

The pyroptosis–hypoxia axis in autoimmune and chronic inflammatory diseases: Emerging mechanisms and therapeutic opportunities

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Abstract: Pyroptosis, a pro-inflammatory form of programmed cell death, mediated by inflammasome activation, inflammatory caspase signalling and gasdermin mediated pore formation, performs as a critical mediator in the progression of several autoimmune and chronic inflammatory conditions. Recent researches indicate about an existing link between hypoxia and pyroptosis, where hypoxic microenvironment can trigger a series of events, including reactive oxygen species (ROS) generation, increased hypoxia-inducible factor 1 α (HIF-1 α) expression and inflammasome assembly and activation, leading to the pyroptotic cell death. Subsequently, pyroptosis can amplify inflammatory signaling through the release of pro-inflammatory mediators, promoting the activation of immune-cell, tissue injury, and persistence of the hypoxic microenvironment. The followed inflammatory response by pyroptotic cell death leads to immune cells recruitment which further gets activated and can elevate an autoimmune response. This review focuses on targeting the axis between pyroptosis and hypoxia in autoimmune diseases through discussing its relevance to disease progression with particular emphasis on emerging therapeutic strategies. Accumulating evidence emphasizes this pyroptosis-hypoxia axis as a vital mediator of autoimmune disorders and a promising therapeutic target for alleviating inflammation and tissue damage.

Key words: Pyroptosis, hypoxia, inflammation, autoimmune disorders, gasdermins, HIF-1 α , immune system, therapeutics.

1 Introduction

‘Programmed cell death’ is widely defined as a broad spectrum of intrinsic genetically regulated pathways through which cells undergo its own termination. [1] Apart from apoptosis, the widely studied and recognized form of programmed cell death, pyroptosis, is a comparatively recently uncovered pathway has drawn a lot of attention due to its ability to act as a double-edged sword in tumor microenvironment (TME) modulation. [2] Pyroptosis can exert tumor growth promotion as well as metastasis; in contrast, it also promotes the immune cell mediated tumor cell killing in the TME. Usually, pyroptosis induction in TME could be validated

as a newly emerging therapeutic approach against cancer. [3,4] In-contrast to moderately elevated pyroptosis that supports the immune mediated host defence against invasive pathogens, unrestricted pyroptosis results in excessive inflammatory outcomes, massive cell destruction and severe tissue impairment. [5]

Pyroptosis has always been thoroughly studied as a pro-inflammatory form of programmed cell death, and existing reviews have provided elaborate insights into the molecular sequence of events underlying pyroptosis, including inflammasome activation, inflammatory caspase activation, gasdermin mediated pore formation, and role of pyroptosis in inflammatory disorders and cancer. [6,7] In the same way, hy-

poxia and hypoxia-inducible factor (HIF) signalling has extensively been studied in cancer and inflammatory disorders. [8,9] Hypoxia is a salient feature of tumor microenvironment and shows its influence on immune cell function, metabolic reprogramming, angiogenesis and therapeutic resistance through the both HIF dependent as well as independent mechanisms. [8,10] The role of hypoxia in autoimmune disorders has been covered in more recent reviews, showing that the alteration in oxygen availability and HIF signalling can modulate immune cell activation and inflammatory responses in these autoimmune disorders. [10] Notably, accumulating evidence has identified a direct connection between pyroptosis and hypoxia; and these findings suggest their interconnected mechanisms have the ability to strengthen the inflammatory responses. [11,12] Our previous work on pyroptosis, primarily focused on the existing gaps in molecular mechanism of pyroptosis, its implications within the TME, while emphasizing the potential intervention points in cancer therapeutics. [13] Whereas that work established the relevance of pyroptosis in mainly the tumor microenvironment, the present review extends this in a different direction through focusing on the combined interplay between pyroptosis and hypoxia in chronic inflammatory diseases.

Despite of the fact that both of the hypoxia and pyroptosis mechanism have thoroughly been linked to different autoimmune disorders but their combined involvement following the hypoxia-pyroptosis axis in autoimmune pathogenesis has gone through limited exploration. Recent findings in both autoimmune and non-autoimmune context have proposed that hypoxia mediate HIF-1 α signaling might trigger inflammasome activation as well as pyroptosis mediated cell death, suggesting a potential yet underexplored mechanism in autoimmune disease progression.

2 Literature search and synthesis

A targeted literature search was executed in order to find relevant evidences on the interactions between hypoxia, HIF-1 α signaling, inflammasome activation, and pyroptosis, with particular attention to their contributions to autoimmune and chronic inflammatory diseases. The search was carried out in the PubMed, Google Scholar, Scopus and Web of science databases. Key search terms were used in combination, including “pyroptosis,” “hypoxia,” “hypoxia-inducible factor-1 α (HIF-1 α),” “inflammasome,” “NLRP3 (NOD-like receptor family pyrin domain containing 3),” “gasdermin,” “autoimmune diseases,” “chronic inflammatory diseases,” “inflammation,” and “therapeutic targeting.” The review was limited to English-language publications. Because this article is a narrative synthesis rather than a systematic review, the purpose of the literature search was to identify and critically synthesize relevant, representative evidence, not to deliver an exhaustive or quantitative appraisal of all available studies.

3 Basic mechanism of pyroptosis

The basic mechanism of pyroptosis follows 4 different pathways, the canonical pathway, the non-canonical pathway, caspase-3/8 mediated pathway and granzyme mediated pathway.

