is crucial for the proper folding and stabilization of various proteins. By inhibiting HSP90, these agents can promote the degradation of pro-survival proteins in senescent cells. Preclinical studies indicate that this class of inhibitors may effectively reduce senescent cell populations, potentially alleviating age-related ailments [218]. Inhibitors that affect the P53/MDM2 interaction are also being explored for their senolytic properties. Notable examples include FOXO-DRI, which activates FOXO transcription factors involved in regulating the cell cycle and apoptosis [219]; UBX0101, known for its ability to selectively induce apoptosis in senescent cells, offering therapeutic promise for age-related diseasesm [219]; and P22077/P5091, which inhibit MDM2 to enhance P53 activity and promote the removal of senescent cells [220]. Galactose-modified

prodrugs, such as Duocarmycin and Gemcitabine, are engineered to selectively target senescent cells. Activated by specific enzymes, these prodrugs can deliver cytotoxic effects primarily to senescent cells, reducing potential harm to healthy tissue and increasing treatment effectiveness [221,222]. Inhibitors of the sodium/potassium pump (Na+/K + ATPase) also show potential as senolytics. By disrupting the ion balance within senescent cells, these inhibitors can induce cell death, making them valuable in treating age-related conditions characterized by the accumulation of senescent cells [223]. The investigation of these senolytic agents Fisetin, HSP90 inhibitors, P53/MDM2 inhibitors, galactose-modified prodrugs, and sodium/potassium pump inhibitors illustrates a comprehensive approach to combating age-related diseases. By specifically targeting and eliminating senescent cells, these therapies have the potential to enhance healthspan and address the fundamental causes of age-associated pathologies. Ongoing research will be essential to uncover their mechanisms and assess their clinical efficacy.

5.2.2. Immune system rejuvenation

Immune system rejuvenation is a vital area of research, particularly in reversing immune senescence, which is the gradual decline in immune function associated with aging. Several factors have been identified that may help to combat this decline, with NAD + Boosters, physical activity, hormonal influences, microbiota composition, and kidney transplantation being key areas of focus [224]. Nicotinamide adenine dinucleotide (NAD+) levels decline with age, contributing to immunosenescence. Boosting NAD + levels using precursors like nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN) can help improve immune cell function [225–227]. Physical activity plays a crucial role in maintaining thymic function, the thymus being central to the development of T cells, which are essential for adaptive immunity. Numerous studies in both animal models and humans have consistently demonstrated that regular physical exercise can boost thymic activity, thereby enhancing immune responses. This therapeutic strategy stands out due to its accessibility and the broad array of health benefits it provides, particularly in older adults [228]. Hormonal pathways significantly influence thymic physiology and immune function. Several hormones are known to be critical for thymic health, including growth factors and sex hormones, yet many of these pathways become dysregulated during chronic illnesses such as renal failure. For instance, the insulin-like growth factor 1 (IGF-1) and growth hormone pathways are essential for thymic function; their impairment can contribute to immune decline. Additionally, cytokines such as IL-7 and interleukin-22 (IL-22), along with keratinocyte growth factor, play important roles in supporting thymocyte development and overall immune homeostasis. Researchers are exploring techniques such as targeting thymic epithelial cells (TECs) to restore thymic function and enhance immune reconstitution [229–233].

The gut microbiota is another critical factor influencing immune health throughout life. The intricate relationship between microbiota and the immune system reveals that dysbiosis an imbalance in microbial composition can lead to chronic inflammation and contribute to various age-related conditions. During the neonatal and early life stages, the microbiota undergoes significant changes, stabilizing in middle age. However, age-associated alterations in gut function, increased inflammation, and comorbidities can further disrupt this delicate balance, exacerbating immune senescence [234]. Kidney transplantation also presents a unique opportunity for rejuvenating the immune system. Successful transplantation not only reverses renal failure but has also been shown to increase life expectancy. However, the effects of kidney transplantation on immune senescence can be complex and may vary widely among individuals. While some patients experience improved immune function post-transplant, others may show contrasting effects, highlighting the intricate interplay between renal health and immune dynamics [224,235]. In summary, reversing immune senescence involves a multifaceted approach that includes promoting physical activity, understanding hormonal influences, modulating gut microbiota, and leveraging the benefits of kidney transplantation. Continued research in these areas holds promise for developing effective interventions to enhance immune resilience in aging populations.

