Review Article

Which one of the types of programmed cell death is reduced by aerobic exercise?

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Abstract

Programmed cell death is a critical element of the body's defense system. Exercise represents a physiological stressor that triggers an adaptive response within the body. It has been suggested that various forms of programmed cell death are essential for the adaptation process associated with exercise. During physical activity, mechanisms such as apoptosis and autophagy are activated to mitigate tissue damage, restore cellular integrity, resolve inflammatory responses, and facilitate direct signals that promote adaptation. The induction of programmed cell death is mediated by specific factors, including reactive oxygen species, cytokines, and hormones. These cell death pathways are initiated by the presence of altered proteins and organelles, with the objective of conserving and recycling cellular resources. In scenarios where cells accumulate damaged molecules and repair mechanisms become overwhelmed, programmed cell death is triggered. In this review article, we have examined the types of programmed death and the effect of aerobic training on these deaths.

Key Words: **Cuproptosis, Ferroptosis, Pyroptosis, PANoptosis, Anoikis, Eryptosis**

Introduction

Cell death refers to the biochemical mechanisms through which a cell loses its capacity to preserve its structural integrity and homeostasis, ultimately ceasing to perform its designated functions. This process can occur in a programmed manner when a cell reaches a stage of senescence, rendering it incapable of fulfilling its normal roles, or it may arise spontaneously due to specific mechanical, ischemic, or chemical insults, leading to unregulated cell death. On one hand, cell death is a crucial process that facilitates the cessation of a cell's morphological and functional characteristics through intricate programmed or non-programmed interactions, thereby contributing to the overall homeostasis of the organism. Conversely, it can have adverse effects, such as inciting inflammation at the site of cell death and potentially triggering the demise of neighboring healthy cells, thus presenting a dual nature (Guha et al., 2023).

Cell death plays a pivotal role in biological growth and development, as well as in the pathogenesis of cardiovascular diseases. The classification of cell death encompasses two primary categories: regulated cell death (RCD) and accidental cell death (ACD). ACD is characterized by its uncontrolled nature, resulting from the physical disruption of the plasma membrane due to unintentional injury. Conversely, RCD encompasses a series of programmed processes, including apoptosis, autophagy, pyroptosis, ferroptosis, and cuproptosis. Programmed cell death (PCD) is a regulated mechanism of cellular demise that is essential for the developmental processes of an organism (Green & Llambi, 2015; Guha et al., 2023). This process is marked by the activation of specific genes that encode proteins responsible for initiating cell death, thereby enabling the elimination of particular cells within the organism (Lyu et al., 2024). Numerous forms of PCD have been identified, each defined by the unique molecular pathways that govern and execute the cell death process, as well as by the distinct morphological features associated with cellular self des-

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-truction. Current classifications of PCD have been established to systematically organize existing knowledge and to emphasize newly recognized forms of cell death observed in differentiated tissues or under specific pathological conditions. To date, approximately 15 distinct types of PCD have been documented, with apoptosis, autophagic death, and programmed necrosis (necroptosis) being among the most thoroughly investigated and acknowledged forms (Ouyang et al., 2012).

Various modes of cell death have been characterized and organized into a fundamental classification system, distinguishing between PCD and non-programmed cell death (non-PCD) based on their dependence on signaling pathways. PCD is further divided into two categories: apoptotic and non-apoptotic cell death. Apoptotic cell death is characterized by processes such as apoptosis and anoikis, which involve membrane blebbing, mitochondrial dysfunction, and detachment from the extracellular matrix (ECM) (Bricmont et al., 2023). Non-apoptotic programmed cell death encompasses several forms, including vacuole-presenting cell death (such as autophagy, entosis, methuosis, and paraptosis), mitochondria-dependent cell death (mitoptosis and parthanatos), iron-dependent cell death (ferroptosis), and immunomodulatory cell death (pyroptosis and NETosis). Non-PCD is typified by necrosis, which plays a significant role in the progression of injuries. The pathways of cell death are critical in the context of disease progression, particularly in cancer and various forms of tissue injury. Each cell death pathway is associated with distinct morphological alterations, including the emergence of fluid-filled vacuoles (paraptosis), mitochondrial impairment (mitoptosis and parthanatos), iron accumulation (ferroptosis), and the formation of extracellular traps and gasdermin D-mediated cleavage (NETosis and pyroptosis), as well as instances of spontaneous cell death (necrosis). Understanding cell death is vital for understanding how some illnesses progress, which leads to new treatment development (Guha et al., 2023; Yan et al., 2020). Figure 1 shows the types of cell death.

In this review, we aim to: (1) examine the current literature regarding the molecular mechanisms underlying PCD; and (2) explore the impact of aerobic training on PCD.

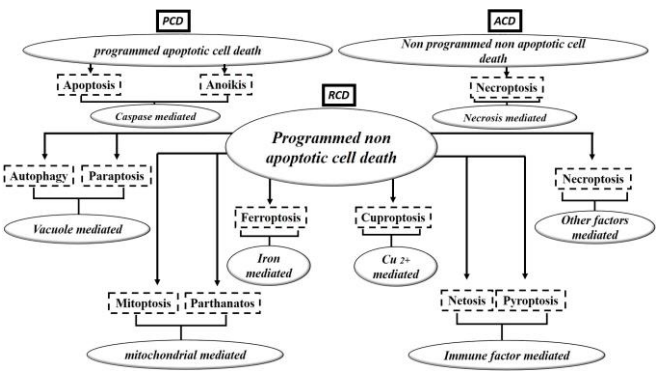

Figure 1. Types of cell death

Programmed cell death

Autophagy: Autophagy (one of the types of RCDs) is a fundamental physiological process wherein cells transport their constituents to lysosomes for degradation through structures known as autophagosomes. The development of electron microscopy in the 1950s allowed Christian de Duve to discover various hydrolases, which facilitated the identification of lysosomes as unique cellular organelles. In 1963, de Duve coined the term autophagy to describe the mechanism by which cells combine vesicles filled with proteins with lysosomes, leading to the degradation of cellular proteins. These vesicles were later termed autophagosomes (Ichimiya et al., 2020). Autophagy is generally classified into three primary types: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy, with the term autophagy predominantly referring to macroautophagy. Macroautophagy plays a critical role in the degradation of cellular materials, allowing for the recycling of the resulting macromolecules (Yamamoto & Matsui, 2024). During cytoplasmic macroautophagy, substrates are encapsulated within a transient double-membrane structure known as the autophagosome, which then fuses with lysosomes and vacuoles (Debnath et al., 2023). This recycling mechanism is essential for maintaining cellular homeostasis. CMA, on the other hand, is a selective autophagic pathway that specifically targets proteins for lysosomal degradation. Initially, it was thought that this pathway mainly supported cellular metabolism by supplying free amino acids from protein degradation (Tasset & Cuervo, 2016). However, recent studies suggest that impairments in CMA can considerably disrupt glucose and lipid metabolism, thereby influencing the overall energy metabolism of the organism and playing a crucial role in the regulation of cellular metabolism in response to fluctuating nutrient availability. Microautophagy represents a non-selective mechanism of lysosomal degradation characterized by the direct engulfment of cytoplasmic constituents via autophagic tubules (Li et al., 2012). This process not only facilitates the entry of materials into the cytoplasmic lumen but also promotes vesicle cleavage (Li et al., 2015). It is crucial for the preservation of cellular homeostasis and overall survival. Furthermore, the diverse mechanisms of autophagy operate in concert to degrade intracellular components and generate degradation products, thereby aiding in the maintenance of homeostasis within living organisms (Liu et al., 2015). A dysfunction in autophagy can lead to decreased ubiquitination, increased levels of reactive oxygen species (ROS), impaired mitochondrial function, and greater genomic instability (Zhou et al., 2022). These elements collectively result in a deterioration of the quality of intracellular components. As a result, the disruption of autophagy undermines cellular homeost-

-asis and is significantly implicated in the development of various diseases (Uddin et al., 2012).

The phenomenon of autophagy is observed across various organs, with the activation in one organ potentially triggering similar processes in others. A notable example is the role of free fatty acids, which inhibit autophagy in macrophages by interfering with the AMP-activated protein kinase (AMPK)-ULK signaling cascade. This interference leads to defective mitophagy, an increase in mitochondrial ROS, and heightened activation of the NOD-like receptor family pyrin domain containing 3 nod-like receptor protein 3 (NLRP3) inflammasome (Yi et al., 2024). As a result, IL-1β released from macrophages can disrupt insulin signaling in key target tissues such as adipose tissue, liver, and skeletal muscle. The implications of autophagy extend beyond cell-autonomous effects, which include the direct autophagic degradation of cellular components and interactions between the endoplasmic reticulum and mitochondria, to encompass non-cell-autonomous effects, such as the regulation of secretory factors and changes in sympathetic nervous system activity (Kim & Lee, 2014).