In case of canonical pathway, various bacterial and viral signalling molecules stimulate the cell, cause pattern recognition receptors (PRRs) to assemble with apoptosis-associated speck-like protein containing a CARD (ASC) and consequently pro-caspase-1 forms the inflammasome. [14-23] Once the inflammasome gets assembled, caspase-1 gets activated and hydrolysed into two separate fragments that gets dimerized later forming mature

and cleaved caspase-1. [24] Caspase-1 cleaves the gasdermin D (GSDMD) at the aspartic acid residue at position 275 (Asp275) resulting in the 31kDa N-terminal fragment (N-GSDMD) and 22kDa C-terminal fragment (C-GSDMD) formation. N-GSDMD causes the cell membrane rupture forming non-selective pores and leads to cellular swelling and ultimately pyroptosis. [25,56]

The non canonical pyroptosis pathway, human caspase-4/5 along with their murine ortholog caspase-11 directly interact with intracellular lipopolysaccharide through their N-terminal caspase activation and recruitment domain (CARD), leading to their activation. [27] Activated caspase-4/5/11 can cleave GSDMD forming the N-terminal fragment, which gets oligomerized and translocated to the plasma membrane where it causes pore formation. [28] These caspase-4/5/11 do not efficiently process pro-interleukin-1 β (pro-IL-1 β) and pro interleukin 18 (pro-IL-18), however in some cells these cy-

tokines attain maturity by following the NLRP3/caspase-1 mediated pathway. [29] In addition, the GSDMD cleavage leads to K⁺ efflux, induces the assemble of NLRP3 inflammasome and ultimately results in pyroptosis. [30-32]

In addition to these canonical and non-canonical pathways, there are caspase 3/8 mediated and granzyme mediated pathways. Caspase-3/8 mediated pathway has been demonstrated to work through chemotherapeutic drugs, promoting caspase-3 regulated gasdermin E (GSDME) cleavage and forming N-terminal GSDME and subsequent pyroptosis mediated tumor cell death. [33] In mouse macrophages, there's an expression of effector protein YopJ under Yersinia infection and this protein promote caspase-8 mediated GSDMD cleavage while inhibiting TAK1 or TGF- β -activated kinase and eventually leading to pyroptosis. [34,35] Common pathways of pyroptosis and their interlinked nature is represented in figure 1.

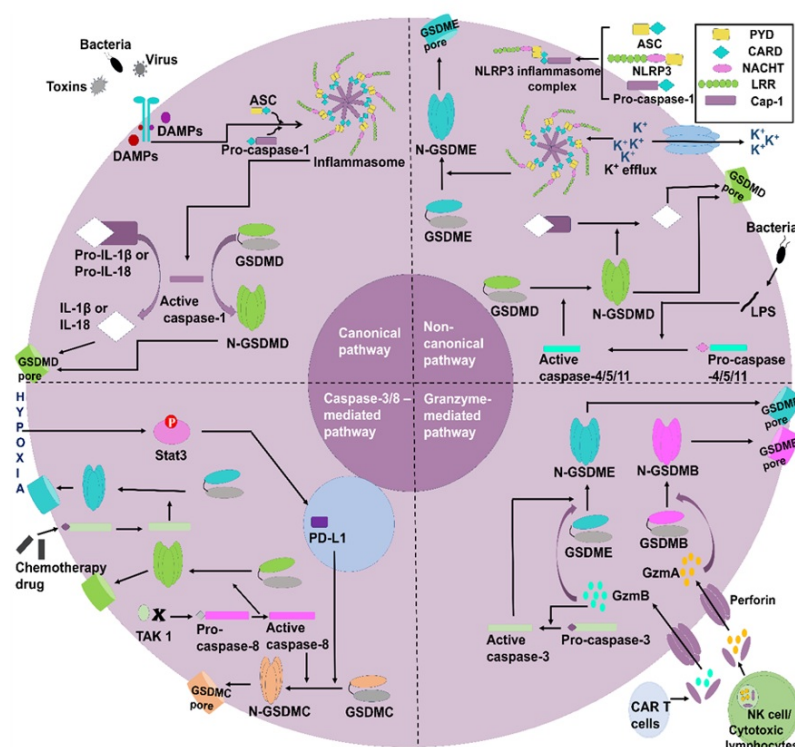


Figure 1: Mechanism of pyroptosis, following the canonical, non-canonical, caspase3/8 mediated and granzyme mediated pathway. Modified from Mahato et al. (2027) [13].

4 Hypoxia a potential inducer of pyroptosis

Hypoxic condition occurs when the oxygen supply is not sufficient in order to maintain the basic cellular functionality. [36] The adenosine triphosphate (ATP) molecules play a crucial role in maintaining the viability of brain tissue, cellular integrity and the electrophysiological activity; to form these ATP molecules, brain uses up around 20 percent of the entire oxygen supply of the body. [37] Under aerobic condition in mitochondria, ATP is synthesized following the oxidative phosphorylation pathway. [38] A hypoxic environment disrupts the mitochondrial ATP generation and consequently it affects the ion channel homeostasis, the mitochondrial metabolism, and causes membrane damage and reactive oxygen species (ROS) production. [39,40]

