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REVIEW

Programmed Cell Death in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic, progressive, systemic autoimmune disease characterised by synovial inflammation, synovial pannus formation and subsequent destruction of articular cartilage and bone. Programmed cell death (PCD), encompassing apoptosis, autophagy, pyroptosis, necroptosis, and ferroptosis, plays a pivotal role in the pathogenesis of RA. An imbalance in PCD causes a variety of immune cells to release large amounts of inflammatory factors and mediators that exacerbate not only chronic synovial inflammation, but also bone and joint damage. The purpose of this article is to review the relevant studies between PCD and RA, with the aim of providing further insights and considerations for a deeper understanding of the pathogenesis of RA and to guide clinical management.

Keywords: rheumatoid arthritis, apoptosis, necroptosis, pyroptosis, autophagy, ferroptosis

Introduction

Rheumatoid arthritis (RA) is a typical chronic, progressive, systemic autoimmune disease characterised mainly by synovial inflammation and synovial pannus formation, which leading to the destruction of articular cartilage and bone. According to studies, the incidence rate of RA has reached 1%, and has been increasing annually.[1] The progressive and incurable nature of RA poses a risk of disability and teratogenicity to patients, thereby significantly reducing patients' quality of life and imposing a substantial economic burden on society. Given the complexity and diversity of the pathogenic factors and pathogenesis of RA, in-depth studies of the regulatory mechanisms of cell death are particularly important. Such studies are essential to elucidate the pathogenesis of RA, to explore new therapeutic strategies and to improve the quality of life of patients.

Programmed Cell Death and Rheumatoid Arthritis

Cell death plays a critical role in maintaining multicellular biological homeostasis and development. Depending on the nature and mechanisms underlying cell death, it can be divided into two broad categories: accidental cell death (ACD) and programmed cell death (PCD).[2] ACD is usually triggered by unexpected injurious stimuli, such as severe physical, chemical, or mechanical damage, that exceed the cell's ability to repair itself, resulting in cell death. PCD refers to the spontaneous and programmed death of cells in the body actively mediated by specific signaling pathways. This process does not involve cytolysis or significant inflammatory reactions and includes various forms such as apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagy.[3] In recent years, an increasing number of studies have shown that PCD plays a key role in the occurrence and development of RA. Under the action of certain pathological factors, the imbalance of PCD could lead to the abnormal release of a large number of inflammatory factors and mediators by a variety of immune cells, which subsequently leads to chronic synovial inflammation and the destruction of bones and joints during RA progression. The purpose of this paper is to review the correlation studies between the above programmed cell death modes and RA, to provide a more in-depth theoretical basis and practical guidance for basic research and clinical treatment of RA, offering valuable references for future studies.

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Apoptosis and Rheumatoid Arthritis

Overview of Apoptosis

Apoptosis is one of the major forms of PCD, also known as type I PCD.[4] It is characterized by distinct morphological features, including cell contraction, chromatin coagulation, DNA fragmentation and apoptotic body formation. These changes eventually lead to cell disintegration, which are subsequently cleared by phagocytes in the innate immune system, effectively preventing the release of pro-inflammatory cell contents.[5] There are two primary apoptosis pathways: exogenous pathway (mediated by death receptors) and endogenous pathway (mediated by mitochondria).[6] The endogenous pathway is usually triggered by alterations in the intracellular environment such as endoplasmic reticulum stress, excess reactive oxygen species, and pro-apoptotic proteins in the BCL-2 family such as BAX, BAK, and PUMA. The aforementioned alterations result in compromised integrity of the mitochondrial membrane, release of cytochrome C into the cytoplasm, subsequent opening of mitochondrial permeability transition pores, mitochondrial rupture, formation of apoptotic bodies, and activation of caspase-9, which cleaves and activates downstream executor Caspase-3/7.[6] The exogenous pathway begins with the activation of death receptors on the cell surface. These receptors including TNFR1/2, Fas and TNF alpha related apoptosis inducing ligand (TRAIL) receptor DR4 and DR5. When these receptors bind to their corresponding ligands (such as TNF alpha, FasL, or TRAIL), they induce caspase - 8 death induced signal complex formation, and then cut and activate the downstream effects of caspase protein - 3/7, in the process of start the apoptosis protein hydrolysis, eventually resulting in destruction of the nucleus and other structures in the cell.[7] In the pathogenesis of RA, the unbalanced regulation of cell apoptosis is a key factor that can lead to abnormal amplification of specific cell types or excessive apoptosis. Therefore, in-depth research into the regulatory mechanisms of apoptosis is crucial for understanding the pathogenesis of RA and developing new therapeutic strategies (Figure 1).

The Regulation of Anti-Apoptotic and Pro-Apoptotic Molecules in RA-FLS Is Imbalanced

In the pathogenesis of RA, excessive proliferation and insufficient apoptosis of synoviocytes are considered to be the main pathological basis.[8] In particular, fibroblast-like synoviocytes (FLS) play a central role in the progression of RA. It has been shown that there is an imbalance in the regulation of anti-apoptotic and pro-apoptotic molecules in RA-FLS, leading to an increased resistance of FLS to apoptosis. In the FLS of RA patients, the expression of anti-apoptotic mediators such as Bcl-2, Bcl-xL, Mcl-2 and FLICE inhibitory protein (FLIP) is upregulated, whereas the expression of

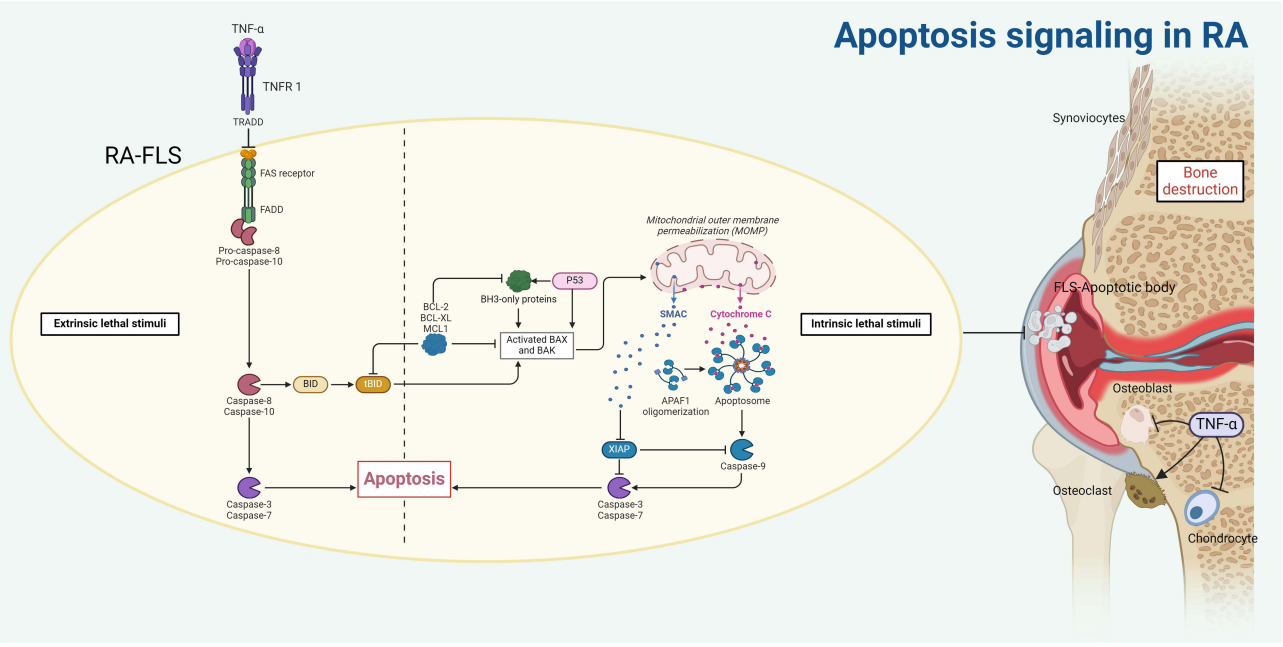

Figure 1 Apoptosis signaling in RA.