Necrosis: Necrosis, one of the types of ACDs, characterized as a toxic process leading to passive cell death, is sometimes considered an inappropriate term for describing the aftermath of cell death. The term oncosis is suggested instead to describe a process resulting in necrosis, marked by karyolysis and cellular swelling (Majno & Joris, 1995). Apoptosis, on the other hand, leads to cell death characterized by shrinkage, pyknosis, and karyorrhexis. While distinctions cross-talk between apoptosis and necrosis, they can be viewed as part of a common biochemical framework known as the "apoptosis-necrosis continuum. " Factors influencing whether a cell undergoes necrosis or apoptosis include the cell death signal, tissue type, developmental stage, and physiological environment (Ai et al., 2024). The cross-talk between apoptosis and necroptosis is influenced by a collective group of regulatory molecules, which includes interleukin-1-like proteins, the cellular Fas-associated death domain, transforming enzyme inhibitory protein (FLIP), A20, and cylindromatosis deubiquitinases, in addition to the cellular inhibitors of apoptosis, specifically cellular inhibitor of apoptosis protein 1 (cIAP1) and cellular inhibitor of apoptosis protein 2 (cIAP2) (Levin et al., 1999).

Distinguishing between apoptosis and necrosis can be challenging as they may occur concurrently and are influenced by factors like stimulus intensity, ATP depletion, and caspase availability (Zeiss, 2003). Necrosis involves uncontrolled, extensive cell damage, while apoptosis is a regulated process affecting single cells or small clusters. Morphological changes in necrosis include cell swelling, cytoplasmic vacuoles, and mitochondrial alterations. Necrosis results in the release of cell contents triggering inflammatory responses, while apoptotic cells are cleared without causing inflammation (Fiers et al., 1999). It is important to note that pyknosis and karyorrhexis, which are typically associated with apoptosis, can also occur in the broader context of changes seen in necrosis. Cell membrane integrity compromises lead to the release of intracellular contents during necrosis, attracting inflammatory cells. However, apoptotic cells are swiftly removed by macrophages or healthy neighboring cells, minimizing inflammation (Hassan Ghomi et al., 2019; Saleh Fard et al., 2021; Samadi et al., 2019).

Apoptosis: Apoptosis, one of the types of PCDs, introduced by Kerr et al. in 1972, describes a specific cell death process characterized by distinct morphological changes (Kerr, 2002). Apoptosis is triggered by several organelles, notably the plasma membrane, mitochondria (Kroemer et al., 2008) endoplasmic reticulum (Yamamuro et al., 2011), Golgi apparatus (Mancini et al., 2000), lysosomes (Kurz et al., 2008), nucleus (Loughery & Meek, 2013), and the centrosome and centrioles (Castedo et al., 2004). During apoptosis, a cross-talk between the mitochondria and the cytosol. A critical event in mitochondrial-dependent apoptosis is the release of cytochrome c and various other proteins from the mitochondria into the cytosol, which occurs as a result of heightened permeability of the mitochondrial membranes. Cytochrome c serves as a necessary substrate for the assembly of the apoptosome, which comprises oligomeric proteins such as apoptosis protease activating factor) Apaf-1(, along with several molecules of procaspase 9 and dATP (Liu et al., 2024).

This process involves biochemical modifications like protein cleavage, DNA fragmentation, and recognition by phagocytes. Caspases, usually inactive, become activated during apoptosis and trigger a proteolytic cascade by activating other procaspases. This unique structural pathology outlined by Hengartner in 2000 is key to understanding apoptotic cell death (Hetz et al., 2005). Certain procaspases possess the ability to aggregate and undergo autoactivation (Hashemi et al., 2024). This cascade, characterized by the activation of one caspase by another, enhances the apoptotic signaling pathway, ultimately leading to swift cell death. Caspases exhibit proteolytic activity, cleaving proteins at aspartic acid residues, although their specificities vary based on the recognition of adjacent amino acids. Once activated, caspases appear to commit the cell irreversibly to the death process. Currently, ten principal caspases have been identified and classified into three categories: initiators (caspase-2, -8, -9, -10), effectors or executioners (caspase-3, -6, -7), and inflammatory caspases (caspase-1, -4, -5) (Sun, 2024) caspases include caspase-11, which is implicated in regulating apoptosis and cytokine maturation during septic shock, caspase-12, which is involved in endoplasmic reticulum-specific apoptosis and cytotoxicity induc-

-ed by amyloid-β, caspase-13, suggested to be a bovine gene, and caspase-14, which is predominantly expressed in embryonic tissues but not in adults (Hu et al., 1998; Kang et al., 2002). Another notable feature of apoptotic cells is extensive protein cross-linking, facilitated by the expression and activation of tissue transglutaminase (Aplin et al., 2024). Additionally, DNA fragmentation occurs through the action of Ca^{2+} and Mg^{2+} dependent endonucleases, resulting in DNA fragments ranging from 180 to 200 base pairs (Bortner et al., 1995). A distinct "DNA ladder" pattern can be observed through agarose gel electrophoresis when utilizing an ethidium bromide stain under ultraviolet light. Another notable biochemical characteristic is the presence of cell surface markers that facilitate the prompt phagocytic recognition of apoptotic cells by neighboring cells, thereby enabling rapid phagocytosis with minimal disruption to the surrounding tissue. This process is mediated by the translocation of phosphatidylserine (PS), which typically resides on the inner leaflet of the lipid bilayer, to the outer layers of the plasma membrane (Bratton et al., 1997). While the externalization of PS is widely recognized as a key ligand for phagocytes on apoptotic cells, recent research has identified additional proteins that are also presented on the cell surface during the clearance of apoptotic cells. These proteins include Annexin I and calreticulin. Annexin V, a recombinant protein that specifically binds to PS, demonstrates a strong affinity for these residues and serves as a valuable tool for detecting apoptosis (Arur et al., 2003; van Loo et al., 2002). Calreticulin, on the other hand, interacts with an LDL-receptor-related protein on the phagocytic cell and is believed to work in concert with PS as a recognition signal (Gardai et al., 2005). Additionally, the adhesive glycoprotein thrombospondin-1 can be found on the outer surface of activated microvascular endothelial cells and, in combination with CD36, caspase-3-like proteases, and other proteins, can trigger receptor-mediated apoptosis (Jiménez et al., 2000).

Cuproptosis: Copper (Cu) is an essential trace element present in cells and tissues in minimal amounts. It exists as oxidized Cu2+ or reduced Cu+. Cu acts as a cofactor for enzymes crucial for biological processes like growth and development. Cell death is categorized into regulated and accidental types (Kordi, Saydi, Azimi, et al., 2024). Cuproptosis (one of the types of RCDs) is a new form of non-apoptotic cell death dependent on copper and mitochondrial regulation. It involves fatty acylated components affecting protein toxic stress and ultimately leading to cell death. Morphological signs of cuproptosis include mitochondrial shrinkage, cell membrane rupture, and chromatin damage. Excessive copper can induce cuproptosis by affecting protein responses and iron-sulfur cluster proteins. Additionally, the formation of a copper-homocysteine complex may contribute to harmful effects on endothelial function and vascular health (Horvath & Kararigas, 2022).

Copper is an important cofactor that is pivotal in mediating the cross-talk among various critical enzymes, such as cytochrome c oxidase, tyrosinase, p-hydroxyphenylpyruvate hydrolase, dopamine beta-hydroxylase, lysyl oxidase, and copper superoxide dismutase (Cu, Zn-SOD) (Kordi, Saydi, Azimi, et al., 2024).

Ferroptosis: A Unlike other forms of cell death that can be described as 'cell suicide,' ferroptosis is characterized by a process of 'cell sabotage.' This phenomenon is marked by metabolic alterations that culminate in cell death, driven by unique genetic, metabolic, and protein factors. Morphologically, cells undergoing ferroptosis exhibit specific alterations in mitochondrial size and membrane density. The process is facilitated by the depletion of glutathione (GSH) and the occurrence of lipid peroxidation, with an excess of iron and a deficiency of sulfur being critical in initiating ferroptosis (Kordi, Saydi, Karami, et al., 2024).

