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REVIEW

The Emerging Roles of Pyroptosis, Necroptosis, and Ferroptosis in Non-Malignant Dermatoses: A Review

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Abstract: Unlike apoptosis, pyroptosis, necroptosis, and ferroptosis are recently identified modes of programmed cell death (PCD) with unique molecular pathways. Increasing evidence has indicated that these PCD modes play a crucial role in the pathogenesis of various non-malignant dermatoses (a group of cutaneous disorders), including infective dermatoses, immune-related dermatoses, allergic dermatoses, benign proliferative dermatoses, etc. Moreover, their molecular mechanisms have been suggested as potential therapeutic targets for the prevention and treatment of these dermatoses. In this article, we aim to review and summarize the molecular mechanisms of pyroptosis, necroptosis, and ferroptosis and their roles in the pathogenesis of some non-malignant dermatoses.

Keywords: pyroptosis, necroptosis, ferroptosis, molecular mechanisms, non-malignant dermatoses

Introduction

Skin disorders are classified as non-malignant and malignant dermatoses based on their etiology and pathogenesis. Non-malignant dermatoses include infective dermatoses, immune-related dermatoses, allergic dermatoses, benign proliferative dermatoses, etc. Although a majority of non-malignant dermatoses are nonlethal, they may affect the aesthetics and quality of life of the afflicted patients, making them vulnerable to the harmful psychological impact. Therefore, the pathophysiology of these dermatoses has been the focus of dermatology research in recent years.

Cell death mechanisms are divided into programmed cell death (PCD) and necrotic cell death in recent years. Previously, apoptosis was considered to be the only mode of PCD; however, several studies in the last decade have identified other forms of PCD, including pyroptosis, necroptosis, and ferroptosis. Pyroptosis occurs mainly through the activation of various caspases, including inflammasome-mediated caspase-1, leading to shear and polyaggregation of various gasdermin family members, including gasdermin D (GSDMD), thereby inducing cell perforation and death.[1] Tumor necrosis factor (TNF), Toll-like receptors (TLRs), interferon (IFN), and other mediators are the primary factors causing necroptosis. Activation of necroptosis by the ligands of cell death receptors requires the kinase activities of receptor-interacting protein (RIP)-1, RIP3, and mixed lineage kinase domain-like protein (MLKL), which are the key downstream mediators of necroptosis.[2] Lastly, ferroptosis, caused by the accumulation of iron-dependent lipid peroxides, was first proposed in 2012.[3] There is increasing evidence that ferroptosis is initiated by the incorporation of poly-unsaturated fatty acids (PUFA) into cell membranes, and its susceptibility is associated with many biological processes, including metabolic pathways of amino acids, iron and polyunsaturated fatty acids, and synthesis pathways of GSH, phospholipids, NADPH and CoQ10. Above all, ferroptosis is a type of metabolism-related PCD.[4] Furthermore, several

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studies have highlighted the correlation between necroptosis, pyroptosis, and ferroptosis and occurrence and development of both malignant and non-malignant dermatoses and it has been discovered that these types of PCD could be applied as the potential targets to treat the dermatoses effectively and safely. In this review, we discuss the molecular mechanism of necroptosis, pyroptosis, and ferroptosis and their roles in the pathogenesis of non-malignant dermatoses.

We obtained the associated studies from the Embase, PubMed, Cochrane Library, and Google Scholar databases and conducted a literature search using a list of Key Medical Subject Headings (MeSH) terms, including ("pyroptosis" [MeSH Terms] OR "pyroptosis") AND ("necroptosis" [MeSH Terms] OR "necroptosis") AND ("ferroptosis" [MeSH Terms] OR "ferroptosis") and an outcome of interest ("non-malignant" AND ("dermatoses" OR "skin diseases" [MeSH Terms] OR ("skin" AND "diseases") OR "skin diseases" OR "dermatoses")). All the manuscripts included in this study were published before January 31, 2023, without language restrictions.