pro-apoptotic proteins such as TRAIL, p53 up-regulator of apoptosis (PUMA) and BAX is downregulated.[9] This imbalance is mainly regulated by members of the Bcl-2 family (including anti-apoptotic proteins such as Bcl-2 and Bcl-xL and pro-apoptotic proteins such as Bax and Bid).[10] Under the pathological conditions of RA, abnormally proliferating T cells and activated fibroblasts further exacerbate this imbalance by stimulating the production of high levels of anti-apoptotic markers such as Bcl-xL. In addition, binding of IL-6 to its receptor activates the Janus kinase-2 phosphorylation signal transduction and activator of transcription 3 (JAK2-pSTAT3) pathway, resulting in increased transcription of Bcl-2 and Mcl-2 genes, further contributing to the anti-apoptotic capacity of FLS.[11] Apoptosis regulators such as Bax and Bcl-2 are also involved in the apoptotic process of chondrocytes and myeloid dendritic cells (MDCs).[12] In recent years, several studies have identified potential strategies to induce apoptosis in RA-FLS by modulating anti-apoptotic and pro-apoptotic molecules. For example, acetazolamide significantly ameliorated the severity of collagen-induced arthritis (CIA) in rats by decreasing Bcl-2, increasing Bax, activating caspase 3 and normalising the Bcl-2/Bax ratio, thereby inducing synoviocyte apoptosis and inhibiting the Wnt/β-catenin pathway.[8] Daphnetin, on the other hand, induced CIA-FLS apoptosis mainly through the mitochondrial pathway, reduced cell viability and exhibited typical morphological and ultrastructural changes.[13] P53, as a key tumour suppressor, also plays an important role in apoptosis and proliferation in RA-FLS. It regulates cell cycle arrest, proliferation and apoptosis of synoviocytes by modulating a variety of anti-apoptotic and pro-apoptotic genes, thereby protecting the cells from transformation and degeneration.[14] In FLS of RA patients, p53 mutants are increased while p53 expression is relatively decreased, whereas p53-derived hybrid peptides promote PUMA and Bax expression and increase apoptosis.[15] In addition, dysfunction of p53 and Tregs leads to dysregulation of T-cell proliferation, which further stimulates proliferation of RA synovial fibroblasts.[12] p53 also controls apoptosis through miRNAs such as miR-34a, miR-15a and miR-16-1, and defective p53 may lead to reduced regulation by these microRNAs, leading to impaired apoptosis in synovial fibroblasts.[14] In addition, p53 is involved in the process of removing dead cells after apoptosis through the induction of death structural domain 1α (DD1α) in apoptotic and phagocytic cells[14](Figure 1). p53 not only directly affects the apoptosis of RA-FLS, but also has complex interactions with cell signaling pathways and molecules such as inflammatory factors. Restoring or enhancing p53 function helps to reduce the level of inflammation, thereby alleviating RA symptoms. However, p53 is not the only regulatory factor, NF-κB, STAT3 and other molecules also play a key role in RA and interact with p53. Future research is needed to further explore the interaction between these molecules and their mechanism in RA pathology.

Inhibition of TNF-α on Apoptosis in RA-FLS Cells

Fibroblast-like synoviocytes play a central role in the pathology of RA. Although RA-FLS show increased sensitivity to Fas-mediated apoptosis in vitro, TNF-α induces resistance to Fas-mediated apoptosis in RA synoviocytes in vivo via soluble Fas (sFas).[16] This finding provides a new perspective for understanding the mechanism of apoptosis in RA.

The pro-inflammatory factors TNF-α and IL-1β have been shown to influence the apoptotic process in RA-FLS through specific molecular mechanisms. They upregulate the expression of Bcl-2 and downregulate the expression of CPP32 and ICH-1L, thereby inhibiting apoptosis induced by anti-Fas monoclonal antibodies.[17] This regulatory effect reveals the complex influence of TNF-α in the apoptotic process of RA synoviocytes. Activation of TNFR1 by TNF-α through an exogenous signalling pathway leads to an imbalanced regulation of Bcl-2 family members in cellular mitochondria. This imbalance further affects the process of apoptosis and necroptosis in RA-FLS. For example, geldanamycin corrected the balance between apoptosis and necrotic apoptosis in human rheumatoid synovial cell lines by disrupting RIPK1 and selectively inhibiting the TNFR1-triggered NF-κB activation pathway, while enhancing the apoptotic pathway following TNF-α stimulation.[18] In addition, another important function of TNF-α in RA patients is to stimulate the activation of HIF-1α and B-cell activating factor (BAFF) through the ERK pathway. This action not only inhibits FLS apoptosis, but also further promotes the inflammatory response and exacerbates the pathological process of RA.[19] Notably, several studies have demonstrated the potential value of IL-35 in the treatment of RA. IL-35 ameliorates CIAinflammation both in vitro and in vivo by promoting TNF-α-induced apoptosis in FLS cells and modulating M2 macrophage polarisation.[20] This provides a theoretical basis for the development of IL-35-based therapeutic strategies for RA. In addition, overexpression of pathological synovial aquaporin 1 (AQP1) has been shown to be associated with proliferation and apoptosis in RA-FLS. AQP1 overexpression promotes TNF-α-stimulated cell proliferation, mainly by

facilitating the transition from the G0/G1 phase to the S phase and by inhibiting apoptosis (manifested by a reduced rate of apoptosis, increased mitochondrial membrane potential, increased Bcl-2 protein levels, and decreased Bax levels and cleaved caspase-3 protein levels). In contrast, knockdown of AQP1 showed the opposite effect.[21]

TNF-α inhibits RA-FLS apoptosis through multiple mechanisms and promotes inflammatory responses and pathological processes in RA. Therefore, anti-TNF-α therapy has significant clinical value in the treatment of RA and offers a substantial theoretical basis for the further development of effective therapeutic approaches against RA.