Ferroptosis (one of the types of RCDs) arises from cross-talk between amino acids (such as leucine, isoleucine, and valine), lipids (increased lipid peroxidase), and iron (ferataxin) (Kordi, Saydi, Karami, et al., 2024).

Ferroptosis inducers can be classified into four categories, each associated with particular signaling pathways. The first category includes compounds such as erastin, which inhibit the cystine/glutamate antiporter, leading to a decrease in GSH levels and subsequent cell death. The second category encompasses agents like RSL3 and DPI7, which inhibit glutathione peroxidase 4 (GPX4), resulting in heightened lipid peroxidation. The third category, represented by FIN56, targets GPX4 and diminishes coenzyme Q10 levels, thereby increasing cellular vulnerability to ferroptosis. The fourth category includes compounds like FINO2, which inactivate GPX4 through the oxidation of unstable iron. Additionally, specific inhibitors, nanoparticles, and compounds such as ferostatin-1, lipoxastatin-1, vitamin E, and iron scavengers have shown promise in preventing ferroptosis, suggesting potential therapeutic applications in desease (J. Li et al., 2020; Stockwell et al., 2017).

While iron chelators have demonstrated efficacy in preventing cell death associated with ferroptosis, their potential toxicity limits their clinical application. Inhibitors of ferroptosis include lipooxygenase inhibitors, which specifically target the accumulation of lipid peroxides within cells during this form of cell death. The oxidation of various lipids, including fatty acids, phospholipids, and cholesterols, is believed to significantly contribute to the ferroptotic process, with unsaturated fatty acids serving as potential inhibitors (Kagan et al., 2017). Antioxidants such as alpha-tocopherol, along with synthetic agents like tetrahydro naphthyridine (THNs), have demonstrated efficacy in interrupting the oxidation chain reaction associated with various

diseases. Additionally, compounds like liproxstatin and frustatins are recognized as potent inhibitors of ferroptosis, showing promise for clinical application. Furthermore, inhibitors of the acyl-CoA synthetase-4 (ACSL4) enzyme, such as thiazolidinediones, present a novel strategy for mitigating ferroptosis by modulating lipid oxidation (Liang et al., 2019).

Pyroptosis: The exploration of pyroptosis (one of the types of RCDs) began in 1986 when Friedlander observed that the introduction of anthrax lethal toxin (LT) into primary mouse macrophages resulted in cell death, characterized by a rapid release of cellular components (Kordi, Azizi, et al., 2024). In 1989, Cerretti et al. and Thornberry et al. identified the interleukin-1β-converting enzyme (ICE), also known as caspase-1, recognizing its role as an inflammatory caspase that converts the precursor form of IL-1β into its active state. The landmark identification of pyroptosis occurred in 1992, when Zychlinsky et al. documented this specific type of cell death in macrophages infected with the Gram-negative bacterium Shigella flexneri (Yu et al., 2021). In 1996, Chen et al. found that the invasion plasmid antigen B (ipaB) from Shigella flexneri could directly engage with ICE, resulting in its activation within the infected macrophages (Li & Zhang, 2024).

In recent years, there has been a cross-talk between pyroptosis and apoptosis through the family of caspases, granzyme and elastase, which makes people have a more comprehensive understanding of pyroptosis. Initially, this cell death mechanism was categorized as apoptosis due to overlapping features such as caspase dependency, DNA fragmentation, and nuclear condensation. However, further studies uncovered significant distinctions between pyroptosis and apoptosis. In 2001, D'Souza et al. coined the term pyroptosis, derived from the Greek terms for fire (pyro) and falling (ptosis), to define this pro-inflammatory PCD, thereby setting it apart from the non-inflammatory nature of apoptosis (H. Wang et al., 2024). The inflammasome concept was introduced in 2002 as a crucial activator of inflammatory caspases and a processor of pro-IL-1β. Subsequently, Petr et al. revealed that non-canonical caspase-11 could induce cell death independently of caspase-1 during Salmonella infection. For a considerable time, pyroptosis was predominantly linked to caspase-1-mediated death in monocytes. Further research demonstrated that during pyroptosis, either caspase-1 or caspase-11/4/5 was activated, resulting in the cleavage of gasdermin D (GSDMD) (Kovacs & Miao, 2017). The N-terminal domain produced exhibits the ability to oligomerize, resulting in the formation of pores within the cell membrane, which ultimately leads to membrane rupture. Recent investigations have highlighted that certain elements can inhibit GSDMD-mediated pyroptosis. In particular, caspase-3/7 cleaves GSDMD at the Asp87 position, effectively inactivating its pyroptotic activity (Taabazuing et al., 2017). Additionally, the endosomal sorting co-mplexes required for transport (ESCRT) machinery can eliminate GSDMD pores from the plasma membrane, thereby preventing GSDMD-mediated pyroptotic cell death and restricting the release of IL-1β following inflammasome activation. Research conducted by Humphries et al. has shown that fumarate, a metabolite of the tricarboxylic acid cycle, can also inhibit pyroptosis. Both fumarate and dimethyl fumarate (DMF) are capable of obstructing the processing and activation of GSDMD by caspases through the succinylation of cysteine residues in GSDMD (Humphries et al., 2020). Studies by Wang et al. and Rogers et al. in 2017 revealed that chemotherapeutic agents could trigger pyroptosis by activating caspase-3, which cleaves GSDME. Following this, caspase-8 was found to induce pyroptosis and modulate inflammasome activity (Rogers et al., 2017; Wang et al., 2017). In 2020, it was discovered that granzyme B (GzmB) can cleave GSDME directly, activating pyroptosis and bolstering the antitumor immune response while inhibiting tumor proliferation (Zhang et al., 2020). That same year, granzyme A (GzmA) from cytotoxic lymphocytes was shown to enter target cells via perforin, inducing pyroptosis by hydrolyzing GSDMB at the Lys229/Lys244 site, thereby enhancing our comprehension of pyroptosis. More recently, research by Hou et al. indicated that under hypoxic conditions, activated phospho-STAT3 (p-Stat3) promotes the translocation of nuclear programmed death-ligand1 (PD-L1) (Zhou et al., 2020). The interaction between nuclear PD-L1 and p-Stat3 amplifies the expression of GSDMC, while caspase-8, activated by Tumour Necrosis Factor alpha (TNF-α) from macrophages, cleaves GSDMC at the D365 site, ultimately culminating in pyroptosis (Yu et al., 2021).

PANoptosis: Recent studies have demonstrated the interconnectedness of three types of cell death (A cross-talk between of pyroptosis, apoptosis, and necroptosis), leading to the proposal of a new concept known as PANoptosis, which encompasses all three types. Research has suggested that PANoptosis is involved in various diseases, including cardiovascular disease and infectious and tumor diseases. Therefore, it is crucial to understand the mechanism of PANoptosis to develop effective treatments for human diseases. PANoptosis is controlled by a series of upstream receptors and molecular signals that form polymeric complexes called PANoptosomes (Kordi, Sanaei, et al., 2024). This new form of cell death, proposed by Malireddi et al. in 2019, is characterized by the combination of necroptosis, apoptosis, and pyroptosis and cannot be fully explained by any of these types alone (Bertheloot et al., 2021).

Pyroptosis, a type of PCD linked to inflammation, can be controlled through training, medication, or genetic methods to benefit heart health. Targeting pyroptosis may help prevent disease by understanding its role in cell death and identifying new

treatment approaches. This process involves inflammatory proteases like caspases, causing cell rupture and releasing proinflammatory factors that increase heart disease risk (Gao & Gao, 2024).

Various antioxidants, anti-inflammatory agents, and lifestyle factors can reduce caspase-1 activity, protecting against pyroptosis. In disease, ubiquitin-specific protease 14) USP14 (stabilizes NLRP3 expression, influencing endothelial cell pyroptosis. miR-15b-5p can limit pyroptosis by targeting USP14. Adjusting USP14 levels affects pyroptosis through the NLRP3/Caspase-1/IL-1 and IL-18 signaling axes. Apoptosis, another PCD form, is regulated by proapoptotic and antiapoptotic genes like B-cell lymphoma-2) Bcl-2 (and Bax proteins, controlling mitochondrial function. Aging and illness can alter the balance of these proteins, impacting cell survival and death. Cyclophilin A plays a role in oxidative stress-induced apoptosis, revealing its potential as a biomarker and therapeutic target for diseases (Gao & Gao, 2024; Hai et al., 2022).