Introduction to Pyroptosis, Necroptosis, and Ferroptosis

Definition and Characteristics

Pyroptosis, also known as cellular inflammatory necrosis, was first identified in 2001 by Cookson et al[5,6] as the caspase-1-dependent cell death of macrophages.[7] The morphological characteristics and molecular mechanism of pyroptosis are distinct from those of apoptosis and necrosis. Pyroptosis occurs primarily through the activation of various caspases, including inflammasome-mediated caspase-1, leading to shear and polyaggregation of various gasdermin proteins, such as GSDMD, further inducing cell perforation and cell death.[8] Furthermore, compared with apoptosis, pyroptosis occurs much faster and is followed by a release of abundant pro-inflammatory cytokines. During pyroptosis, this nuclei undergo shrinkage and DNA breakdown, while the cells swell and develop bulges and pores on the cell membrane, disrupting its integrity of cell membrane and causing the release of cellular contents, eventually leading to inflammation.[9]

In contrast, necroptosis is activated by the ligands of cell death receptors, including TNF, TLRs, and IFN, and requires the kinase activities of some key downstream mediators, such as receptor-interacting protein kinases (RIPK1), RIPK3, and MLKL.[10–12] It is characterized by cell swelling and cell membrane rupture, causing an outflow of cytoplasmic material, inflammatory response, and tissue damage.[13,14]

Lastly, ferroptosis is activated by the accumulation of reactive oxygen species (ROS) and iron (Fe^{2+}) lipid peroxidation and by the incorporation of PUFAs into the cell membrane.[15,16] Under abnormal cellular antioxidant conditions, Fe^{2+} accumulation can induce the Fenton reaction to produce excessive ROS (especially hydroxyl free radicals), which further react with PUFAs on the cell membrane. This causes the disruption of cell membrane integrity and disintegration of the cell membrane, thus activating ferroptosis.[3,17] Ferroptosis is characterized by plasma membrane integrity damage, cytoplasmic and organelle swelling, and chromatin condensation. Furthermore, mitochondrial morphology changes significantly during ferroptosis, with the shrinkage of linear grain volume, increase in membrane density, reduction/disappearance of the ridge, and rupture of the outer membrane. Additionally, ferroptosis is accompanied by cell shedding and aggregation and an increase in intracellular autophagosomes, which are distinct from the morphological features of necrosis and apoptosis.[3,18]

Molecular Mechanisms

Pyroptosis is primarily regulated by caspase-1, -4, -5, and -11-dependent signaling pathways.[19,20] Among these, the caspase-1-dependent signaling pathway is known as the classical inflammasome signaling pathway, in which the pathogen- or damage-associated molecular patterns activate the corresponding pattern recognition receptors, Nod-like receptor protein (NLRP1b and NLRP-3), NLR CARD domain-containing protein 4 (NLRC4), absent in melanoma 2 (AIM2), or Pyrin. The activation of NLRP3 and NLRC4 inflammasome also requires never-in-mitosis-A-related kinase 7 and ligand-bound neuronal apoptosis inhibitory protein.[21,22] Upon activation, the inflammasome recruits apoptosis-associated speck-like protein (ASC) and caspase-1 to form a macromolecular complex. To initiate pyroptosis.[23] Caspase-1 directly lyses GSDMD, after which the cleaved N-terminal GSDMD fragment forms a pore in the host cell membrane to regulate the release of cytoplasmic contents.[24,25] Additionally, the N-terminal fragment activates the NLRP3 inflammasome to induce caspase-1-dependent cleavage of pro-interleukin (IL)-1β and pro-IL-18 precursors to form IL-1β and IL-18. The caspase-4, -5, and -11-dependent signaling pathways, respectively, are also known as caspase-