The Imbalanced Regulation of Cell Apoptosis in Chondrocytes and Osteoclasts Leads to Bone Destruction in RA

In the pathological process of RA, an imbalance between chondrocyte and osteoblast apoptosis plays a key role in driving bone destruction. Both in vitro and in vivo studies have shown that inflammatory factors such as IL-1β and TNF-α upregulate the expression of ASIC1a, which promotes chondrocyte apoptosis, as demonstrated in both a rat adjuvant arthritis model and a primary articular chondrocyte model.[22] On the other hand, certain biomolecules, such as nesfatin-1, can reduce ASIC1a protein levels through the MAPK/ERK and NF-κB pathways, thereby inhibiting acidosis-induced oxidative stress, inflammation and apoptosis in chondrocytes, which has a beneficial effect on alleviating arthritis symptoms.[23]

In RA, insufficient macrophage and osteoclast apoptosis is one of the major reasons for the continued progression of joint inflammation and destruction. Studies have shown that macrophage and osteoclast apoptosis in inflamed joints can be selectively promoted by specific interventions such as intravenous administration of CEL-PRNPs, which effectively reduced ankle and paw swelling and reversed bone erosion in a rat model of advanced arthritis.[24] In addition, IL-18 binding protein (IL-18BP) has shown potential therapeutic value in regulating apoptosis in RA. It not only corrects the imbalance of Th17/Treg cells and reduces the production of pro-inflammatory cytokines, but also increases apoptosis of FLS, while reducing necrotic apoptosis of FLS/chondrocytes and apoptosis of chondrocytes.[25] Further studies also showed that IL-18BP was able to reduce IL-17-induced osteoclastogenesis in peripheral blood mononuclear cells (PBMCs) from RA patients.[26]

Defective apoptosis of FLS can lead to synovial dysplasia, pannus formation, and inflammatory cell infiltration, which further erodes bones and destroys joints. Therefore, promoting FLS apoptosis, inhibiting synovial hyperplasia, while promoting osteoclast apoptosis, all while avoiding excessive cartilage apoptosis, are important clinical significance for the treatment of RA. Future studies should further explore the role of these apoptosis-related mechanisms in RA to provide a theoretical basis for the development of new therapeutic strategies.

Autophagy and Rheumatoid Arthritis

Overview of Autophagy

Autophagy, as type II PCD, plays a crucial role in maintaining cell homeostasis and homeostasis regulation.[27] Under stress conditions, cells transport denatured, damaged and non-functional proteins and suborganelles to lysosomes through autophagy mechanism for degradation and recycling, thus maintaining the structural, functional and metabolic stability of cells.[28] Autophagy is regulated by a variety of signaling pathways,[29] among which the signaling pathway dependent on the target protein of rapamycin is one of the most critical regulatory pathways.[30] mTOR can be further divided into mTORC1, which is sensitive to rapamycin, and mTORC2, which is not sensitive to rapamycin. mTORC1 is mainly involved in the regulation of cell growth, development, energy metabolism, autophagy and apoptosis. mTORC2, on the other hand, is mainly involved in cytoskeletal protein formation and cell survival.[31] Studies have found that the expression of autophagy related proteins in the synovium of RA patients is significantly increased, such as Beclin1, ATG5, LC3, etc. These increased expressions are significantly correlated with the levels of serum inflammatory markers (such as CRP, ESR) and autoantibodies (such as cyclic citrulline peptide CCP and rheumatoid factor RF).[31] Abnormal autophagy may further aggravate the development of synovial inflammation by affecting the function and activity of synovial cells, exacerbating symptoms such as joint swelling and pain. Excessive or insufficient autophagy may further promote the process of bone destruction by affecting bone cell metabolism and apoptosis, leading to joint deformities and dysfunction. Abnormal autophagy may destroy the homeostasis of immune cells, lead to abnormal activation and attack

of immune cells, further aggravate the pathological process of RA, and affect the overall health of patients. Autophagy plays an important role in the pathogenesis of RA. By further studying the mechanism of autophagy in RA, we can provide new ideas and methods for the treatment of RA. At the same time, the regulation of autophagy may serve as a therapeutic target for RA, potentially improving treatment outcomes for patients (Figure 2).

Role of Autophagy in Synovial Inflammation of RA

There is a close relationship between autophagy and apoptosis in RA, in which autophagy shows a significant antagonistic effect on apoptosis. Studies have shown that compared with normal fibroblast-like synovial cells, proteasome and autophagy levels in FLS of RA patients are up-regulated. This up-regulation of autophagy results in FLS having higher autophagy rates and lower apoptosis rates. In particular, the induction of autophagy is closely related to the anti-apoptotic properties of RA-FLS.[32] Further studies have shown that tumor necrosis factor TNF-α produced in RA-FLS can induce the expression and activation of autophagy related proteins such as LC3-II, Beclin-1, p62, etc.,[33] thus enhancing the autophagy ability of FLS in RA patients. The apoptosis rate of FLS was significantly increased when treated with anti-TNF-α drugs. This suggests that the upregulation of autophagy diminishes the apoptosis of FLS by clearing the damaged and aging FLS, thus promoting the persistence of inflammation and the aggravation of RA disease. PI3K/Akt/mTOR signaling pathway, as the central signaling pathway for protein synthesis, cell proliferation and metabolism, plays an important role in the proliferation of RA synovial cells.[34] This pathway transmits mitosis signals to the ribosome through PI3K, accelerates the G phase of cell mitosis, and thus promotes the continuous proliferation of RA-FLS.[35,36] At the same time, stimulated by TNF-α, AKT kinase activity in RA-FLS is increased, further enhancing autophagy in joint synovial cells.[37] It was also found that inhibition of PI3K/Akt/mTOR signaling pathway can reverse TNF-α-mediated autophagy and cytokine secretion, thereby reducing the inflammatory response of RA, inhibiting RA-FLS cell proliferation, and promoting apoptosis. As a form of mTOR complex, mTORC2 can activate Akt and autophagy related gene 1(Atg1) after phosphorylation, thereby inhibiting autophagy. In addition, mTORC2 can also up-regulate the expression of hypoxic cytokine-1α (HIF-1α), which is a major regulator of cell response to hypoxia[38] and a key cytokine in synovial vascular hyperplasia of RA, and can further promote the inflammation of RA synovial tissue.[39] Finally, PINK1/Parkin-mediated mitochondrial autophagy was confirmed to be involved in H2O2-induced abnormal proliferation of RA-FLS. Therefore, targeting PINK1/ Parkin-mediated mitochondrial autophagy may represent a key therapeutic target in the treatment of RA[40](Figure 2).