5.2.3. TME, immune checkpoint inhibitors, and lifestyle interventions

Another approach to modulating immunosenescence in cancer therapy involves targeting the TME to enhance the effectiveness of immunotherapy. Senescent cells release pro-inflammatory cytokines that foster an environment conducive to tumor growth. By inhibiting these inflammatory pathways with anti-inflammatory agents, tumor progression can be mitigated.

Additionally, reprogramming the TME to a more immunogenic state can be achieved through agents that target immune checkpoint pathways or stromal cells within the tumor. Immune checkpoint inhibitors, such as PD-1/PD-L1 blockers, tend to be more effective when used alongside therapies aimed at eliminating senescent cells, which can suppress immune responses. Moreover, rejuvenating T cells prior to their reinfusion into the patient can significantly enhance the efficacy of adoptive cell therapy, utilizing various cytokines and growth factors for this purpose. Lifestyle and dietary modifications also play a vital role; practices like caloric restriction and fasting have been shown to enhance immune function and decrease inflammation, potentially slowing immunosenescence and improving cancer therapy outcomes [154,166,236]. Additionally, key regulators or biomarkers of immunosenescence can be strategically targeted to optimize cancer treatments. Promising biomarkers related to immunosenescence have been identified as potential candidates for clinical trials, as outlined in Table 1.

6. Clinical implications and future directions

The interplay between cuproptosis and immunosenescence presents several clinical implications and future research directions. Understanding the mechanisms of cuproptosis offers significant potential for enhanced cancer treatment by targeting copper metabolism, which could improve treatment outcomes. By modulating copper levels, it may be possible to optimize immunotherapy, particularly for older patients who experience immunosenescence, thereby enhancing the effectiveness of these treatments. For instance, research has demonstrated that copper chelators and copper ionophores can effectively induce cuproptosis in cancer cells, leading to improved therapeutic outcomes [241,242]. Incorporating biomarkers related to copper metabolism and immunosenescence into personalized medicine could help tailor treatments to individual patients, improving efficacy and minimizing side effects. Research has indicated that the expression of copper transporters, such as SLC31A1, correlates with immune infiltration in various

Table 1
Various biomarkers associated with immunosenescence have been identified as promising candidates for clinical trials.

Biomarkers	Name	Description
Biomarkers Related to Immunosenescence	PD-1/PD-L1	Increased [237]
	$CD19^+$ cells	Decreased [238]
	CD4 T cells	Decreased [238]
	CD8 T cells	Increased [238]
	CD4/CD8 ratio	Decreased [238]
	CD45RA + $CD28^-$	Increase [239]
	sCD28	Increase [240]
	sCD80	Increase [240]
	sCTLA-4	Increase [240]
	IL-6	Increase [240]
	TNF-α	Increase [240]
	IFN-γ	Increase [240]
	sCD163	Increase [240]

s: Soluble.

cancers, highlighting their potential as biomarkers [243].

Future research should focus on elucidating the precise molecular mechanisms by which copper dysregulation affects immune cell function and cancer progression. Developing therapeutic strategies that modulate copper levels in a controlled manner could open new avenues for treating both cancer and age-related immune decline [244,245].

Conducting clinical trials to test the efficacy and safety of copper-targeting therapies in cancer patients, especially those with compromised immune systems due to aging, will be crucial. A phase II trial showcased Tetrathiomolybdate (TM), a novel copper-depleting compound, which exhibited promising survival rates in patients with high-risk and triple-negative breast cancer [246]. These findings emphasize the considerable potential of copper modulation as an important therapeutic strategy in oncology, particularly for populations at risk of immune decline.