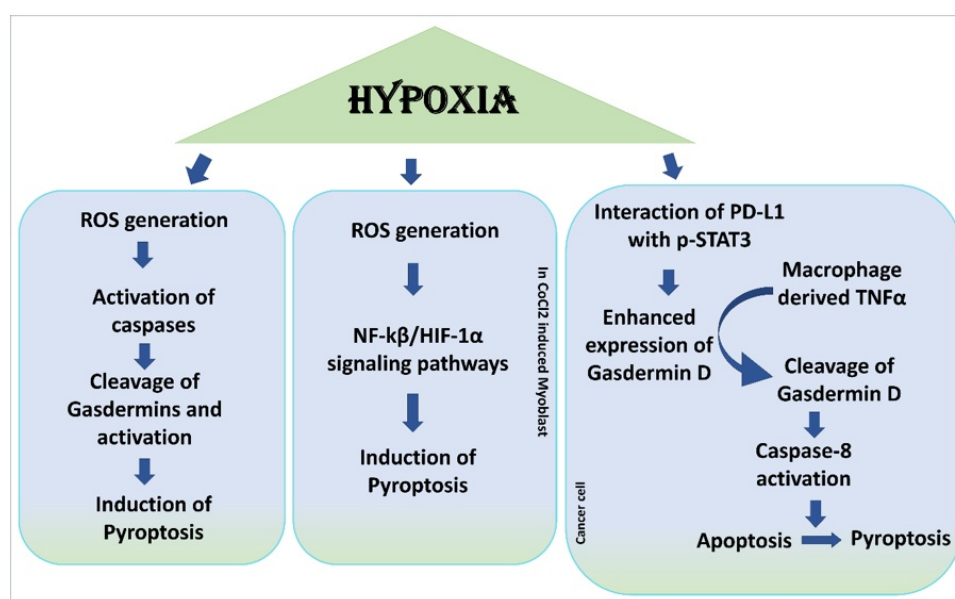


Figure 2: Major molecular mechanisms through which hypoxia promotes pyroptosis in different cellular conditions.

Numerous emerging evidence showed hypoxia has the ability to induce pyroptosis. [41,42] [Figure: 2] In neuronal cells, hypoxia driven ROS production can activate the caspase dependent gasdermins and promote pyroptosis. [43] Following the NLRP3 inflammasome and caspase-1 activation, chronic hypoxia triggers Gasdermin D (GSDMD) mediated pyroptosis in renal tubular epithelial cells. [44] In CoCl₂ myoblasts ROS overgeneration caused by hypoxia, elevates NF-κB/HIF-1α signaling pathways and results in pyroptosis following caspase-1/GSDMD activation. [45] In intracerebral hemorrhage (ICH) model, hypoxia preconditioning elevates the functionality of olfactory mucosa mesenchymal stem cells (OM-MSCs) and

reduce microglial pyroptosis. [46] In hypoxic environment, PD-L1 shows its physical interaction with p-Stat3, gets translocated to nucleus and increases expression of gasdermin C (GSDMC). Macrophage-derived TNFα leads to GSDMC cleavage and caspase-8 activation, this leads to apoptosis to pyroptosis switch of cancer cells. [47] NLRP3 gets activated through the direct binding of HIF-1α to the promoter region of the gene, increasing availability of components needed for inflammasome assembly. This sensitized state gets influenced by bacterial components or ROS and promotes caspase-1 mediated GSDMD cleavage, enhancing pyroptosis mechanism. [11] Moreover, through the modulation of caspase-8/GSDMD reg-

ulated pathway and inflammatory mediators HIF-1 α can trigger pyroptosis, functioning simultaneously with the classical caspase-1 regulated pathway of pyroptosis and exacerbating inflammation as well as tissue damage. Pulpitis, a disease that displays common pathological characteristics with osteomyelitis like hypoxia, bacterial colonization and inflammation. Here NLRP3 activation has been demonstrated by HIF-1 α via NF- κ B-signalling pathway, therefore triggering activation of caspase-1 and secretion of IL-1 β . [48] Knocking down of HIF-1 α resulted a significant reduction of mRNA as well as the protein expression of pyroptosis associated molecules like GSDMD, caspase-1, NLRP3, IL-18 and IL-1 β . On the other hand, activation of HIF-1 α works in expression enhancement of these proteins, aggravating the inflammation. [49] Considerably, salidroside (Sa) mitigates inflammation and pyroptosis of macrophage through ROS-HIF-1 α positive feedback loop disruption. By eliminating excess intracellular ROS, Sa shows the antioxidant effects. This mechanism leads to the restoration of prolyl hydroxylase (PHDs) activity and triggering the degradation of HIF-1 α , interrupting the positive feedback circuit and eventually limits the downstream pyroptotic pathways activation. [50]

4.1 Oxygen as a critical regulator of wound healing

Chronic wounds are described as wounds, not having a usual explicit step by step procedure of healing but are stuck in a disorganized and self-sustaining inflammatory phase. [49] Even though there can be numerous underline reasons for chronic wounds but majority of them follow the same behavioural and progress pattern. This homogeneity comes from the integral components of predominant chronic wounds, including local hypoxic condition in tissue, microbial colonization, the repeated ischaemia-reperfusion cycles coupled with age-related cellular and systemic

changes etc. [51-54] Protracted wounds offer a significant example of how persistent hypoxic environment can take part in compromised tissue repair and chronic inflammation. [55] Sustained deficiency of oxygen can promote inflammasome activation through ROS generation and thus sustaining inflammatory cell death pathways. [56] Hence, for better understanding the interplay between pyroptosis, hypoxia and inflammation, wound healing offers a relevant pathological context.