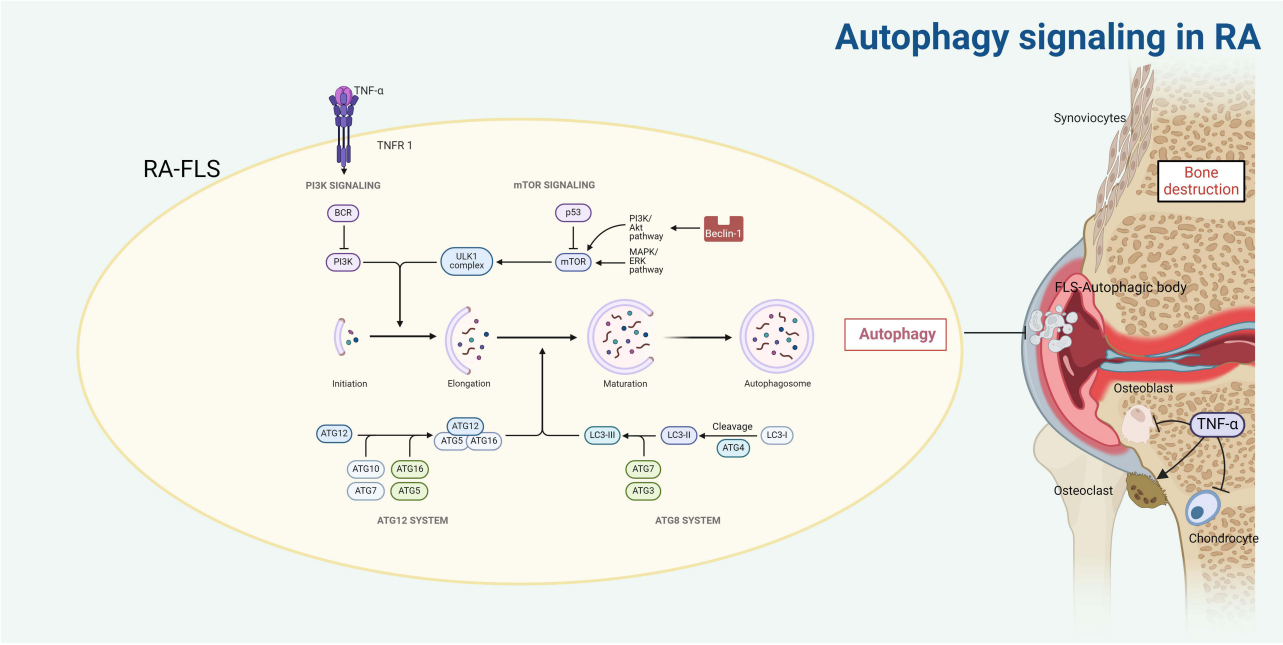

Figure 2 Autophagy signaling in RA.

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The Role of Autophagy in RA Bone Destruction

Autophagy plays an important role in the bone destruction process of RA. TNF-α can induce increased expression of autophagy related gene Atg7 in osteoclasts in vivo and in vitro, and stimulate the transformation of LC3-I to LC3-II. In addition, Beclin-1 overexpression can also activate the autophagy of osteoclasts, and further stimulate the activation of osteoclasts by up-regulating the expression of Atg7 and Beclin-1.[41] This process leads to an increase in the number of osteoclasts and enhanced bone absorption capacity. On the contrary, inhibition of autophagy can block the function of osteoclasts, reduce the number of osteoclasts, and reduce bone absorption capacity.[42,43] In a mouse model of experimental arthritis, inhibition of autophagy significantly reduced signs of bone erosion and the number of osteoclasts, further demonstrating the key role of autophagy in bone tissue degradation.[44] As a key component in the pathogenesis of RA, TNF-α not only coordinates synovial inflammation, but also regulates the activation of osteoclast through autophagy, thus aggravating the bone destruction of RA and aggravating joint symptoms.

Effects of Autophagy on Immune System Homeostasis in RA

In patients with RA, the autophagy rate of CD4 T cells is significantly increased, and the resistance to apoptosis is correspondingly enhanced. This increased rate of autophagy and enhanced resistance to apoptosis may contribute to the pathogenesis of RA. When autophagy is inhibited, resistance to apoptosis in CD4 T cells is significantly reversed,[45] suggesting an important role of autophagy in RA immune response. In a mouse model of collagen-induced arthritis, inhibition of autophagy similarly reduced the incidence and disease severity of arthritis. These findings suggest that autophagy is involved in several key pathologic aspects of RA, including pannus formation, synovial inflammation, and bone destruction. Therefore, targeting the regulation of autophagy provides a new therapeutic strategy to intervene in the progression and prognosis of RA disease, and may be a potential therapeutic target for the treatment of RA (Figure 2).

Role of Pyroptosis in Rheumatoid Arthritis

Overview of Pyroptosis

Pyroptosis is a regulated, highly pro-inflammatory pathological PCD that relies on gasdermin family proteins to form pores in the plasma membrane. Its occurrence mainly depends on two pathways: the classical pathway mediated by caspase-1 and the non-classical pathway mediated by Caspase-4/5/11.[46] The activation of the classical corticoplasmic pathway is initiated by intracytoplasmic pattern recognition receptors (PRRs) to recognize pathogens or specific stimuli from the body itself,[47] and these go on to assemble Inflammasomes to recruit and activate caspase-1 proteins and form activated Caspase-1.[47] Activated Caspase-1 cuts gasdermin D (GSDMD), causing GSDMD to form pores in the cell membrane and release pro-inflammatory factors such as IL-1β, IL-18, etc.,[48] thus triggering cell pyrosis and tissue inflammation[49](Figure 3).

Role of Pyroptosis in Synovial Inflammation of RA

In recent years, research on RA has revealed a strong link between it and pyroptosis. A number of studies have indicated that in the rat model of adjuvant arthritis, the expression of NLRP3, Caspase-1, GSDMD, IL-18 and IL-1β in macrophages is significantly enhanced,[50] and the pyroptosis is observed. Similarly, the expression of these pyroptosis related proteins in synovial tissues, especially macrophages, is also up-regulated in RA patients, and the expression of IL-1β and IL-18 in serum peripheral monocytes is significantly higher than that in normal population.[51,52] The latest scientific progress shows that n-pentamerin 3 (PTX3) has emerged as a novel biomarker for the diagnosis of RA.[53] PTX3 promotes pyroptosis of RA monocytes in a C1Q-dependent manner, and enhances the secretion of TNF-α, IL-1β and IL-6 inflammatory cytokines. It is worth noting that compared with RA patients with low disease activity, serum cultured cells from patients with high disease activity showed higher expression of GSDMD and greater release of IL-1β and IL-6.[54] These findings suggest that pyroptosis is not only involved in the pathogenesis of RA, but also that its incidence may be positively correlated with the disease activity of RA. In RA, the frequent activation of Caspase-1 in lymph node T cells also results in pyroptosis, becoming a key factor in aggravating the inflammatory response of RA.[55] In addition, the NLRP3 inflammasome is composed of receptor proteins NLR or ALR, adaptor proteins ACS, and effector proteins Caspase, and its upregulation depends on the activation of the NF-κB pathway.[56] The NF-κB pathway plays an important