This emerging field holds promise for advancing our understanding of cancer biology and developing innovative treatments that could significantly improve patient outcomes. As research continues to unfold, the potential for integrating cuproptosis and immunosenescence in clinical settings may revolutionize cancer therapy and offer new hope for patients [44]. The interplay between these processes offers significant advantages for cancer therapy. Combining the induction of cuproptosis, which directly kills cancer cells, with strategies to combat immunosenescence can create a synergistic effect, maximizing therapeutic efficacy. This dual approach not only targets tumor cells but also revitalizes the immune system, providing a robust defense against cancer progression and recurrence (Fig. 4). Consequently, integrating cancer treatment with cuproptosis and interventions against immunosenescence holds substantial promise for advancing cancer therapy and improving patient outcomes [247,248]. By exploring the mechanisms of cuproptosis and immunosenescence, researchers can develop targeted therapies that exploit the vulnerabilities of cancer cells while bolstering the immune system's capacity to fight cancer. This comprehensive approach underscores the importance of continued research and innovation in the field of cancer therapy, with the ultimate goal of improving survival rates and quality of life for cancer patients.

7. Nanodelivery systems and ionophores in cuproptosis and immunosenescence

Nanodelivery systems have emerged as a promising option for increasing copper's medicinal potential by boosting bioavailability and stability. These methods allow for targeted administration and regulated release of copper ions, which can efficiently cause cuproptosis in tumor cells. They improve therapeutic outcomes by reducing systemic toxicity, especially when combined with other treatments like photodynamic therapy (PDT) or immunotherapy [249,250].

Ionophores are critical in the uptake of copper ions into cells, which contributes to oxidative stress and cytotoxicity in tumor settings. They also can alter immunological activities, particularly in elderly people, by renewing immune cells and improving their responsiveness to therapy. This dual action may boost the efficacy of immunotherapies in elderly patients, making nano-delivery devices and ionophores critical components in the advancement of copper-based cancer treatments [251].

The findings from various studies highlighting the roles of nano delivery systems and ionophores are summarized in Table 2. These studies collectively demonstrate the significant impact of these innovative approaches on enhancing copper therapy in cancer treatment.

8. Conclusion

Exploring the relationship between cuproptosis and immunosenescence opens new avenues for cancer treatment strategies. By targeting cuproptosis, we can exploit the specific vulnerabilities of cancer cells linked to copper dysregulation, thereby promoting selective cell death. Simultaneously, addressing the effects of immunosenescence can rejuvenate the immune response, particularly in elderly patients facing cancer, enhancing their ability to fight tumors. Integrating therapies that

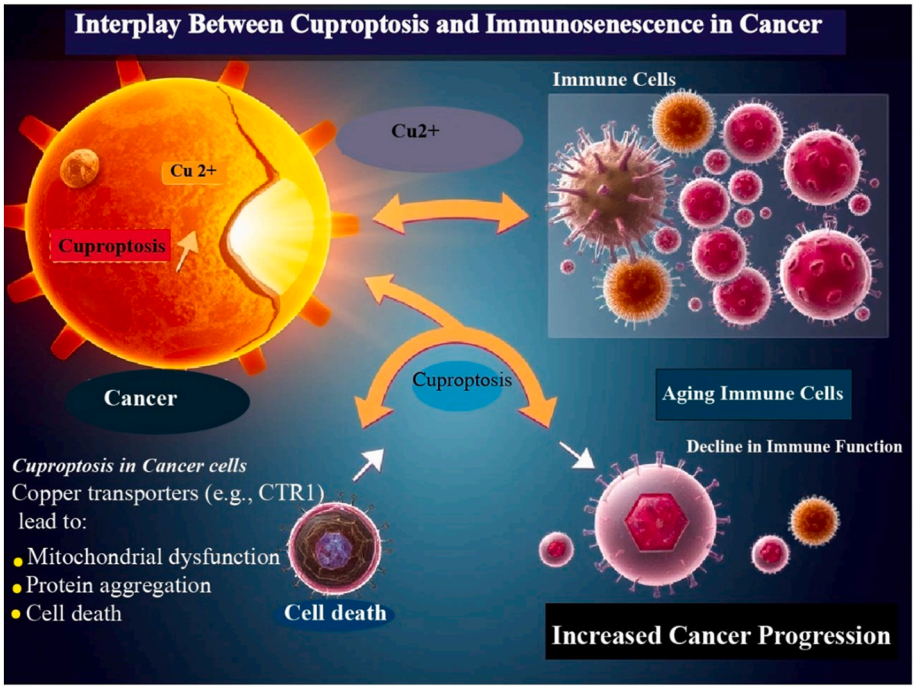

Fig. 4. Interplay Between Cuproptosis and Immunosenescence in Cancer Progression. The left side illustrates cuproptosis, depicting copper ions (Cu^{2+}) entering cancer cells and causing mitochondrial damage, ultimately leading to cell death. The right side shows aging immune cells, including T-cells and macrophages, highlighting their decline in function and the resultant increase in cancer progression. Central arrows demonstrate the feedback loop between cuproptosis and immunosenescence, emphasizing how copper-induced stress can exacerbate immune aging, while aging immune cells may further contribute to copper toxicity. This figure underscores the complex interactions between these two processes and their implications for cancer therapy. Created with the assistance of AI.