Necroptosis, a caspase-independent cell death mode, can be initiated by TNF with a caspase inhibitor, highlighting the importance of different regulatory molecules in cell death pathways. Upstream components like receptor interacting protein kinase1) RIPK1 (and nuclear factor kappa B) NF-kB (are involved in signaling and regulation of cell death processes. Understanding these various cell death mechanisms and their molecular pathways is crucial for developing effective treatments for diseases (Chai et al., 2024).

Anoikis: The initiation and execution of anoikis is mediated by cross-talk between a variety of signaling pathways that converge upon the activation of caspases, leading to a series of molecular events. This cascade culminates in the activation of endonucleases, resulting in DNA fragmentation and, ultimately, cell death (Paoli et al., 2013). The commencement of the anoikis (one of the types of PCDs) program is mediated by the interplay of two apoptotic pathways: the intrinsic pathway, characterized by mitochondrial dysfunction, and the extrinsic pathway, which involves the activation of cell surface death receptors. A key component of both pathways is the Bcl-2 family of proteins, which can be classified into three main categories: (i) anti-apoptotic proteins, including Bcl-2, B-cell lymphoma-extra-large) Bcl-XL (and myeloid cell leukemia sequence 1 (Mcl-1); (ii) multidomain pro-apoptotic proteins such as Bax, Bak, and Bok; and (iii) pro-apoptotic BH3-only proteins, which include Bid, Bad, Bim, Bik, Bmf, Noxa, Puma, and Hrk (Mohan et al., 2024).

The intrinsic pathway is triggered by various intracellular signals, such as DNA damage and endoplasmic reticulum stress, with mitochondria playing a crucial role in apoptosis regulation. In response to apoptotic stimuli, the pro-apoptotic proteins Bax and Bak translocate from the cytosol to the outer mitochondrial mem-brane (OMM) (Shimizu et al., 1999). Their oligomerization at this location creates a channel that leads to mitochondrial permeabilization and the release of cytochrome c. In addition to the intrinsic pore-forming function of Bax, membrane permeabilization may also occur through interactions with mitochondrial channel proteins, including voltage-dependent anion channels. The release of cytochrome c promotes the formation of the "apoptosome," which comprises caspase-9, the Apaf, and cytochrome c itself, ultimately activating effector caspase-3 and advancing the apoptotic process (S. Wang et al., 2024).

The extrinsic pathway significantly contributes to the process of anoikis, alongside the intrinsic pathway. This pathway is activated when ligands bind to members of the tumor necrosis factor receptor (TNFR) superfamily, such as the Fas receptor, TNFR1, and tumor necrosis factor-related apoptosis-inducing ligand) TRAIL (receptors 1 and 2. This binding event triggers the assembly of the death-inducing signaling complex (DISC) (Taylor et al., 2008; Wajant, 2002). Following this, DISC interacts with adaptor proteins, including the Fas-associated death domain protein (FADD), which recruits and activates multiple caspase-8 molecules. Once activated, caspase-8 is released into the cytoplasm, where it cleaves and activates effector caspases -3, -6, and -7, resulting in substrate proteolysis and ultimately leading to cell death. Additionally, the activation of caspase-8 can cleave and activate Bid, which, in its truncated form (t-Bid), promotes the release of cytochrome c from the mitochondria and the formation of the apoptosome, thereby linking the extrinsic apoptotic pathway to the intrinsic pathway (Valentijn & Gilmore, 2004). Recent studies have revealed that upon detachment from the ECM, a mitochondrial protein named Bit1 is released into the cytoplasm, acting as a pro-apoptotic mediator that initiates a caspase-independent form of apoptosis (Jan et al., 2004; Jenning et al., 2013). In some instances, the activation of the death receptor pathway may result from mitochondrial damage, highlighting the interaction between extrinsic death signals and the intrinsic pathway. Previous investigations have demonstrated that loss of anchorage to the ECM leads to an upregulation of Fas and Fas ligand, along with a downregulation of FLIP, which functions as an endogenous inhibitor of Fas-mediated signaling, emphasizing the essential role of the extrinsic pathway in anoikis. Furthermore, changes in cell morphology can also trigger extrinsic anoikis; specifically, cell rounding upon detachment may induce the "induced proximity" of Fas receptors (Aoudjit & Vuori, 2001). Changes in cell morphology are significant in the context of extrinsic anoikis; in particular, the rounding of cells upon detachment can facilitate the "induced proximity" of Fas receptors, which subsequently activates them (Gulia et al., 2023).

Eryptosis Eryptosis (one of the types of PCDs) is characterized by the reduction in cell size and the reorganization of the cell

membrane, a process initiated by the influx of calcium ions through Ca (2+) permeable cation channels that are activated by prostaglandin E2 (PGE2). This phenomenon is influenced by various factors such as ceramide, caspases, calpain, complement, hyperosmotic stress, energy depletion, oxidative stress, as well as cross-talk and the relationship between the activity of several kinases such as AMPK, GK, p21-activated kinase 2 (PAK2), Ck1 alpha (Casein kinase 1α), Janus kinase 3 (JAK3) and Protein Kinase C (PKC) (Pretorius et al., 2016). The underlying mechanism operates as follows: hyperosmotic stress, energy depletion, or the removal of extracellular chloride ions activates non-selective Ca^{2+}-permeable cation channels in the cell membrane, resulting in elevated intracellular calcium levels. Furthermore, subnanomolar concentrations of PGE2 can activate calpain, leading to the degradation of ankyrin-R. PGE2 is produced from membrane phospholipids through the sequential actions of Ca^{2+}-independent phospholipase A2 (PLA2), cyclooxygenase (COX), and PGE-synthase. The removal of chloride ions triggers the synthesis of PGE2 and the activation of COX, which subsequently generates arachidonic acid and activates membrane Ca^{2+}-channels. Oxidative stress also plays a role in the opening of these Ca^{2+} channels (Lang et al., 2005). During osmotic stress, the shrinkage of red blood cells (RBCs) is a consequence of calcium influx. The rise in cytosolic calcium activates calcium-sensitive potassium channels, leading to the efflux of KCl and subsequent cell shrinkage. Similarly, energy depletion promotes calcium entry, which stimulates sphingomyelinase to produce ceramide (Rotordam, 2021). The presence of calcium and ceramide activates a scramblase, resulting in the exposure of PS and the disruption of membrane asymmetry. Elevated intracellular calcium levels also activate μ-calpain, which degrades cytoskeletal components such as the ankyrin R complex, culminating in membrane blebbing. The exposure of PS is associated with stressed RBCs and may also be induced by PGE2 from various sources (Muravyov & Tikhomirova, 2013).

Crosstalk between cell death pathways

The aforementioned modalities of cell death are characterized by specific causes and unique morphological alterations throughout the cell death processes. However, the signaling molecules that activate these pathways frequently exhibit interconnections due to their pleiotropic characteristics (Ai et al., 2024). For instance, RIPK1 plays a crucial role in mediating both apoptosis and necroptosis in a kinase-dependent fashion, while also acting as an adaptor protein that facilitates apoptosis through the conformational activation of RIPK3. The release of cytochrome c from the mitochondria triggers apoptosis, and the subsequent disruption of the mitochondrial electron transport chain (ETC) leads to the generation of ROS, which may further promote ferroptosis (Karki et al., 2021). Common chemotherapy agents are known to induce apoptosis via caspase-9 and activate GSDME, thereby initiating pyroptosis. The combination of TNF-α and IFNγ, or pathogen-associated molecular patterns (PAMPs), can even elicit a hybrid form of cell death termed "PANoptosis," which involves the concurrent activation of pyroptosis, apoptosis, and necroptosis. Moreover, IFNγ has been shown to facilitate ferroptosis by downregulating the expression of SCL7A11 and SLC3A2, key components of the anti-ferroptosis system xc−-glutathione-GPX4 axis. Additionally, the endosomal sorting complex required for transport-III (ESCRT-III) plays a significant role in membrane remodeling and scission, regulating various cell death modalities by aiding in the shedding and repair of MLKL, GSDMD, and plasma membranes damaged by peroxidized lipids, thereby influencing the kinetics of cell death (Ai et al., 2024).

PCD and aerobic training

Autophagy and aerobic training: Exercise has been identified as a key driver of autophagy in vivo, with research dating back to 1984, showcasing a growing interest in this field. Studies have shown that physical activity activates autophagy in skeletal muscle, aiding in the removal of damaged structures post-exercise. Human subjects undergoing ultra-endurance exercise displayed elevated levels of autophagy-related genes and proteins in muscle samples. Exercise poses challenges to cellular integrity, triggering intracellular proteases and ROS production. Autophagy is crucial for maintaining cellular health and energy balance during and after exercise. Notably, BCL2AAA mice lacking stimulus-induced autophagy displayed altered glucose metabolism and reduced exercise capacity during acute physical activity (He et al., 2012; Mooren & Krüger, 2015).