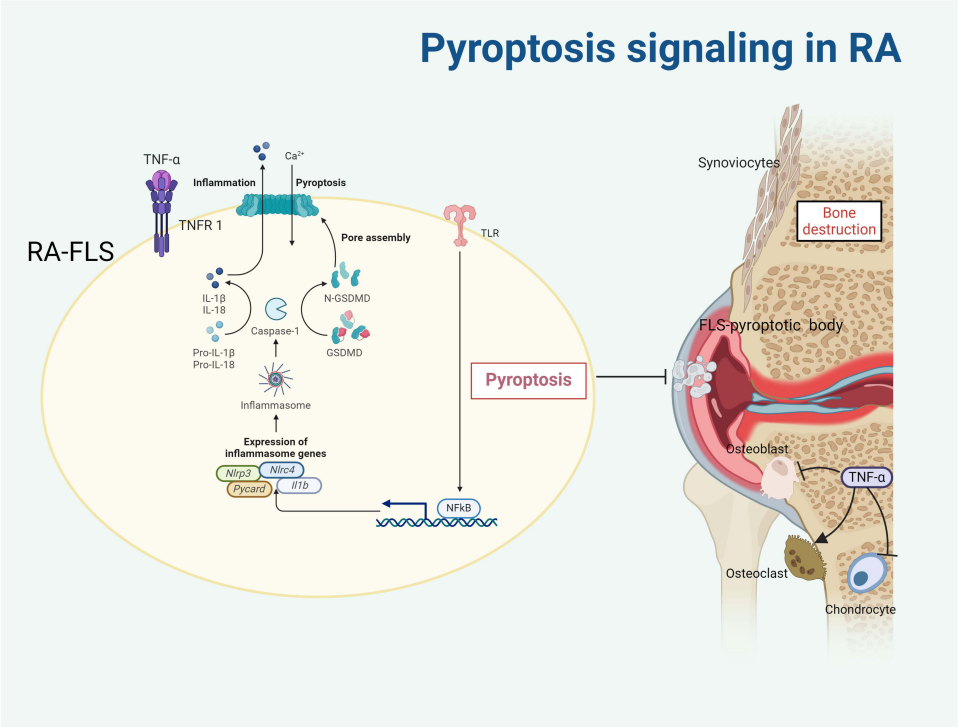

Figure 3 Pyroptosis signaling in RA.

role in osteoclast activation,[57] with high NLRP3 expression leading to bone mass loss, primarily due to inflammatory factors like IL-1β.[58] As downstream signaling molecules of the pyroptosis pathway, IL-1β and IL-18 play a crucial role in the pathological process of RA. IL-1β can induce inflammation, promote immune cell extravasation and vasodilation, and thereby contribute to the formation of an adaptive immune response.[59,60] IL-18 is present at a high level in RA synovium, inducing neutrophil recruitment and mast cell activation, enhancing the proliferation and activity of T cells and NK cells,[61] and promoting the shift of helper T cell balance to Th1 response[62](Figure 3).

Hypoxia is an important developmental factor in the pathologic process of RA, which induces FLS pyroptosis through the ROS/GRK2/HIF-1α/NLRP3 pathway.[63] On the other hand, inhibition of NLRP3 by inhibiting the activity of NF-κB can further regulate the secretion of macrophage inflammatory cytokines IL-1β and IL-18, which has a potential protective effect on RA.[64] In addition, extracellular acidification can activate ASICIa of articular chondrocytes, induce scorched death and aggravate synovial inflammatory response and local destruction of articular cartilage, while blocking ASICIa can significantly inhibit scorched death of articular chondrocytes in RA rats.[65]

Pyroptosis plays a key role in the pathogenesis and development of RA. Key protein molecules in the pyroptosis signaling pathway network, such as NF-κB, NLRP3, Caspase-1, GSDMD, IL-1β and IL-18, all play an important role in RA such as NF-κB, NLRP3, Caspase-1, GSDMD, IL-1β and IL-18, all play an important role in RA. Therefore, inhibition of these core protein molecules could represent a key strategy to halt the progression of RA synovial inflammatory activity. In addition, the pyroptosis signaling pathway and its inflammatory molecules offer novel avenues for understanding RA pathogenesis and developing targeted therapies.

The Role of Necrotic Apoptosis in Rheumatoid Arthritis

Overview of Necrotic Apoptosis

Necrotic apoptosis, as a new mode of cell death, has been clearly distinguished from traditional apoptosis and necrosis processes.[66] As a non-Caspase-dependent mode of cell death, necrotic apoptosis triggers a complex cell death process by binding specific death receptors (such as TNFR, toll-like receptors, Fas, and interferon receptors) to corresponding ligands.[67] Among them, TNFR-mediated necrotic apoptosis has emerged as a significant focus of research. When TNF-α

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binds to TNFR1, TNFR1 is activated and recruits a series of downstream protein molecules at the cytoplasmic end, These include receptor interacting protein kinase 1 (RIPK1), tumor necrosis factor receptor-associated factor (TRAF2), tumor necrosis factor receptor-associated death domain protein (TRADD), and apoptosis suppressor protein (cIAPs). These signaling molecules aggregate on the cell membrane to form complex I, which modifies RIPK1 according to the different signal stimuli received, thus determining whether the cell goes towards apoptosis or necrotic apoptosis.[68] Within this pathway, Caspase-8 plays a key role. When RIPK1 recruits pro-caspase-8 and TRADD and other molecules to form complex IIa, Caspase-8 is activated, which inhibits RIPK3 activation, directing cells towards apoptosis. However, when Caspase-8 is absent or activity is reduced, RIPK1 undergoes deubiquitination, enabling its binding to death domain proteins such as RIPK3 and Fas to form complex IIb. This complex in turn recruits and phosphorylates mixed lineage kinase domain-like protein (MLKL), triggering the execution of necrotic apoptosis.[69] Necrotic apoptosis is crucial in the pathogenesis and progression of numerous diseases, especially in inflammatory diseases such as RA. Studies have shown that plasma levels of RIPK1 and MLKL in RA patients are significantly elevated and positively correlated with the severity of the disease. Therefore, the regulation of necrotic apoptosis-related molecules may provide new strategies and methods for the treatment of RA (Figure 4).

Association Between Necrotic Apoptosis and Rheumatoid Arthritis

As a specific cell death signaling pathway, necrotic apoptosis plays an important role in the pathogenesis of RA. Recent studies have revealed that plasma levels of RIPK1 and MLKL in RA patients are significantly increased, and this increase is positively correlated with the severity of RA.[70] In adjuvant arthritis model, RIPK3, MLKL and the expression of IL - 6 levels rise, and irisin by inhibiting HMGB1 / MCP1 Chitotriosidase I mediated necrotic apoptosis, showed the potential of its anti-inflammatory and antioxidant.[71] High expression of Baculoviral IAP repeat-containing 2 (BIRC2), TRADD and other molecules was observed in the pathological process of RA. In particular, BIRC2 knockdown significantly alleviates the necrotic apoptosis, oxidative stress and inflammatory response of C28/I2 cells in the LPS-mediated RA cell model in vitro by regulating TRADD expression,[72] which provides a new target for the treatment of RA.