Role of oxygen has been extensively documented in case of wound healing mechanism. Under hypoxic condition, the alteration in oxygen gradient elevates the hypoxia responding pathways attempting to restore the sufficient oxygen supply to cells. [57] In the initial inflammatory stage, the disrupted vascular structures neighbouring the wound causes compromised oxygen delivery and makes the wound sites hypoxic. The situation further gets intensified with the accumulating inflammatory cells engaged in the healing process having a high metabolic oxygen requirement. Through their localization in the hypoxic areas, these inflammatory cells take part in re-epithelialization, granulation and various other healing mechanisms. [58] The functionality of stromal cells also gets affected due to this hypoxic gradient, as human dermal fibroblasts have been shown significantly more proliferation under acute hypoxic condition. [59] The secretion of transforming growth factor - β 1 (TGF- β 1) from the stromal cells have been increased by 9-fold once they got exposed to hypoxic environment. [60]

This oxygen insufficiency not only trigger the hypoxia-associated pathways but also impair tissue repair mechanism, which usually alleviate inflammatory injuries. Compromised wound healing would accumulate the damaged cells and danger associated molecular patterns (DAMPs), which in turn leads to inflammasome activation and pyroptosis induction. Further amplification of local inflammation is influenced by secretion of pro-inflammatory cytokines

like IL-1 β and IL-18, thereby sustaining the hypoxia and establishing a feed-forward loop of hypoxia, pro-inflammatory programmed cell death and autoimmune tissue impairment.

5 Interplay between hypoxia and pyroptotic axis in autoimmune disorders

Whereas pyroptosis and hypoxia have conventionally been explored as separate biological processes, according to numerous recent researches these two distinct mechanisms are intertwined with each other within the autoimmune microenvironment. [Figure: 3] The early onset and development of autoimmune disorders (AIDs) have closely been linked to the hypoxic microenvironment. [61,62] Continuous interaction between numerous

factors results in hypoxic microenvironment formation. Infiltration and activation of various immune cells start including T and B lymphocytes, macrophages, neutrophils, myeloid derived suppressor cells (MDSCs), once the target tissue undergo destruction. These infiltrated immune cells take part in hypoxic environment formation. The continuation of inflammatory reactions and unusual activation of immunity give rise to enhanced oxygen uptake, ultimately aggravating hypoxia in local tissue. [63-65] A handful of researches have targeted the link between hypoxia-inducible factor 1- α (HIF-1 α) and B, T lymphocytes in case of adaptive immunity. However existing reports exhibited that the secretion of inflammatory cytokines is modulated by HIF-1 α , resulting in an imbalance of Th1, Th2, Th17, Treg cells, and CD8+ T cells, involved in different autoimmune disorders. [61].

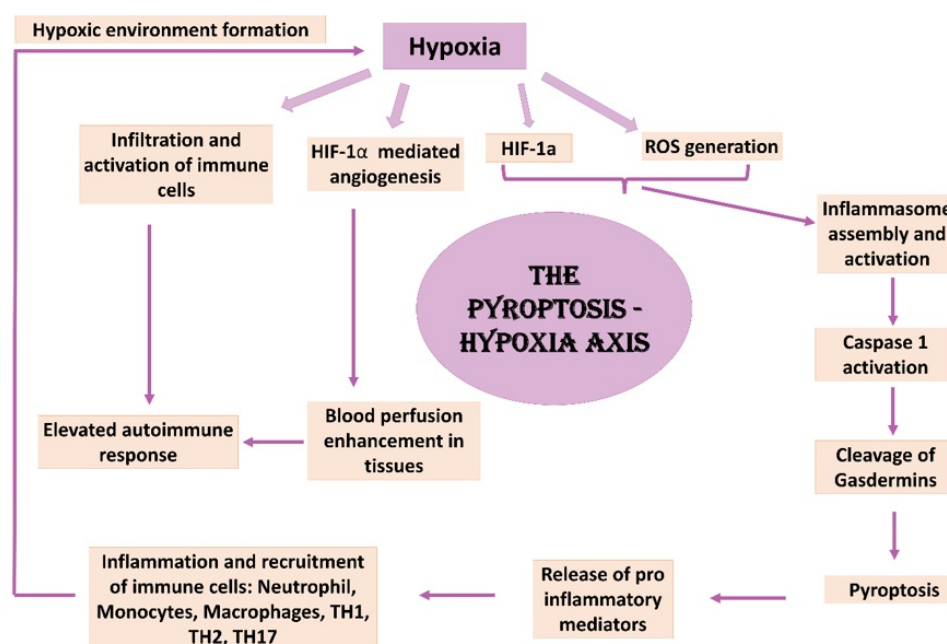


Figure 3: Schematic representation of interplay between Pyroptosis, hypoxia and autoimmune response..

In hypoxic microenvironment, HIF-1 α induced mTOR signalling pathway activation might work on the Warburg effect enhancement, that facilitates the upregulation of glycolysis involved genes Which, in

turn promotes increased uptake and usage of glucose by cells, coupled with the existing elevation in lactate production. [66-68]

For enhancing their ability to adapt in hypoxic environment, the rapidly proliferat-

ing immune and tumor cells utilize this metabolic reprogramming as a vital energy source. As a consequence, it might worsen the closely linked hypoxia and underlying autoimmune mechanism. [66,69] In autoimmune disorders, angiogenesis mediated by HIF-1 α might results in blood perfusion enhancement within affected tissue, alleviating the local hypoxia, while simultaneously inducing inflammatory cells infiltration and aggravating autoimmune responses. [70] Additionally, through the interaction with TCR, HIF-1 α -responsive genes undergo activation, making an impact on differentiation and regulation of Th1, Th2, Th17, and Treg subsets, thus modulating the inflammation while maintaining immune equilibrium, and mitigating autoimmune responses.