Table 2
The results from multiple studies emphasizing the roles of nano delivery systems and ionophores.

Study	Focus	Key Findings	Role of Nanodelivery Systems	Role of Ionophores
Zhang et al. (2024) [252]	Nanoparticle-Mediated Cuproptosis and Photodynamic Synergistic Strategy: A Novel Horizon for Cancer Therapy	Nanoparticle-mediated cuproptosis combined with photodynamic therapy (PDT) enhances anticancer efficacy.	Enhances bioavailability and stability of copper; facilitates targeted delivery and controlled release of copper ions; induces cuproptosis in tumor cells.	Not directly addressed.
Yang et al. (2025) [253]	Advances in using copper-based nanomaterials for cancer therapy	Copper-based nanomaterials induce mitochondrial damage and toxic protein stress in cancer cells.	Targeted delivery of copper ions to tumor cells; enhances therapeutic efficacy; and reduces systemic toxicity.	Not directly addressed.
Pangrazzi et al. (2025) [254]	Molecular and Cellular Mechanisms of Immunosenescence: Modulation Through Interventions and Lifestyle Changes	Modulation of key signaling pathways in aged immune cells through interventions.	Not directly addressed.	Rejuvenates aged immune cells; enhances immune function; modulates NF-κB and mTOR pathways.
Liu et al. (2023) [105]	Immunosenescence: Molecular Mechanisms and Diseases	Investigation of mechanisms underlying immunosenescence and potential interventions.	Not directly addressed.	Enhances immune response; improves efficacy of immunotherapies in elderly patients.
Liu et al. (2024) [255]	Targeting cuproptosis with nano materials: A New way to enhance the efficacy of immunotherapy in colorectal cancer	Nanoparticle-mediated cuproptosis enhances the efficacy of immunotherapy in colorectal cancer.	Facilitates targeted delivery of copper ions; improves outcomes in cancer therapy; combines with immunotherapy for synergistic effects.	Potential to enhance the efficacy of copper-induced cytotoxicity.
Lu et al. (2024) [251]	Glutathione-Scavenging Celastrol-Cu Nanoparticles Induce Self-Amplified Cuproptosis for Augmented Cancer Immunotherapy	Development of self-amplified cuproptosis nanoparticles (Cel-Cu NP) using celastrol, enhancing copper accumulation and immune response.	Cel-Cu NP improves copper ion delivery and amplifies cuproptosis; induces immunogenic cell death for robust immune response.	Cel acts as a copper ionophore and scavenges GSH to amplify cuproptosis.
Hu et al. (2024) [250]	Stimulus-Responsive Copper Complex Nanoparticles Induce Cuproptosis for Augmented Cancer Immunotherapy	Development of copper complex nanoparticles (Cu(I) NP) that efficiently deliver copper complexes to induce cuproptosis and elicit immune responses.	Cu(I) NP enable efficient delivery of copper complexes and stimulus-responsive release, leading to mitochondrial dysfunction.	Not directly addressed; focuses on copper complex delivery.

focus on both cuproptosis and the immune system may lead to more tailored and effective treatment options, potentially improving patient outcomes and addressing the limitations of existing therapies. Future investigations should aim to deepen our understanding of these processes and identify relevant biomarkers, facilitating their application in clinical settings. Ultimately, leveraging the insights gained from cuproptosis and immunosenescence could pave the way for groundbreaking advancements in cancer therapy, significantly benefiting patient care and survival rates.

CRediT authorship contribution statement

Ali Ahmadizad Firouzjaei: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Seyed Hamid Aghaee-Bakhtiari:** Writing – review & editing, Supervision, Investigation.

Data availability

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Declaration of competing interest

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