Regulation of Necrotic Apoptosis and Treatment of RA

In the joints of RA patients, neutrophils activate RIPK3 and MLKL under the influence of CD44 and GM-CSF (granulocyte-macrophage colony-stimulating factor), thereby triggering necrotic apoptosis. It has been found that this

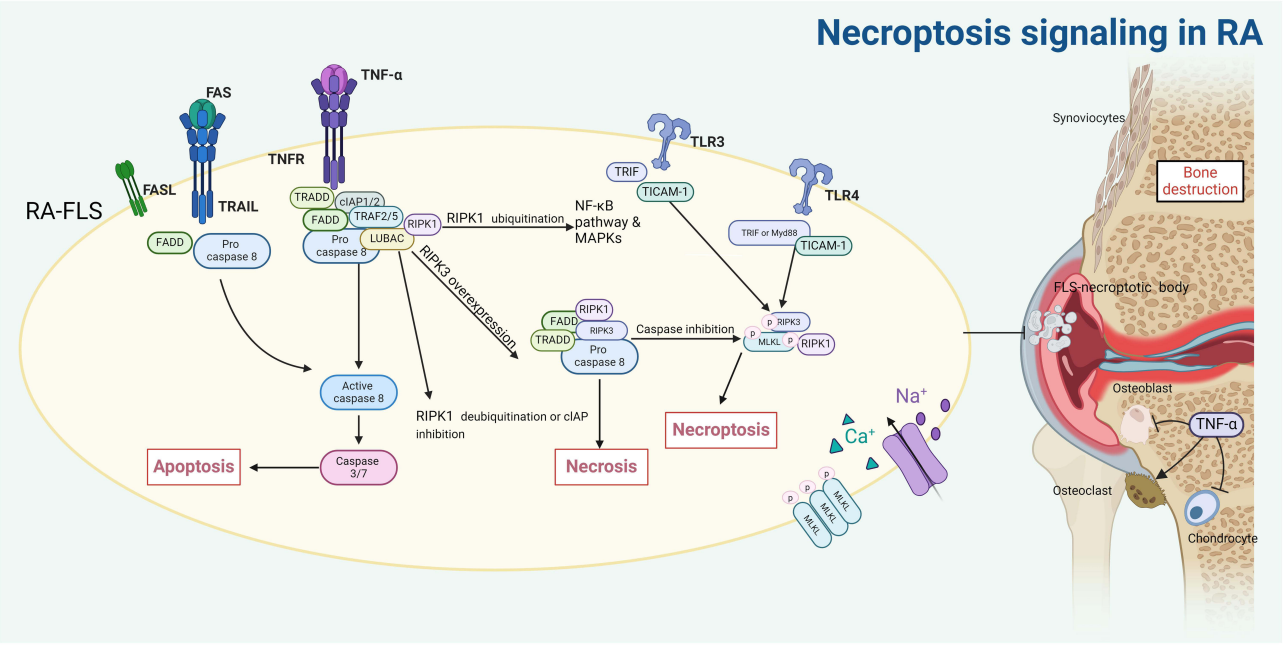

Figure 4 Necroptosis signaling in RA.

process can be effectively blocked by the application of FAP-α (fibroblast activating protein-α) and MLKL inhibitors, indicating the therapeutic potential of these inhibitors in RA treatment.[73] M1 macrophages are closely associated with RA, and SMAC mimics (SMs) provide a new strategy for the treatment of RA by inducing M1 macrophages to die through the necrotic apoptotic pathway.[74]

It is worth noting that in the serum and synovium of RA patients, the presence of 14-3-3η is closely related to the level of anti-cyclic citrulline peptide antibody and disease activity, and TNF-α promotes the release of 14-3-3η by inducing macrophage necrotic apoptosis.[75] Studies of adjuvant arthritis (AA) and acid-induced rat chondrocytes in vitro have revealed the key role of ASIC-1a (acid-sensitive ion channel-1A) in chondrocyte necrosis, which provides a new potential therapeutic strategy for the treatment of RA.[76] In a CIA (Collagen-induced arthritis) mouse model lacking IFN-γ (interferon gamma), increased expression of RIPK1, RIPK3, and MLKL promotes proliferation of Th17 cells and the release of IL17 and TNF-α, which exacerbates inflammation and joint damage in RA. This finding reveals the potential role of IFN-γ in the regulation of inflammatory cell death and the treatment of RA.[77] Similarly, the RIPK1 inhibitor NST-1s inhibited the expression of necrotic apoptosis-related molecules (RIPK1, RIPK3, and MLKL) in experimental CIA arthritis mice, reducing the number of Th1 and Th17 cells, and increasing the number of Th2 and Treg cells. These results suggest that NST-1s slows the progression of CIA by inhibiting osteoclast formation, indicating its potential as a therapeutic agent for RA treatment[78](Figure 4).

The Role of Ferroptosis in Rheumatoid Arthritis

Overview of Ferroptosis

Ferroptosis, a new form of PCD, is driven by a combination of iron accumulation and lipid peroxidation. Its main characteristics are the morphological changes of mitochondria, such as the reduction of volume, the reduction of ridge number, the increase of membrane density and the increase of membrane rupture. The mechanism of ferroptosis involves non-enzymatic Fenton reaction and enzymatic lipoxygenase action. Excess circulating Fe^{3+} enters the cell by binding to the transferrin receptor 1 (TFR1) on the cell membrane, which is converted by ferric reductase into $Fe^{2+}$and transported by DMT1 to the cytoplasm, where $Fe^{2+}$and ROS are produced by a Fenton reaction.[79] On the other hand, ferroptosis inducers such as Erastin inhibit the glutamate/cystine transport system, leading to GSH depletion and GPX4 inactivation,[80] which in turn accumulates ROS in the form of lipid hydroperoxides. Together, these two aspects promote lipid peroxidation and ultimately induce cell ferroptosis. Recent studies have revealed that FSP1-CoQ10 plays a similar role to GPX4 in inhibiting ferroptosis,[81] further expanding our understanding of the mechanism of ferroptosis (Figure 5).

Ferroptosis and Bone Damage in Rheumatoid Arthritis

The iron metabolic status of patients with RA differs markedly from that of the general healthy population.[82,83] Compared with non-RA patients, RA patients exhibit a significantly increased concentration of free iron in synovial fluid and heightened iron deposition in the synovial membrane.[84] This abnormal state of iron metabolism has a significant impact on bone tissue health. Low concentrations of iron ions can promote the growth of osteoblast precursor cells (MC3T3-E1), whereas high concentrations of iron ions can inhibit the growth of osteoblast precursor cells and increase the level of intracellular reactive oxygen species (ROS). Further studies have shown that excessive iron ions can activate the p38-MAPK signaling pathway, while blocking the PI3K/AKT and JAK/STAT3 signaling pathways, thereby inducing MC3T3-E1 cell cycle to stall in G1 phase and triggering autophagy.[85]

Mitochondrial ferritin (FtMt) is a key protein that stores iron ions in mitochondria and intercepts toxic ferrous ions. The expression level of FTMT plays an important role in ferroptosis and osteoblast function. Wang et al[86] observed the role of FtMt in the ferroptosis process of osteoblasts through lentivirus-mediated gene silencing and overexpression techniques. Overexpression of FtMt significantly reduced the incidence of ferroptosis in osteoblasts under high glucose conditions, while inhibition of FtMt induced mitochondrial autophagy through ROS/PINK1/Parkin pathway, and then observed an increase in ferroptosis in osteoblasts. This finding suggests that FtMt can inhibit the occurrence of ferroptosis in osteoblasts by reducing oxidative stress caused by excess ferrous ions. In addition, iron overload not only inhibits osteogenic differentiation and bone formation of osteoblasts, but also enhances osteoclast differentiation.[87] The abnormal proliferation and activation of osteoclasts further aggravate the bone metabolism disorder and bone injury in RA patients.