There is conflicting evidence regarding the relationship between exercise-induced autophagy and metabolic processes. Some studies suggest that autophagy enhances fat metabolism, glucose regulation, and insulin sensitivity in models of diet-induced obesity, while others report conflicting findings. Recent research has indicated that autophagic activity is influenced by exercise intensity and nutritional status; increased exercise intensity and fasting have been associated with heightened autophagic flux. Studies on resistance exercise have shown mixed results, with some reporting diminished autophagy following resistance training, while others have found increased autophagic activity (Kim et al., 2012; Schwalm et al., 2015).

Chronic exercise training has been shown to impact autophagy-related proteins in a variable manner, with some studies reporting significant changes while others show no alterations. The response of the autophagic system is dependent on factors such as muscle fiber type and oxidative phenotype. For instance, young mice exhibited downregulated expression of certain autophagy-related proteins after aerobic exercise training, while

aged mice showed an upregulation. Additionally, autophagy-related gene 6 (Atg6)-deficient mice experiments indicate that autophagy is crucial for skeletal muscle adaptations and aerobic performance in response to endurance exercise (Lira et al., 2013). Furthermore, chronic resistance training has been linked to increased autophagic activity, reflected in elevated levels of autophagy regulatory proteins. Upregulated signaling pathways such as AMPK and FOXO3 were associated with reduced muscle apoptosis. The effects of exercise on autophagy are complex and dependent on various factors such as exercise type, intensity, and duration. More research is needed to fully understand the intricate relationship between exercise and autophagy and its implications for metabolic health and physical performance (Luo et al., 2013; Mooren & Krüger, 2015).

It is a well-established fact that lipids are the main energy substrate utilized in aerobic activities. In cells, triglycerides are stored in lipid droplets. During aerobic training and nutrient starvation, these triglycerides are broken down by cytosolic lipases into glycerol and free fatty acids (FFAs), which provide energy for ATP production through glycerol-phosphate shuttle and β-oxidation. Recent studies have indicated that autophagy contributes to the breakdown of lipid droplets. During starvation, lipid droplets are taken up by autophagosomes and sent to lysosomes, where lysosomal acid lipases degrade the lipids. Blocking autophagy can lead to the buildup of triglycerides in cells and lower ATP production because of fewer FFAs available for β-oxidation (Kim & Lee, 2014; Koga et al., 2010). Recent research has shown that a chronic high-fat diet (HFD) or obesity can impair autophagy in different cells and tissues. This can occur by blocking autophagosome formation and fusion with lysosomes or harming lysosomes. When autophagy is inhibited in the liver, it can lead to increased fat storage and endoplasmic reticulum (ER) stress, resulting in hepatic steatosis and insulin resistance. Interestingly, a study found that in HFD-fed liver-specific Atg7-knockout mice, liver fat content did not increase, possibly due to non-cell-autonomous effects of autophagy deficiency (Inami et al., 2011).

Conversely, autophagy activity appears higher in the adipose tissue of obese individuals, potentially due to reduced mTOR signaling or increased autophagy-related gene expression. Inhibition of autophagy can raise inflammatory cytokines in adipose tissue, suggesting a protective role against obesity-related inflammation and insulin resistance. However, further investigation is needed to better understand autophagy's role in inflammation and insulin resistance without the complications from developmental defects in specific knockout mouse models (Inami et al., 2011; Kim & Lee, 2014; Koga et al., 2010; Las et al., 2011).

Necrosis and aerobic training

The manner of death resembling necrosis is linked to ATP depletion and has a strong association with mitochondrial function (Sun et al., 2018). Aerobic glycolysis is notably less effective than oxidative phosphorylation in ATP production, yielding approximately 4 mol ATP per mol glucose compared to 36 mol ATP. Additionally, research has demonstrated significant glucose oxidation in glioma cells. Mitochondria serve as the primary organelles for the elimination of ROS, and any impairment in mitochondrial function diminishes the cells' capacity to manage ROS levels (Lai et al., 2018). The overproduction of ROS can be detrimental, potentially leading to necrosis in human embryonic stem cells. Within the antioxidative defense system, GSH plays a pivotal role in the detoxification of ROS (Marí et al., 2009). GSH necessitates continuous replenishment, with NADPH being crucial for its regeneration during cellular responses to oxidative stress, thereby promoting the survival of diseased cells. NADPH plays a crucial role in the synthesis of fatty acids, and a decline in the aerobic respiration capabilities of mitochondria results in reduced NADPH production. In our investigation, we observed an upregulation of ROS alongside a downregulation of GSH and NADPH, indicating compromised mitochondrial function. Notably, N-acetylcysteine (NAC) did not prevent cell viability or ATP depletion, suggesting that the death of glioma cells was not a consequence of ROS overexpression but rather a result of ATP depletion. Both MEK and ERK are significantly localized to the mitochondria, and the inhibition of ERK activity leads to an early and substantial reduction in cellular ATP levels. Targeting MEK to inhibit ERK1/2 activation presents a promising approach in cancer therapy. The ERK inhibitor U0126 was employed to assess the impact of ERK on T98G cells. Additionally, the inhibition of ERK resulted in increased glycogen synthase kinase-3 beta (GSK-3β) activity, while GSK-3β inhibition offered protection against the opening of the permeability transition pore (PTP), potentially safeguarding compromised cells from death. Furthermore, the viability of cells was restored by indomethacin (IND) (Gailhouste et al., 2010; Monick et al., 2008; Yung et al., 2004). The findings indicated that the inhibition of ERK protein led to a suppression of mitochondrial aerobic respiration, which significantly decreased ATP levels and ultimately caused glioma cell death through a non-canonical necrotic pathway. Non-apoptotic cell death mechanisms, due to their ability to bypass traditional anti-apoptotic resistance, hold considerable promise for anti-cell death strategies. Additionally, the pharmacological inhibition of mitochondrial metabolism is emerging as a viable therapeutic approach to counteract cell death (Diederich & Cerella, 2016; Jaber et al., 2016; Maleki et al., 2018; Rasola et al., 2010).

Apoptosis and aerobic training: Aerobic training has been demonstrated to initiate apoptosis via both intrinsic and extrinsic signaling pathways. Studies reveal that in peripheral human lym-

-phocytes, activities such as intensive treadmill running, marathon running, and vigorous exercise lead to an upregulation of CD95 receptors and their corresponding ligands (Krueger et al., 2003). Furthermore, research involving intestinal lymphocytes indicates that aerobic training also activates the intrinsic apoptosis pathway. This pathway is marked by mitochondrial membrane depolarization, an increase in cytosolic cytochrome c, and a significant reduction in Bcl-2 protein levels following aerobic exercise. The factors that mediate exercise-induced apoptosis are currently under thorough investigation (Phaneuf & Leeuwenburgh, 2001). It is widely recognized that intense physical activity affects the balance between the production of free radicals and their neutralization by antioxidant systems. ROS are crucial in modulating specific apoptotic pathways (Saydi et al., 2024), as they can lower, cellular Bcl-2 levels and induce depolarization of the OMM. Additionally, ROS may connect the intrinsic and extrinsic apoptosis pathways by promoting Fas expression. Glucocorticoids are also known to induce apoptosis in monocytes, macrophages, and T cells through their binding to intracellular glucocorticoid receptors. The initial stage of glucocorticoid-induced apoptosis is characterized by mitochondrial dysfunction, which is subsequently followed by the release of cytochrome c into the cytosol. The later phases of this apoptotic process involve the activation of the caspase cascade (Cai et al., 1998).

The phenomenon of cellular "self-destruction" observed during apoptosis exhibits notable parallels with the "self-eating" processes characteristic of autophagy. Consequently, the interplay between these two degradation mechanisms warrants significant investigation. Both autophagy and apoptosis can be triggered by analogous stress signals, and both are similarly regulated by BCL-2, which possesses both anti-autophagic and anti-apoptotic properties. It is important to note that the anti-autophagic influence of BCL-2 relies on a functional apoptotic signaling pathway that includes pro-apoptotic proteins such as BAX and BAK. In contrast, proteins associated with autophagy, including Beclin-1, Atg 5, 7, and 12, play a role in the modulation of apoptosis. It can be hypothesized that during physical exercise, these two processes collaborate to achieve common objectives—namely, minimizing tissue damage and restoring cellular integrity—albeit potentially activated at different thresholds. Autophagic pathways are likely to be initiated shortly after exercise due to the presence of altered proteins and organelles, aiming to conserve and recycle cellular resources. When cells become overwhelmed with damaged molecules, the repair mechanisms may become insufficient, leading to the induction of apoptosis. Nevertheless, both autophagy and apoptosis appear to contribute to the adaptive response to exercise, with autophagy facilitating local conditions conducive to muscle plasticity and apoptosis mobilizing stem and progenitor cells on a systemic level. Following exercise training, the upregu-

-lation of ROS defense systems and autophagic machinery seems to represent adaptive responses that mitigate the release of damaged proteins and organelles, ultimately resulting in a reduction of exercise-induced apoptosis, as evidenced by recent findings (Krüger & Mooren, 2014; Mooren & Krüger, 2015).