A study showed an increase expression of BCL2/adenovirus e1B 19kDa protein interacting protein 3 (BNIP3) and Microtubule-Associated Protein 1 Light Chain 3 Beta was found in synovial tissue of individual suffering from Rheumatoid arthritis (RA). In hypoxic microenvironment, fibroblast-like synoviocytes (FLS) of RA underwent NLRP3 mediated pyroptosis and BNIP3 mediated mitophagy. It came across as the entire expression of NLRP3 and BNIP3 is modulated by hypoxia via transcription factor HIF-1. Through reduction in intracellular ROS, mitophagy activation efficiently showed inhibition of hypoxia mediated pyroptosis. [71] Another independent research demonstrated that by following the ROS/ G protein-coupled receptor kinase 2 (GRK2) /HIF-1 α /NLRP3 mediated pathway, hypoxia triggered pyroptosis and monomeric derivatives of paeoniflorin (MDP) showed a successful reduction in FLS pyroptosis through suppressing the GRK2/ HIF-1 α axis. [72] Through a dual modulation of HIF-1 α /BNIP3 regulated mitophagy and HIF-1 α /NLRP3-mediated pyroptosis, emodin ameliorates RA progression. [73]

6 Therapeutic Targets of the Hypoxia-Pyroptosis Axis in Autoimmune and Chronic Inflammatory Diseases

Accumulating reports indicate about a close association of chronic inflammation in autoimmune diseases and tissue hypoxia and hypoxia-mediated signalling pathway activation.

Uncontrolled pyroptosis might result a chronic inflammatory response, which may exacerbate the autoimmune disease development. Tumor necrosis factor (TNF) and NLRP3 tend to enhance pyroptosis in rheumatoid arthritis (RA), aggravating the disease. Nuclear antigen secretion in systemic lupus erythematosus (SLE) induce the disease development. Activation of caspase-11 in primary astrocyte trigger pyroptosis of oligodendrocytes, promoting the multiple sclerosis (MS).

a. Rheumatoid arthritis

Hypoxia represents as a significant microenvironmental trait associated with rheumatoid arthritis (RA). Within the RA synovium hypoxia-inducible factors (HIF), serving as key transcriptional regulators exhibit their elevated expression in order to modulate adaptive responses to this hypoxic environment. Numerous reports facilitate the role of hypoxia and HIFs in modulating several significant pathophysiological features of RA, that covers angiogenesis, synovial inflammation and destruction to cartilage. The enhanced expression of both HIF-1 α and HIF-2 α in the context of RA have been reported in both experimental and clinical results. [74]

Accumulating evidence exhibited that different immune cells release various types of immunomodulatory cytokines and infiltrate, as well as migrate into the joints resulting to pyroptosis elicited chronic synovitis and degradation of cartilage. [75,76] So, if the imbalanced “immune-inflammation” system can be reversed,

particularly through suppressing pyroptosis, might be a future therapeutic strategy against RA. According to a research work, mangiferin (MG) and cinnamic acid (CA), a combination from Baihu-Guizhi decoction (BHGZD) which is a traditional Chinese medicine, might show interaction with TLR4/PI3K/AKT/NF- κ B signalling pathway in order to suppress the activation of NLRP3 inflammasome and eventually regulate pyroptosis. [77]

b. Systemic Lupus Erythematosus (SLE)

As a typical inflammatory autoimmune disease, Systemic Lupus Erythematosus (SLE) is marked by antibodies production and various tissues and organs impairment, like joints, skin and kidneys. Lupus nephritis (LN) serves as the most complex disease in SLE and also as the leading cause of death in lupus patients. [78] Level of the urinary HIF-1 α were elevated in patients with LN in comparison to the healthy ones and displayed its association with estimated glomerular filtration rate (eGFR) and histopathological chronicity indexes. Another study demonstrated HIF-1 α showed higher expression in both tubulointerstitial and glomerular areas of LN patients and MRL/lpr lupus mice. Additionally, a major enhancement in intraglomerular HIF-1 α ⁺ cells were also found. [61] If HIF-1 α gene is silenced in MRL/lpr mice, it can show inhibition in IL-17 serum, proteinuria and anti-nucleosome antibody levels and depositions of IgG and C3 in kidney. In MRL/lpr mice, inhibiting glutaminase influences the glycolysis pathway via lowering the expression of HIF-1 α and lowers the CD3⁺CD4⁺CD8⁺ T cells percentage as well as decrease the glomerular pathology scores. [61]

Recent studies have established a link between pyroptosis and SLE. According to a latest report, the SLE patients increased expression of NLRP3 inflammasome related components, like mono-

cytes/macrophages, bone marrow derived mesenchymal stem cells. In addition, active caspase-1 content in monocytes displayed a positive correlation with the anti-double-stranded DNA antibody (anti-dsDNA Ab) titers. [79,80] These anti-dsDNA Abs serve as hallmark antibodies of SLE. The activation of NLRP3 inflammasome in monocyte/macrophages of SLE patients can be induced by these anti-dsDNA Abs antibodies; this works through the TLR4-NF- κ B signalling pathway and production of mitochondrial ROS. [81] The epithelial stem cells (EpSCs) having the storage of inflammatory memories can trigger the wound tissue healing. As a pathway analysis, it showed the participation of AIM2 inflammasome along with its downstream effectors IL-1 β . [82] From an alternative perspective, the foundation of frequent recurrence of autoimmune dermatological disorder like SLE might be established by EpSCs. AIM2 inflammasome might have a significant role here. Elevated P2X7 receptor (P2X7R) expression in Th17 cells from patients with SLE has been reported and a positive correlation was found with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). [83] Apart from the pyroptotic cell death damage, the immune mediated inflammation in case of SLE can be enhanced by the intracellular components secreted from the pyroptotic cells. The nucleus of the pyroptotic cells display chromatin condensation only, keeping the nucleus intact without any rupture. This may facilitate the vital pathogenic factors antinuclear antibodies (ANA) generation in SLE. [84,85]

c. Multiple sclerosis

Multiple sclerosis, a persistent inflammatory demyelinating nervous system disorder, distinguished by degradation of myelin sheath, inflammation, gliosis and axonal injury, collectively result permanent functional impairments. [86] At a very beginning stage in the pathogenesis of MS, ac-