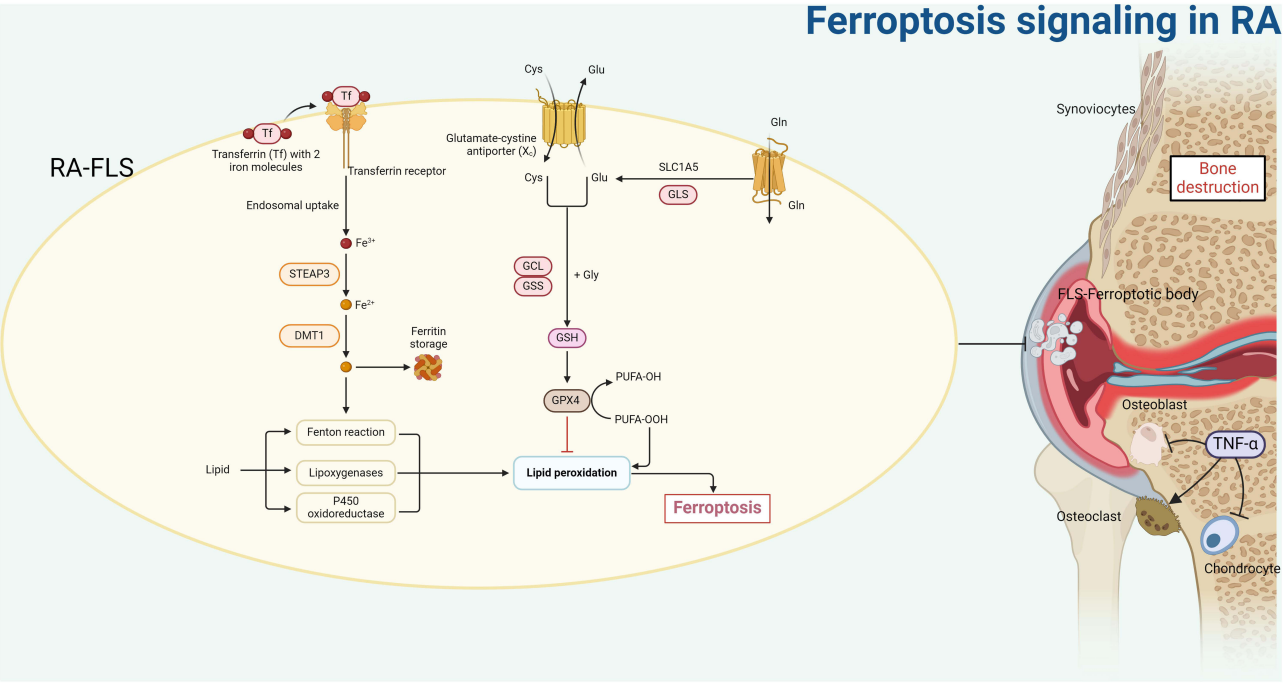

Figure 5 Ferroptosis signaling in RA.

Compared with the normal group, an abundance of ferroptosis occurred in the articular chondrocytes of RA patients and arthritis model rats. However, inhibiting ferroptosis of chondrocytes can effectively protect arthritic model rats from articular cartilage injury.[88]

Research Progress of Ferroptosis Mechanism in Rheumatoid Arthritis

Previous studies have revealed that the levels of ROS and lipid peroxidation in serum and synovial fluid of patients with RA are significantly increased, and the antioxidant system also shows abnormal changes.[89] These features are highly consistent with ferroptosis, further suggesting that ferroptosis plays an important role in the pathologic course of RA. There is a significant positive correlation between ROS level and disease severity score in RA patients,[90] suggesting that the increase of ROS level may be one of the key factors in the progression of RA disease. Abnormally elevated lipid ROS levels are regulated by GPX4,[91] which can effectively repair the oxidative damage of mammalian unsaturated fatty acids and thus inhibit the occurrence of ferroptosis.

Earlier studies have shown that erastin, as a systemic XC-inhibitor, inhibits glutathione (GSH) synthesis and increases lipid ROS production, ultimately leading to ferroptosis.[92] Similarly, both ROS and erastin can induce the activation of metalloproteinases, thus inhibiting the expression of type II collagen, inhibiting the synthesis of chondroproteoglycan, and promoting the apoptosis of chondrocytes. These effects jointly lead to cartilage destruction and bone erosion, and exacerbate the pathological progression of RA.[93,94] ROS is not only an important element of the ROS/TNF-α feedback loop, but also stimulates the activation of the NF-κB signaling pathway, thereby promoting the release of TNF-α, activating the p38/JNK signaling pathway, and accelerating the progression of RA.[95] TNF (tumor necrosis factor), as a key pro-inflammatory cytokine in the pathogenesis of RA, can promote cystine uptake and GSH biosynthesis, protecting fibroblasts from ferroptosis. However, TNF antagonists have been shown to increase sensitivity of RA-FLS to ferroptosis.[96]

Recent studies indicate a significant reduction in ferroptosis levels in RA synovial cells, which may be related to the activation of PI3K/AKT/mTOR signaling pathway, which inhibits ferroptosis by enhancing GPX4 expression.[97] In contrast, glycine promotes the ferroptosis of FLS in RA by decreasing the expression of GPX4 and ferritin heavy chain 1 (FTH1), thereby improving the proliferation and inflammatory infiltration of FLS.[98] In addition, ferroptosis inducer RSL3 can bind and inactivate GPX4, and in vitro cell experiments have confirmed that RSL3 treatment of RA-FLS can down-

regulate the expression of ferroptosis related gene SLC2A3 and induce ferroptosis of RA-FLS.[99] This finding provides new ideas for developing targeted therapies for ferroptosis that target specific cell types in RA (Figure 5).

As an important cellular metabolic process, ferroptosis is finely regulated by different signals and substances in the metabolic microenvironment, and GPX4 is its classic regulatory pathway. In the pathological changes of RA, FLS, chondrocytes, osteoblasts and osteoclasts were different in sensitivity to ferroptosis. Much research is still needed to explore the unique mechanisms of ferroptosis in different cells of arthritis and to provide guidance for specific targeted therapies for RA.

Interaction of Programmed Cell Death with Rheumatoid Arthritis

Interaction of Programmed Cell Death

It has been found that inflammasome is not only associated with pyroptosis, in fact, there is a complex interaction between apoptosis and pyroptosis. In the regulatory network of apoptosis, caspase-8 plays a pivotal role, activating caspase-3, which subsequently cleaves Pannexin-1 channel protein.[100] Activation of Pannexin-1 channel protein promotes the efflux of potassium ions and triggers the assembly of the NLRP3 inflammasome.[101] Notably, caspase-8 serves as a crucial regulatory point in cell death pathways. When it is recruited by the NLRP3. ASC inflammasome, if caspase-8 remains active, it further activates downstream caspase-3, thereby inducing apoptosis. If the activity of caspase-8 is suppressed, caspase-1 is activated in turn, resulting in pyroptosis.[102] In addition, caspase-3/8, which is closely related to apoptosis, can even directly act on GSDMD family proteins to trigger pyroptosis. However, if the pore-forming effect of GSDMD is delayed, cells that were originally destined for pyroptosis may instead enter the apoptotic program. These findings not only underscore the intricate nature of cell death mechanisms, but also provide new perspectives and strategies for the treatment of related diseases.