Research findings regarding the impact of regular exercise on anti-apoptotic and pro-apoptotic factors are inconsistent. Nonetheless, it can be generally asserted that regular aerobic exercise tends to lower certain apoptosis-related factors. Other beneficial effects of consistent exercise include an increase in the ADP to ATP ratio, suppression of BAX gene production, and enhancement of Bcl-2 synthesis. Additionally, methamphetamine consumption is known to elevate tumor necrosis factor alpha and inflammatory cytokines. The release of tumor necrosis factor alpha occurs one hour after methamphetamine intake, while interleukin 6 levels rise 24 hours later, indicating that the former may stimulate the latter's release. In contrast, aerobic exercise is associated with a reduction in tumor necrosis factor alpha, likely due to its modulatory effects on the nervous and hormonal systems. Moreover, aerobic physical activity promotes an increase in interleukin 10 gene expression, leading to a decrease in pro-inflammatory factors, including tumor necrosis factor alpha and interleukin 6, as well as their gene expression in the heart (Kazemipour et al., 2022).

Cuproptosis and aerobic training: Regular moderate aerobic training positively impacts cellular adaptations to oxidative stress by upregulating antioxidant enzymes like NF-kB and heat shock proteins (HSPs), inhibiting inflammatory mediators. This boosts GSH production, enhancing resistance against oxidative reactions (Kruk, 2011). Exercise elevates sex hormone binding globulin (SHBG) levels, reduces inflammation, and lowers glucose, insulin, and toxic Quinone levels. It prevents age-related muscle loss by improving mitochondrial plasticity and oxidative stress responses and treats various diseases. Studies show exercise improves the pro-oxidant/antioxidant balance, boosts the antioxidant system, and enhances LDL resistance to oxidation (Joseph et al., 2016; Kruk et al., 2015). Research on physical activity's impact on oxidative stress measures free radicals, ROS/RNS, enzymatic antioxidants, GSH/GSSG ratio, vitamins levels, lipid peroxidation, protein modification, and DNA modification. Studies found increased free radicals and lipid peroxidation post-exercise. New methods are being developed to identify redox status biomarkers. Regular, moderate-intensity physical training can help prevent obesity-related redox responses before and after exercise, leading to a temporary pro-inflammatory response followed by an anti-inflammatory effect. Exercise can also upregulate the antioxidant defense system and decrease oxidative damage in the body (Bouzid et al., 2018; Friedenreich et al., 2016). Trained individuals are less likely to experience cellular homeostasis disruption towards ROS during intense exercise compared to untrained individuals. Muscle ada-

-ptation to exercise involves increased expression of antioxidant genes, offering protection against oxidative stress (Kordi, Saydi, Azimi, et al., 2024; Shafiee et al., 2023).

Research has shown a significant focus on developing new methods to identify biomarkers and indicators of redox status in body fluids and tissues. Physical exercise interventions varied in aerobic training intensity, duration, frequency, experience, and gender. Studies also showed that endurance training can reduce exercise-induced increases in tricarboxylic acid cycle intermediates without affecting endurance capacity. Endurance-trained individuals have reduced ubiquitin-proteasome signaling activation in skeletal muscle. Oxidative stress and redox imbalance can impact satellite cell functionality, potentially contributing to skeletal myopathy. Sedentary individuals may have reduced insulin-like growth factor 1 (IGF-1) signaling in skeletal muscle, affecting satellite cell activation and muscle regeneration. These findings underline the complex relationship between physical training, molecular muscle responses, and the impact of oxidative stress on muscle function, emphasizing the importance of regular exercise in maintaining muscle health and function (Goguet-Rubio et al., 2016; H. Li et al., 2020; Zhang et al., 2022).

The adaptability of limb muscles is evident as they rapidly adjust and enhance their functionality when animals resume normal movement after extended periods in low-gravity environments. this process, termed reloading, likely instigates muscle remodeling and amplifies the activity of the ubiquitin-proteasome pathway. Research by Taillandier et al. (2003) on rat muscles subjected to reloading revealed that after 18 hours, there was a significant increase in ubiquitin-conjugated protein levels (Taillandier et al., 2003). Furthermore, mRNA levels for ubiquitin and two proteasome subunits were elevated, while E2–14k mRNA levels showed a decline. Notably, after 7 days of unloading, mRNA levels returned to baseline, although ubiquitin conjugates remained elevated. These changes in molecular markers were correlated with a sustained increase in protein synthesis rates during the reloading process (Willoughby et al., 2000; Willoughby et al., 2002; Willoughby et al., 2003). The authors concluded that both increased degradation and synthesis are critical for muscle remodeling following reloading, with the regulation of pathway elements enabling more efficient targeting of proteins for degradation (Kee et al., 2002).

Ferroptosis and aerobic training: Engaging in physical activity in adults can lead to a decrease in the body's iron stores, which are linked to various health issues like cancer, neurological disorders, arteriosclerosis, and specific cardiovascular diseases. Hemojuvenin (Hjv) is a protein that plays a role in activating the BMP/SMAD signaling pathway, promoting hepcidin expression. Inflammation, injures and elevated iron levels contribute to hepcidin upregulation, while hepcidin levels decrease over time (Mleczko-Sanecka et al., 2010). There is a positive relationship between post-exercise hepcidin levels and blood ferritin concentrations. Additionally, inflammation induces the expression of the hepcidin antimicrobial peptide (HAMP) gene, encoding hepcidin, showcasing the impact of inflammation on hepcidin fluctuations. The interaction between hepcidin and iron absorption can reduce iron stores, potentially serving as an anti-inflammatory hormone. Research suggests a significant relationship between c-reactive protein (CRP) and blood ferritin levels before and after exercise, indicating a potential reduction in systemic inflammation in older adults. Vitamin D levels may also influence iron metabolism (Kortas et al., 2015). Physical activity can impact iron levels and hepcidin expression in older adults, potentially influencing inflammation and overall health outcomes. Further research is needed to fully understand the biological mechanisms underlying these interactions (Andrews, 2004).

Aerobic training impacts muscle protein metabolism by boosting muscle protein synthesis in both fed and fasted states. Prolonged aerobic training enhances muscle protein synthesis even during periods of inactivity, albeit mainly affecting mitochondrial proteins more than myofibrillar proteins. After aerobic exercise, myofibrillar protein synthesis increases, leading to improvements in muscle strength and size. However, the efficacy of aerobic training in increasing muscle mass in the elderly depends on muscle responsiveness to insulin's anabolic effects. The mammalian target of rapamycin complex 1 (mTORC1) signaling pathway, activated post-aerobic exercise, plays a crucial role in regulating muscle protein metabolism, evidenced by an increase in pMTC1 (Ser2448) levels. Aerobic training also elevates peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1α) and PGC1β mRNA expression, signaling rapid adaptive mechanisms preceding mitochondrial biogenesis (Benziane et al., 2008; Camera et al., 2010; Mascher et al., 2007). Aerobic training stimulates plasma protein production, particularly fibrinogen, in both younger and older individuals. Age does not seem to impact leg blood flow response to moderate-intensity aerobic exercise. High-intensity aerobic training increases albumin synthesis, especially with higher plasma volume and total content. Fibrinogen synthesis post-exercise may act as a compensatory mechanism in response to physical stress. Lastly, protein breakdown during exercise leads to the initial release of nitrogen from muscles, emphasizing the importance of adequate protein intake for muscle recovery and growth. Adipose tissue undergoes significant changes as individuals age, becoming a crucial endocrine organ that influences insulin resistance, metabolic dysfunction, and inflammation. The ratio of body fat to weight rises with age, with obesity more prevalent in older adults compared to younger individuals. Changes in subcutaneous and visceral fat in older adults may contribute to metabolic syndrome and reduced insulin

sensitivity (Egan et al., 2010; Wright et al., 2007).