cumulation of HIF-1 α and hypoxia like tissue alterations take place. [87-90] In pre-demyelinating lesions, the HIF-1 α showed upregulated expression without any accompanying alterations in the normal-appearing white matter (NAWM) of individuals with MS. [90,91] Within the spinal cord of mice, subjected to experimental autoimmune encephalomyelitis (EAE), expression of HIF-1 α is stimulated in microglia/macrophages and astrocytes at the peak of the disease. In alliance with this observation, the transcriptional activity of HIF-1 α target genes, specifically *iNOS* and *EPO* showed involvement in neuronal damage and neuroprotection was markedly elevated. In nervous system the functionality of HIF-1 α can either provide protection through a survival increase in neurons and oligodendrocytes, or make damage through triggering BBB disruption. [89] In astrocytes and other myeloid lineages, genetic ablation of HIF-1 α has no effect on the neuroinflammatory disease development. [92] Based on the various sources of cells, HIF-1 α might be positively or negatively effective in inflammatory demyelination. Through amplifying the inflammatory infiltration and BBB opening HIF-1 α can promote the disease pathogenesis; on the other hand, HIF-1 α might also provide protection to neuronal as well as oligodendrocyte survival. Advanced studies that would target HIF-1 α in different glial cell types is required at this point in order to establish the functionality of HIF-1 α in inflammatory demyelinating disease. [93]

In case of both murine model and individuals with MS, there has been an enhanced expression of GSDMs, caspase-1, NLRP3, NLRC4, ASC, IL-1 β , and IL-18 in both brain tissue and serum. [94,95] Therapeutically, caspase-1 inhibition eventually led to reduced neurodegeneration and demyelination and eventually pyroptosis inhibition in MS model. [96] Through activating toll-like receptor (TLR4)/NF- κ B signaling pathway, high mobility group box 1 (HMGB1) can promote MS and trig-

ger pyroptosis in microglial and other cell types. [97] Within the neuroinflammatory microenvironment, caspase 3/7, the key regulator of apoptosis takes part in GSDMD mediated microglial pyroptosis. [98]

d. Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD), covering Crohn's disease (CD), ulcerative colitis are classified as chronic intestinal inflammation mediated disease, distinguished by intestinal mucosal hypoxia and compromised intestinal barrier function. Elevated HIF-1 α expression was reported in M1-type macrophages and the cells of intestine of CD patients in comparison to healthy controls. [99,100] The balance between M1 and M2 macrophages and secretory function of neutrophil is considerably impaired by HIF-1 α /glycolytic pathway, consequently affecting the colitis pathological condition. [101-103] HIF-1 α mediated IL-1 β production is facilitated by an intermediate metabolite of tricarboxylic acid cycle, succinate. This mechanism also promotes the aerobic glycolysis in M1 macrophages preferentially support the M1 phenotype. On the contrary, M2 macrophages predominantly adequate their energy from oxidative phosphorylation and fatty acid metabolism. [104]

Epithelial derived GSDMD showed elevated expression in patients with IBD and experimental colitis, indicating GSDMD might have a vital role in IBD. [105] In case of DSS induced colitis GSDMD performs a protective role. [106] GSDMD mediated cell pyroptosis results in forming pores in cell membrane, which leads to ionic fluxes. [31] Potassium (K⁺) efflux from cells results in inhibition of cytosolic DNA (DAMP)-mediated cGAS signalling. [107] In dextran sulfate sodium (DSS) induced model of colitis, damaged caused in the epithelial lining permits the intestinal pathogens to get through mucosa and inducing acute inflammation in lamina propria. [108] Moreover, cyclic dinucleotides or CDNs can be secreted from both ex-

tracellular bacteria and cells undergoing death. These CDNs further induces cGAS-STING signalling mediated activation of NF- κ B, and transcription factors IRF3; resulting in cytokine production and ultimately promoting inflammatory responses. [109]

e. Tumor microenvironment

Though the primary focus of the review is the interplay between hypoxia, inflammation, and pyroptosis in autoimmune and chronic inflammatory diseases, cancer is discussed as a comparative model to provide mechanistic and therapeutic insights. The TME is an extensively studied environment, where hypoxia, inflammatory signalling, tumor and immune cell interactions tend to modulate pyroptotic responses. Many of these mechanisms may also be relevant when considering autoimmune and chronic inflammatory diseases, where prolonged inflammation, disrupted tissue oxygenation, and impaired immune responses may also modulate cell death pathways. Accordingly, the discussion of cancer-related mechanisms is added with the intention of complementing the understanding of hypoxia-associated pyroptosis in autoimmune and chronic inflammatory diseases while highlighting conserved mechanisms and potential therapeutic strategies.

As hypoxia facilitates tumor growth and cancer progression, the enhancement of TME oxygen concentration is crucial. Generally, the blood vessels formed in cancers are impaired and non-functional, yet the increased vessels formation in cancer leads to increased oxygen supply in the TME. [110] Oxygen delivery to tumor, following the intravenous route is not practical due to the less solubility of oxygen in blood and the associated risk of systemic ROS exposure. [111] Pharmacological vasodilation has been proposed in order to increase the supply of oxygen via enhancing blood flow, however this precise modulation of blood flow to tumor tissue is dif-

ficult to accomplish. [112]