Although the signal transduction pathways of apoptosis, necrotic apoptosis, autophagy, ferroptosis, pyroptosis and other cell death pathways are different, there are close interconnections and mutual regulation mechanisms among them, and this interaction constitutes the material basis of "crosstalk". Recent studies have shown that proteasome and autophagy levels in FLS in RA patients are significantly upregulated compared to normal FLS. This up-regulation of autophagy leads to low apoptosis rate and high autophagy activity in FLS, and the induction of autophagy is closely related to the anti-apoptotic properties of RA-FLS.

During cell death, when cells are subjected to TNF and oxidation factors, mitochondria release apoptosis factors to induce apoptosis. However, when caspase-8 activity is inhibited, cells may turn to necrotic apoptosis.[103,104] In addition, the presence of GSDME protein in cells can facilitate the swift transition from apoptosis to pyroptosis.[104] There is also a possibility of conversion between apoptosis and ferroptosis. According to the study of Yuan et al[105] iron accumulation can inhibit the proliferation of bone marrow mesenchymal stem cells (MSCs), and increase the ROS (reactive oxygen species) level and NOX4 (oxidase 4) protein expression in MSCs cells, and then induce the apoptosis of MSCs through caspase-3, leading to bone loss. Liu et al[106] revealed the mechanism of iron accumulation regulating osteoblast apoptosis through XIST/miR-758-3p/caspase-3 axis. Tian et al.[107] Further pointed out that ROS plays a key role in regulating the necrotic apoptosis induced by iron overload in osteoblasts, and the RIPK1/RIPK3/MLKL pathway is a key mechanism for the necrotic apoptosis induced by iron overload in vitro. In addition, iron ion mediated ferroptosis is also involved in the induction process of pyroptosis. Tian et al[108] treated MC3T3-E1 osteoblasts with different concentrations of iron ions, and observed that the level of unstable iron in the osteoblasts was increased, accompanied by the production of ROS and the activation of caspase-3. However, activation of caspase-3 can cut GSDME, thereby converting TNF-α-induced apoptosis into pyroptosis.[109] GPX4 signal and GSDMD signal are the important material basis for triggering ferroptosis and cell pyrosis, respectively, which may lead to excessive ferroptosis and pyrosis of osteoblasts in the course of RA disease, and then cause abnormal function or death of osteoblasts. This influence relationship is likely to be triggered by the "crosstalk" between GPX4 and GSDMD signals, providing new research directions and potential targets for the treatment of RA.

The Mechanism of Cross-Interaction Between Ferroptosis and Various Programmed Cell Death Modes

The depletion of GPX4 significantly revealed its sensitivity to multiple PCD modes such as apoptosis,[110] necrotic apoptosis,[111] and pyroptosis,[112] suggesting that lipid peroxidation may play an accelerated role in these different PCD modes and suggesting a possible switching mechanism between cell death modes. In particular, the ferroptosis inducer erastin enhances cell sensitivity to apoptosis induced by TNF-associated apoptosis-inducing ligands by activating the p53-dependent CHOP/PUMA axis.[113] In the process of ferroptosis caused by mitochondrial damage, the opening of mitochondrial permeability transition pore is closely related to the intensification of the phosphorylation of RIPK1/3, which ultimately promotes the occurrence of necrotic apoptosis. However, the upregulation of RIPK3 promotes the opening of the mitochondrial permeability transition pore through the endoplasmic reticulum stress/calcium overload / ROS pathway, and further increases the sensitivity of cells to ferroptosis.[114–116] In recent years, an increasing number of studies have revealed a strong link between ferroptosis and autophagy mechanisms, suggesting that ferroptosis may be an autophagy dependent form of cell death.[117,118] Further studies found that the knockout of autophagy associated genes significantly inhibited erastin induced ferroptosis and reduced intracellular Fe^{2+} and lipid peroxidation levels.[119] In addition, abnormal intracellular accumulation of iron and ROS has been shown to induce both pyroptosis and ferroptosis, two forms of cell death.[120]

The study of Kang et al[112] revealed that GPX4 deficiency in myeloid cells promoted the production of GSDMD mediated by caspase-1/11, thus promoting the occurrence of pyroptosis death. Together, these studies indicate that there is a complex cross-interaction between ferroptosis and various PCD modes, though the specific molecular mechanisms require further exploration.

Discussion

Programmed cell death (PCD) plays a central role in the pathological mechanisms of RA, with its dysregulation promoting disease progression.[121] Existing therapeutic drugs, such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs), and biologics, regulate apoptosis through distinct pathways. Methotrexate, for instance, elevates adenosine levels,[122] NSAIDs inhibit synovial cell proliferation and induce apoptosis,[123] whereas biologics promote apoptosis and regulate cytokines through multiple mechanisms.[124] Autophagy and apoptosis exhibit an antagonistic relationship in RA, making autophagy a novel therapeutic target.[125] For example, celastrol inhibits autophagy via the CaMKKβ-AMPK-mTOR pathway,[126] and dexamethasone demonstrates potential by inhibiting apoptosis via the AKT/FOXO3 signaling pathway.[127] Additionally, astragalus polysaccharides regulate autophagy and promote apoptosis via the PI3K/AKT/mTOR pathway, thereby demonstrating promising therapeutic potential.[128] In RA, increased activation of caspase-1 in CD4+ T cells, with MRE11A regulating pyroptosis by maintaining mitochondrial homeostasis, modulates inflammation levels.[18] Geldanamycin enhances caspase-8 activation and reduces TNF-α-induced necroptosis by inhibiting RIPK1 and NF-κB, which demonstrates significant effects in the collagen-induced arthritis (CIA) model.[129] Furthermore, TNF-α produced by fibroblast-like synoviocytes (FLS) drives inflammation, and ROS imbalance contributes to ferroptosis.[18] GPX4, a ferroptosis inhibitor, is upregulated and associated with reduced TNF-α levels, indicating the potential of targeting ferroptosis as a therapeutic approach.[130] In summary, the mechanisms of cell death are critically significant in RA treatment, and future research should further explore their molecular mechanisms and novel targeted therapies.[131]

Under normal physiological conditions, PCD maintains a moderate balance in the organism to ensure the stability of the intracellular microenvironment. However, during the pathological process of RA, the balance of PCD is disturbed and multiple PCD pathways may work together to regulate the onset and progression of RA through complex interaction mechanisms. As a modifiable mode of cell death, PCD plays a key role in promoting organismal development, maintaining homeostasis of the internal environment, immune regulation and physiopathological processes. Although significant progress has been made in recent years in identifying key molecules and pathways of PCD, the specific mechanisms of how these programmed death pathways interact and collectively regulate the development of RA remain poorly understood.

Future studies should further explore the relationship between PCD and RA, especially the interactive effects between different PCD pathways. We should integrate forms of PCD such as apoptosis, necroptosis, autophagy, ferroptosis and pyroptosis into a unified research framework to comprehensively examine their interactions and impact on RA. Further exploration of the signaling and regulatory mechanisms of PCD, we expect to provide a richer experimental basis for studying the pathogenesis of RA and strongly support the development of new therapeutic strategies. Therefore, an in-depth study of the relationship between PCD and RA will not only help us to better understand the pathogenesis of RA, but may also open up new avenues for the treatment of RA and bring better therapeutic effects and quality of life to patients.

Data Sharing Statement

Not applicable. This is a review paper; only bibliographical data were used (see reference list). No data in this study have been deposited into a publicly available repository.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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