Regular physical activity reduces the risk of age-related metabolic disorders by decreasing cardiovascular diseases and type 2 diabetes. It can positively impact metabolic changes in older adults, including reducing fat in both subcutaneous and visceral areas. Endurance training improves fatty acid oxidation in older adults without affecting fatty acid availability or lipolysis significantly, indicating a shift in muscle fatty acid metabolism with exercise and changes in lipolysis in adipose tissue. Aerobic training enhances the oxidation of long-chain and medium-chain fatty acids, improving muscle metabolism and insulin sensitivity. While the impact of aerobic or resistance training on obesity in adults remains unclear, consistent physical activity in individuals can increase mitochondrial content in adipose tissue. Additionally, aerobic training can inhibit ferroptosis through modifications in iron, amino acids, and lipids. In sum, physical activity plays a crucial role in improving metabolic health in adults, even though the effects on fat metabolism (Gillen et al., 1991; Imoberdorf et al., 2001; Koch & Röcker, 1977; Proctor et al., 2003).

Pyroptosis and aerobic training: Aerobic exercise has been shown to play a crucial role in preserving cellular function (Hu et al., 2022; Kourek et al., 2021). Importantly, it has the potential to significantly mitigate cellular dysfunction and lower the likelihood of developing cardiovascular diseases (Neunhäuserer et al., 2021). Research indicates that aerobic exercise enhances blood circulation and laminar shear stress while simultaneously decreasing leukocyte adhesion (Yue et al., 2021), which in turn diminishes inflammation risk and bolsters the antioxidant enzyme system and immune responses. Numerous studies have established that aerobic exercise can inhibit pyroptosis in endothelial cells (J. Lee et al., 2018). Specifically, Lee et al. (2018) demonstrated that voluntary running reduces the activation of the NLRP3 inflammasome within the endothelial cells of coronary arteries. Their research further indicated that aerobic exercise enhances cellular function by suppressing NLRP3 inflammasome signaling (J. Lee et al., 2018). Additional investigations have reported that a treadmill exercise regimen lasting over 12 weeks can decrease pyroptosis in endothelial cells associated with arteriosclerosis (Hong et al., 2018; Hong et al., 2021).

A growing body of evidence underscores the critical role of the NLRP3 inflammasome in the inflammatory process (Y. Wang et al., 2016). Within cells, NLRP3 inflammasomes can be activated by various stimuli and are implicated in cellular pathology (Lee et al., 2020). Factors such as oxidative stress, mitochondrial dysfunction, and lysosomal rupture have been identified as activators of NLRP3 inflammasomes (Hoseini et al., 2018), which are key initiators in the progression of vascular diseases.

Furthermore, oxidized low-density lipoprotein (ox-LDL) and cholesterol crystals trigger the activation of nuclear factor-κB (NF-κB) and the secretion of TNF-α (Steyers & Miller, 2014). Subsequently, the activated NF-κB influences NLRP3 signaling, thereby contributing to the pathogenesis of atherosclerosis (Hoseini et al., 2018). The activation of the NLRP3 inflammasome has been shown to enhance the expression and secretion of high-mobility group box 1 (HMGB1) in endothelial cells (Lee et al., 2020), which contributes to increased endothelial hyperpermeability and subsequent endothelial dysfunction (Bagherzadeh-Rahmani et al., 2023; L. Wang et al., 2016; Y. Wang et al., 2016). Numerous studies indicate that engaging in aerobic exercise can effectively mitigate inflammation by suppressing the NLRP3 inflammasome, HMGB1, and their associated downstream effects (Goh & Behringer, 2018; Heidari et al., 2016; Kar et al., 2019; Lee et al., 2020).

Aerobic training has the potential to mitigate pyroptosis and lipotoxicity. This effect may be attributed to alterations in PPARγ signaling pathways. Furthermore, exercise appears to confer protective benefits by decreasing levels of inflammatory cytokines, including IL-1β, enhancing the production of antioxidants, and diminishing autophagy processes (Kar et al., 2019). Mitochondrial impairment and heightened inflammation are known to trigger pyroptosis. Research indicates that certain elements of the NLRP-1 inflammasome, including caspase-1 and its activation through caspase-1, exhibit decreased levels following physical training. Engaging in regular exercise diminishes the baseline activity of the inflammasome, leading to a reduction in caspase-1 activity and subsequently lowering the release of IL-β and IL-18 (Kordi, Azizi, et al., 2024).

PANoptosis and aerobic training: Aerobic training helps prevent cell death by suppressing NLRP3 inflammasome activation, a key factor in desease development. Aerobic training decreases oxidative stress and NLRP3 expression, potentially benefiting health (Li et al., 2022; Qiao et al., 2021). Training can reduce apoptosis in cardiac and skeletal muscles, with varying effects on Bcl-2 expression. Studies show a decrease in apoptosis extent and caspase-9 levels with exercise duration, although there is inconsistency in Bcl-2 response (Akbar et al., 2023). Notably, exercise can reduce Bax expression in trained muscles, emphasizing its potential to inhibit pyroptosis and attenuate apoptosis for cardiovascular and muscle health. Overall, these findings highlight the importance of physical activity in promoting cardiovascular health and skeletal muscle function (Kwak et al., 2011).

Necroptosis, a form of controlled necrotic cell death, is being investigated as a potential target for cardiovascular diseases, particularly age-related disease. Studies induced by calcium chl-

-oride and acetylcholine (CaCl2-Ach) have shown that inhibiting necroptosis with Nec-1 reduced atrial fibrillation (AF) burden and atrial remodeling (C. Li et al., 2020). Necroptosis has been linked to fibrosis in various conditions, including lung fibrosis, indicating its involvement in cardiovascular disease development (Wang et al., 2023). Research has extensively examined the relationship between necroptosis and atrial remodeling in diseases, with evidence supporting the presence of inflammation and fibrosis in these patients. The upregulation of necroptosis, inflammation, and fibrosis is common in elderly populations, highlighting necroptosis as a potential mechanism for age-related disease. Metabolic syndrome, particularly insulin resistance, also contributes to disease development (J. M. Lee et al., 2018).

Compensatory fibroblast proliferation in response to cell loss from necroptosis helps maintain tissue balance. However, necroptotic cells can trigger inflammation and fibrosis, leading to myocardial fibrosis in severe cardiac conditions. Studies show a link between necroptosis, inflammation, and fibrosis in patients, with this process being commonly observed in the elderly. Exercise may reduce cardiac apoptosis and necrosis by targeting necroptosis, with high-intensity interval training preventing cardiac remodeling and aerobic training inhibiting necroptotic signaling in unhealthy mice induced by CaCl2-A (Fu et al., 2021; J. M. Lee et al., 2018; Wang et al., 2023).

Anoikis, Eryptosis and aerobic training: No study was found regarding the effect of aerobic exercise on Anoikis and Eryptosis. It seems that due to the effect that aerobic exercise has on Bax, Bak, and Bok factors; and (iii) pro-apoptotic BH3-only proteins, which include Bid, Bad, Bim, Bik, Bmf, Noxa, Puma, and Hrk, as well as PGE2, AMPK, GK, PAK2, Ck1 alpha, JAK3, and PKC. Probably, this peak of activity can modulate Anoikis and Eryptosis (Tkachenko, 2024) (refer to the sections Apoptosis and aerobic training and Autophagy and aerobic training). However, investigation of aerobic activity pathway or cell death pathways requires more studies.