In numerous targeted cancers, such as colorectal cancer, pancreatic ductal adenocarcinoma, melanoma, fibrosarcoma, usage of nano and bio-based approaches have been established in order to transport oxygen generators to produce sufficient oxygen. This facilitates drug delivery and shows a considerable improvement in therapeutic efficacy of chemotherapy, radiotherapy and immunotherapy. [113-116]] However, due to excessive generation of ROS, following the reoxygenation leads to DNA damage and eventually cell death. Though the damage faced by neighbouring normal cells is worth concerning. Inhibiting the hypoxia regulated HIF as well as its downstream targeted genes has

come out as a successful approach. Such as, in HCC cells, HIF-1/2-regulated gene expression is inhibited by 32-134D; also resulted enhancement in HCC elimination rate (from 25% to 67%), when combined with anti-PD1 in murine model. [117] Inhibition of HIF-1/2 α mechanism as well as expression of their downstream target genes are accomplished by both HIF-1 α inhibitors, including bortezomib (PS-341), topotecan and HIF-2 α inhibitors, including PT2399, PT2385 and PT2977. [118,119] The level of VEGF in circulating cancer cells are decreased by these inhibitors; resulting in inhibition of tumor angiogenesis and enhancement of chemotherapeutic drug effectiveness, acting as a barrier in cell proliferation in colorectal cancer. [120-122] In case of in vivo studies, reduced hypoxia in TME leads to immune checkpoint blockade (ICB) efficacy against cancer progression. In cancer cells MHC-1 expression is upregulated by hyperoxia, inducing anticancer effects of NK cells, elevating the T-cell mediated cytotoxicity, [116] and inhibiting the release of MDSC-derived exosomes, thereby attenuating cancer cell stemness. [113,123] Restricting the HIF pathway regulated PD-L1 acts as a vital measure for increasing immune cancer responses. Inhibiting the HIF-1 α synthesis contributes to sup-

pressed expression of PD-L1 and induction of its lysosomal degradation, elevating CTLs mediated tumor cell killing. An improvement in survival of patients was accomplished by HIF-1 α deletion in NK cells via triggering the NF- κ B mediated pathway, followed by elevating the effector molecules (IL-18) expression. [124,125]

As a double-edged sword, pyroptosis is associated with inducing tumor growth and metastasis; on the other hand, it works in enhancing the immune cell mediated tumor cell killing. Usually, pyroptosis induction in TME might act as a future therapeutic strategy against cancer. [3,4]

The TME establishes a multiplex of system, where tumor cells show significant interaction with both immune cells and stromal cells. [126] Simultaneously the interaction between immune infiltrated cells and the existing immune cells of the TME is also significant because it can influence the fate of tumor progression. [127] The inflammatory TME has complex response to the immune checkpoint inhibition therapy. Through pyroptosis induction, ‘cold’ tumors can convert into ‘hot’ tumor, resulting in microenvironment alteration and tumor-infiltrating lymphocytes (TILs) infiltration. [128,129] Pyroptosis mediated immune response includes a lengthy mechanism, starting from the secretion of damage associated molecular patterns (DAMPs) and other inflammatory modulators which shows direct regulation of immune response, elevating adaptive immune cell

recruitment with escalated antigen presen-

tation and activation of TLR, ultimately resulting in amplified immune responses. [130] Resolving the complicated pyroptotic mechanism and the exact molecular mechanism involved in alteration of TME might contribute to future therapeutics. [131,132]

In particular contexts, pyroptosis mediated inflammatory cell death (ICD) might also be pro-tumorigenic. This displays consistency with complex inflammatory roles in both triggering as well as inhibiting tumor progression, proposing that the time, level and pyroptosis induction components are in requirement of strict regulation. As a main alarmin HMGB1 are secreted by cells undergoing pyroptosis, can induce the survival of tumor cells, indicating HMGB1 driven MDSCs accumulation via triggering autophagy, and consequently maintaining viability of MDSCs. [133-135] Additionally, HMGB1 shows immune suppression enhancement of MDSCs via inducing the differentiation from bone marrow progenitor cells and suppressive function on activation of CD4⁺ and CD8⁺ T cells. [136] When combined with other inflammatory cytokines, IL-18 shows anti-tumor activity. In absence of additional cytokine signals, the induction of Th2 responses and angiogenesis can also be induced by IL-18, leading to elevated migration and invasion in tumors. [137] Table 1 Summarizes the key regulators of the pyroptosis-hypoxia axis: mechanisms, disease associations, and therapeutic implications.

7 Discussion and conclusion

In our previous review, we pointed out several unresolved questions regarding the regulation and context-specific outcomes of pyroptosis in cancer [13]. Many of these knowledge gaps remain relevant to autoimmune diseases as well, particularly concerning the exact molecular mechanisms through which environmental stres-

sors such as hypoxia modulate inflammation activation, gasdermin-mediated pore formation, and the downstream inflammatory responses.

As per accumulating evidence there's a crucial link between pyroptosis and hypoxia and this interconnection shows significant contribution in autoimmune disease progression. [61] Limited oxygen availability might lead to the induction

Table 1: Key regulators of the pyroptosis-hypoxia axis: mechanisms, disease associations, and therapeutic implications.