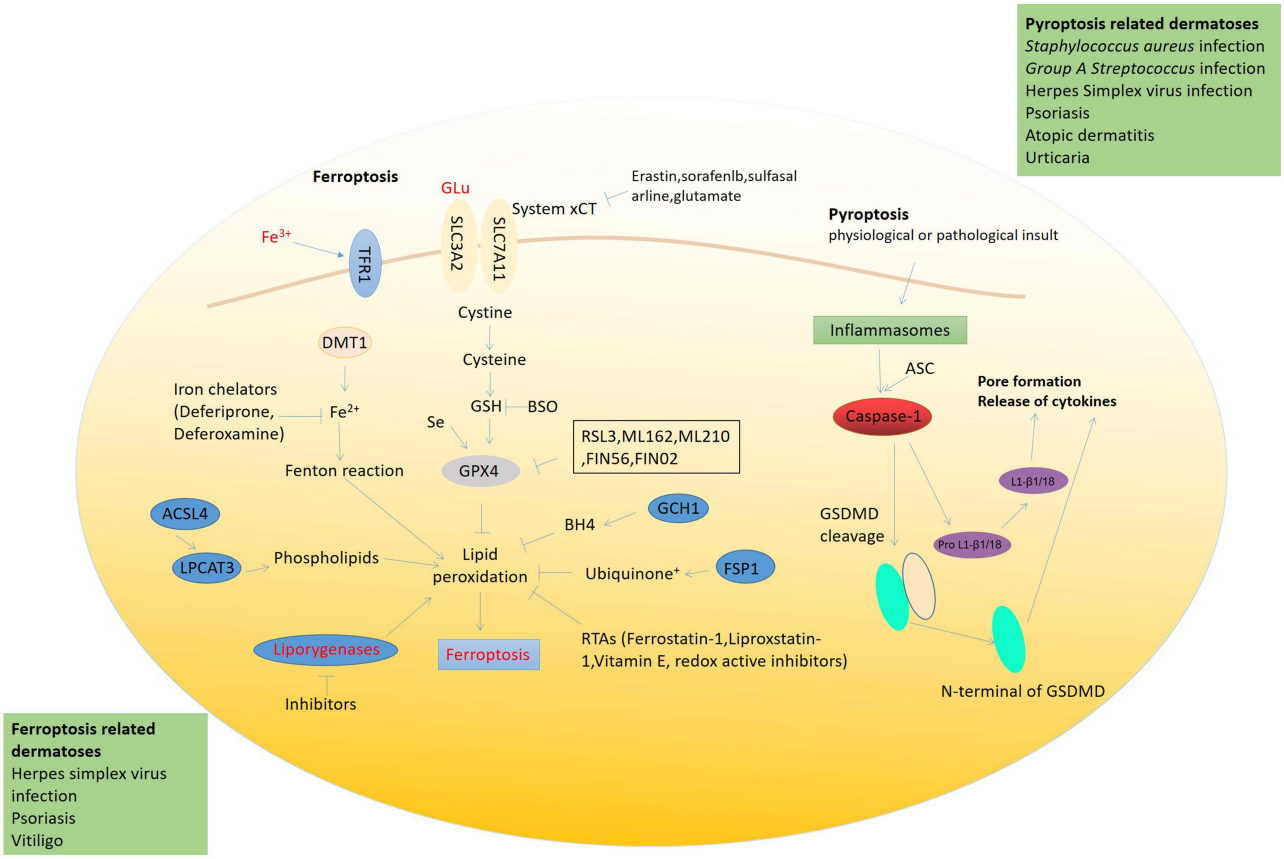

Figure 1 The molecular mechanisms of pyroptosis and ferroptosis.
Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; DMT1, divalent metal transporter 1; TFR1, transferrin receptor 1; Glu, glutamate; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GPX4, glutathione peroxidase 4; BSO, L-buthionine-(S,R)-sulfoximine; Se, selenium; RSL3, RAS-selective lethal 3; FIN, ferroptosis inducer; ML, molecular libraries; BH4, tetrahydrobiopterin; GCH1, GTP cyclohydrolase-1; FSP1, ferroptosis suppressor protein 1; RTAs, radical-trapping antioxidants; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; GSDMD, gasdermin-D; IL-1β/18, interleukin-1β/18.

1 independent signaling pathways or non-classical inflammasome signaling pathways and these pathways can directly lyse GSDMD and activate pyroptosis[26] (Figure 1).

Ferroptosis is regulated by several metabolic events, including autophagy, lipid synthesis, and mitochondrial tricarboxylic acid (TCA) cycle, and signaling pathways, including the E-cadherin-NF2-Hippo pathway, glucose-regulated adenosine 5‘-monophosphate (AMP)-activated protein kinase (AMPK) signaling pathway, and p53- and BRCA1 associated protein 1 (BAP1)-associated tumor suppressive pathways.[27] PUFA-binding phospholipids, which are mediated by the long chain of fatty acyl-CoA synthase family 4 (ACSL4) and a variety of enzymes, are required for phospholipid peroxidation and ferroptosis.[28–30] Cellular Fe^{2+} content, which is regulated by transferrin receptor-mediated iron input and autophagy-mediated ferritin degradation, is another important factor in ferroptosis. Additionally, ferroptosis can be induced by an imbalance in the intracellular reduction–oxidation (REDOX) homeostasis. For instance, under deficiency of reducing agents (such as cysteine), cellular metabolism, especially mitochondrial oxidative metabolism, leads to ROS accumulation, thus triggering ferroptosis.[31] Furthermore, glutamine catabolism plays an important role in cysteine-deficient ferroptosis, possibly by replenishing cysteine via mitochondrial TCA cycle.[32] Several transcriptional regulators and signal transduction pathways regulate cellular ferroptosis sensitivity by regulating lipid synthesis, iron homeostasis, cell metabolism, and oxidative stress processes. For instance, AMPK signaling inhibits ferroptosis by inhibiting lipid synthesis, while glucose promotes ferroptosis by antagonizing AMPK function. The E-cadherin-NF2-Hippo signaling pathway inhibits ferroptosis by weakening Yes-associated protein (YAP)-mediated transcription, including TfR and ACSL4.[16] Furthermore, tumor suppressors, p53[33] and BAP1[34], reduce cystine input in the cells by inhibiting