Mitochondria serve as the primary organelle responsible for the elimination of ROS, and any dysfunction within these organelles can significantly impair cellular capacity to manage ROS levels (Kim & Lee, 2014; Kotoulas et al., 2006; Kroemer et al., 2010). The excessive production of ROS is detrimental and has been associated with oncosis in human embryonic stem cells. Within the antioxidative framework, GSH is pivotal for the detoxification of ROS. The maintenance of GSH levels necessitates continuous replenishment, with NADPH playing a crucial role in its regeneration during the cellular response to oxidative stress, thereby facilitating the survival of cancer cells (Singh & Cuervo, 2012). Additionally, NADPH is vital for the synthesis of fatty acids, and any disruption in mitochondrial aerobic respiration can lead to a reduction in NADPH production. In our investigation, we observed an upregulation of ROS alongside a downregulation of GSH and NADPH, indicating compromised mitochondrial function. However, the application of NAC did not prevent cell viability or ATP depletion, suggesting that glioma cell death was not a direct consequence of ROS overproduction but rather a result of ATP depletion (Kim & Lee, 2014; Onodera & Ohsumi, 2005). Figure 2 shows the effect of aerobic exercise on changes

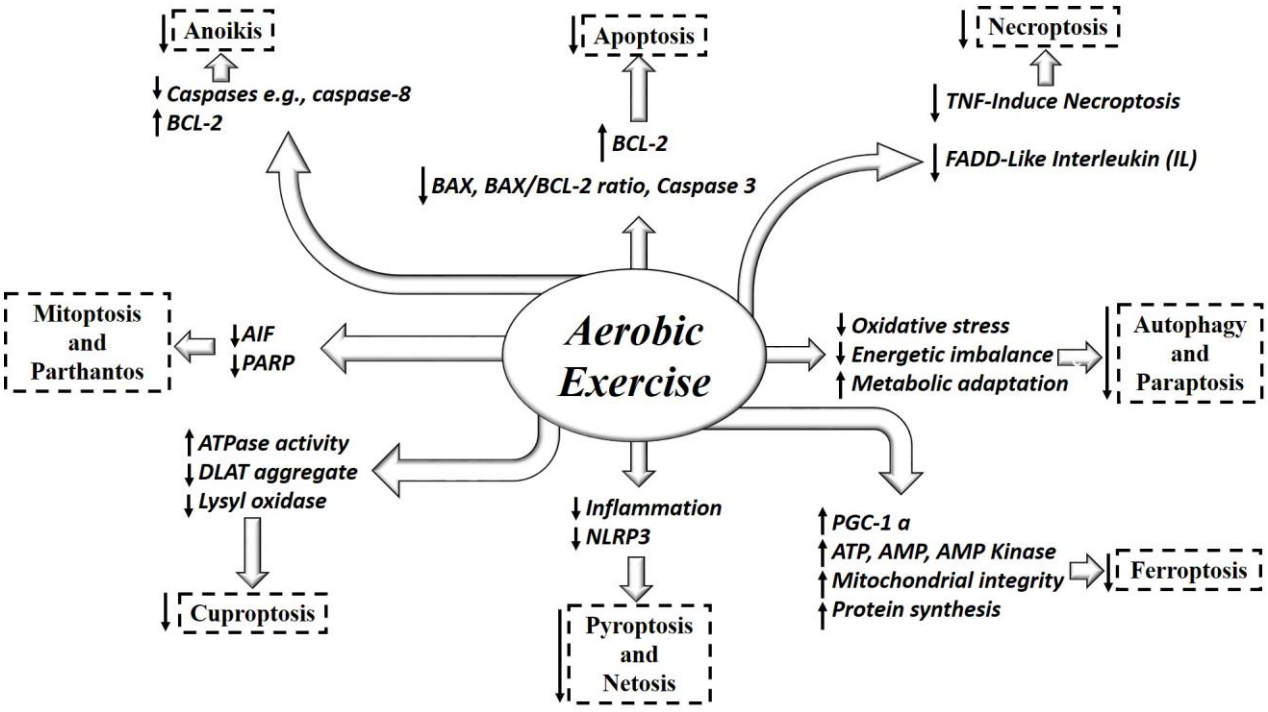

Figure 2. The effect of aerobic exercise on changes in cell death types

in types of cell death.

Conclusion

Aerobic exercise serves as an anti-inflammatory agent, influencing the balance between cellular autophagy and apoptosis, as well as modulating immune function through the regulation of specific mechanisms and the activation of certain cytokine signaling pathways. Several novel avenues warrant further investigation: assessing whether newly identified cytokine subgroups affect the beneficial impacts of aerobic exercise on compromised cells; tailoring exercise regimens based on the dual effects of specific cytokines at various stages of tissue damage; and exploring how the duration and intensity of exercise influence the proliferation of unhealthy cells. The phenomenon of cellular "self-destruction" in apoptosis bears resemblance to the "self-eating" process observed in autophagy, suggesting a need for deeper exploration of their interrelationship. Both processes can be triggered by analogous stress signals and are modulated by BCL-2, which exhibits both anti-autophagic and anti-apoptotic functions. The anti-autophagic role of BCL-2 is contingent upon an apoptotic signaling pathway that involves pro-apoptotic proteins such as BAX and BAK, while proteins associated with autophagy, including Beclin-1, Atg 5, 7, and 12, play a role in the modulation of apoptosis. These mechanisms likely work in concert during physical activity to safeguard tissues and maintain cellular integrity, albeit they may be activated at different thresholds. Autophagy is typically initiated following exercise to recycle cellular components; however, if the repair processes become overwhelmed, apoptosis may be triggered. Both autophagy and apoptosis are integral to the adaptive response to exercise, with autophagy facilitating muscle plasticity and apoptosis aiding in the mobilization of stem cells. Post-exercise, enhanced defenses against ROS and the upregulation of autophagic processes diminish the release of damaged molecules, resulting in a reduction of exercise-induced apoptosis.

Recent research has emphasized the role of elevated iron levels in causing various diseases, such as cardiovascular conditions, in both animal models and humans. Ferroptosis has been identified as a key factor in disease progression, with inhibitors like frustatin-1 and dexrazoxane showing promise in preventing cell death. Inhibiting ferroptosis is seen as a potential therapeutic approach in clinical settings to prevent cellular damage. Lipid peroxidation is a central mechanism in ferroptosis, with radical scavenging antioxidants considered effective inhibitors. New inhibitors targeting the ACSL4 enzyme are also being explored. Moreover, the inhibition of other cellular processes like glutaminolysis and lysosomal function may suppress ferroptosis, although their effectiveness remains uncertain. Certain factors like p53 influence both ferroptosis and apoptosis, but ferroptosis operates independently of other cell death pathways. Identifying novel molecular targets related to ferroptosis has become a focus of research, particularly in preventing cardiac cell death, which could be a valuable therapeutic strategy for managing diseases in the elderly. Aging affects lipid, amino acid, and iron metabolism, potentially leading to increased ferroptosis levels. Engaging in regular exercise can positively impact metabolic processes and reduce the risk of conditions like metabolic syndrome and cardiovascular diseases among older individuals. Exercise may help mitigate ferroptosis by influencing hormonal balance, enhancing antioxidants, and improving blood circulation. Studies have shown that long-term aerobic training can improve blood fluidity and circulation, making it advisable for older adults to participate in such activities at suitable intensities to reduce cell death and ferroptosis.

Current understanding of cuproptosis suggests that copper buildup, abnormal protein oligomerization, and reduced iron-sulfur cluster protein levels contribute to a protein-toxic stress response, potentially linked to diseases like cardiovascular conditions. Despite research efforts, a clear molecular biological expression pattern for cuproptosis remains elusive. Identifying these patterns could aid in disease diagnosis and treatment, as inhibiting cuproptosis may offer therapeutic benefits. Known inhibitors include ammonium tetrathiomolybdate (VI) and DL-penicillamine. Additionally, regulating lipoyl proteins and ferritin may protect against cuproptosis. Physical training has been shown to modify oxidative stress and inhibit cuproptosis, though the exact mechanisms are not fully understood, necessitating further exploration. Various stimuli can activate different signaling pathways in cells, influencing death pathways. The cell's state determines the speed of cell death, with factors like cellular stress impacting the choice of death pathway, such as pyroptosis or apoptosis. The interaction between pyroptosis, apoptosis, and necroptosis can lead to PANoptosis, which involves specific death genes and molecules. PANoptosis plays a significant role in disease pathogenesis and presents new treatment perspectives. Regular physical activity and exercise have been shown to prevent and treat various diseases, particularly heart conditions, by reducing inflammation, promoting anti-apoptotic and anti-pyroptosis factors, and decreasing apoptosis and pyroptosis occurrence, highlighting the importance of exercise in managing cardiovascular diseases.

In general, it seems that the emergence of a specific type of cell death in an organism may lead to dysfunction or the onset of cell death in other organs. Aerobic training can play a crucial role in preventing cell death by regulating homeostasis, curtailing inflammation, reducing oxidative stress, and enhancing both anti-inflammatory and antioxidant responses.

What is already known on this subject?

So far, several cell death pathways have been identified with va-

factors contributing to this cell death. Although the positive effects of physical activity on inflammation, the antioxidant system, etc. have been identified, it is still unknown whether physical activity can actually reduce cell death.

What this study adds?

Research indicates that aerobic exercise can lower the incidence of programmed cell death by interacting with inflammatory and antioxidant systems, along with other biological processes. However, the implications of different types of exercise are not yet fully elucidated. This complexity renders exercise a double-edged sword, fostering ongoing discussions about its efficacy and safety.

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