Targets	Mechanism of action in pyroptosis	Hypoxia associated mechanism	Types of cancer involved	Involved autoimmune disorders	Therapeutic	References
GSDMD	Activation of inflammatory response followed by cell swelling and lysis	Terminal pore formation	Gastric cancer, NSCLC, Bladder cancer, Colorectal cancer	SLE, MS	Punicalagin, Disulfiram, Itaconate, Dimethyl fumarate, Necrosulfonamide	138–140
NLRP3	NLRP3 triggers inflammatory response by inducing pro-inflammatory cytokines like IL1 β , IL1B and promoting pyroptotic cell death	Gets activated by hypoxia produced ROS	Breast cancer, Lung cancer, Gastric cancer, Colorectal cancer, Endometrial cancer, Cervical cancer, Ovarian cancer	RA, Inflammatory bowel disease and related models, Multiple sclerosis or experimental autoimmune encephalitis	MCC950, Dapansutrile, Odonin, CY-09, Celastrol, Edaravone, Dapagliflozin, Trandolast, Ticagrelor; CP 456, 773, INF39, FC11A 2, CP 456, 773 JC 171, IFN β	141–147
Caspase-1	Induce the cleavage of Gasdermin D and release of N-terminal fragment which stimulate the membrane pore formation and leads to pyroptosis.	Activated by ROS generation and assembly of inflammatory, leading to GS-DMD cleavage	Breast cancer, Ovarian cancer, Prostate cancer, Colon cancer	MS, RA	VX-765, Boc-OvX, VX-765, VX-765	84, 96, 148–151
IL18	The precursors of IL-18 are cleaved by caspase-1 in order to get converted into their mature forms, which are subsequently released through the GS-DMD formed pores, resulting in pyroptosis.	In hypoxia mediated pyroptosis, gets released as a pro-inflammatory mediator which further leads to recruitment of immune cells.	Colorectal cancer, Pancreatic cancer, Multiple myeloma, Gastric cancer, Prostate cancer	SLE, RA, IBD, T1D	Alliin, Resveratrol, Salidroside, Oroxylin, GSK1070806, Anakinra	148, 152–155

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Targets	Mechanism of action in pyroptosis	Hypoxia associated mechanism	Types of cancer involved	Involved autoimmune disorders	Therapeutic	References
IL1B	Caspase-1 cleave the precursor form of IL1B and the mature form that leads to GSDMD mediated pyroptotic cell death	In hypoxia mediated pyroptosis, gets released as a pro-inflammatory mediator which further leads to recruitment of immune cells.	Breast cancer, Cervical cancer, NSCLC, Ovarian cancer, Nasopharyngeal carcinoma, Glioma, Sarcoma, Melanoma	RA, gout, Type I diabetes (T1D), MS, IBD	MCC950, Baicalin, Dihydroxyacetone, Resveratrol, Quercetin, Salidroside, Pralinasan	148, 156–158
NF- κ B	Promotes the canonical NLRP3 mediated pyroptosis	Priming transcription factor; elevates NLRP3, pro-IL1B and pro-IL18 expression	Lung cancer, Breast cancer, Melanoma, Prostate cancer, Bladder cancer, Colorectal cancer	RA, SLE, MS	Aesculin, Notoginsenoside R1, Geniposide, Catalpol, Methotrexate, Icaritin	148, 159–163
STAT3	STAT3 promotes the activation of Caspase-1 and induced pyroptosis. It also regulated GSDMD mediated pyroptosis.	Works in cooperates with PD-L1 to activate GSDMC transcription.	Non-alcoholic steatohepatitis, Glioblastoma, Breast cancer, Gastric cancer	RA, SLE, MS, IBD	Luteolin, R001, Tofacitinib, Ruxolitinib, Metformin, Curcumin	164-168
TXNIP	Inducing the activation of NLRP3 inflammasome as well as GSDMD and trigger pyroptosis.	Works as a sensor for ROS, bridging hypoxia to NLRP3	Breast cancer, Melanoma	RA, SLE, MS	Thioredoxin, Vorinostat, Silibinin, Lapatinib	169-172

in mitochondrial dysfunction and excessive ROS production, which may contribute in HIF-1 α stabilization and inflammatory signalling pathways activation. HIF-1 α further shows its interaction with NF- κ B-dependent signalling pathway and might promote the activation of inflammasome components, particularly NLRP3 [61] [Figure: 2]. This sensitized state gets influenced by bacterial components or ROS and promotes caspase-1 mediated GSDMD cleavage, enhancing pyroptosis mechanism and subsequent release of pro-inflammatory mediators like IL-1 β and IL-18. [173] Thus, hypoxia, HIF-1 α signalling, inflammasome activation, and pyroptosis can be considered as interrelated elements of an inflammatory signalling network. [72] Notably, this connection might a self-reinforcing inflammatory loop within the TME. Hypoxia-mediated ROS and HIF-1 α - connected inflammatory signalling can trigger the activation of inflammasome and pyroptosis, while this pro-inflammatory form of programmed cell death further modulates the microenvironment helping in sustaining the inflammation [72] [Figure: 3]. HIF signalling, the NLRP3 inflammasome, caspase-1, GSDMD might act as potential therapeutic targets; however, their precise contributions and therapeutic windows require further investigation.

Despite of the new emerging researches linking pyroptosis and hypoxia, numerous limitations like the HIF-1 α signalling might vary in different cellular as well as disease context, uncontrolled pyroptosis might lead to tissue injury, limited evidence supporting the therapeutic targeting of the complete hypoxia-pyroptosis axis etc remain unresolved. Further studies are required at this point to validate these mechanisms in clinically relevant models and patient samples.

Getting more insights into this pyroptosis-hypoxia axis gives significant perception into autoimmune disease pathogenesis and opens door for new targeted therapeutics. Mechanisms aimed at modulation of this cycle, through modulation of pyroptotic or

hypoxia signalling might offer promising future therapeutics.

Authors contribution

MM prepared the original draft, collected all literature and performed data mining. PM helped with data mining and visualization of concept. SB conceived the original concept, supervised the manuscript preparation and edited the draft manuscript and prepared final manuscript. This version of the manuscript is agreed upon by all authors.

Declaration from Authors

Authors declare no conflict of interest. Authors also declare that the manuscript is hitherto unpublished and no paper mill service involved in preparation of the manuscript and LLM AI tools were not used for generation of the concept, structure of the manuscript, collection and evaluation of data.

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