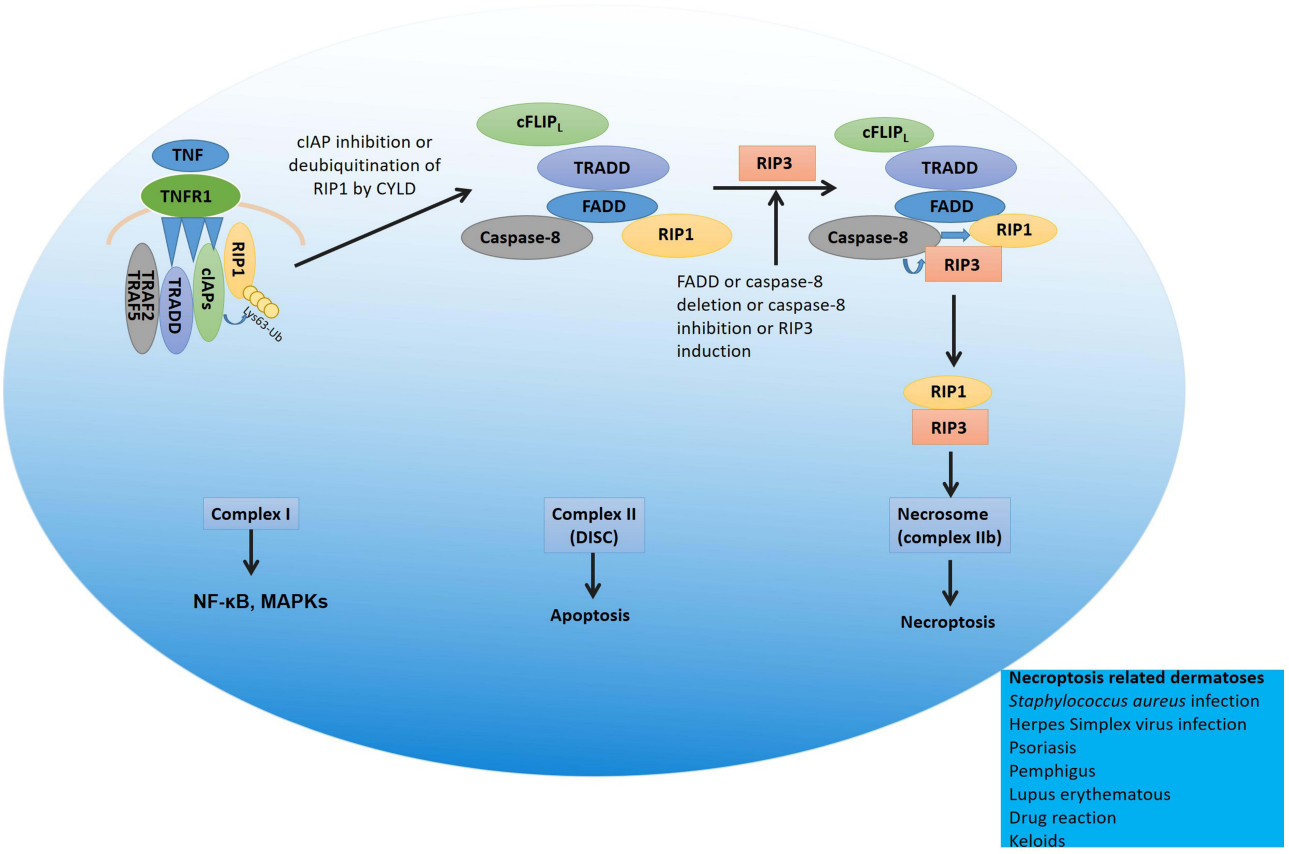

Figure 2 The molecular mechanism of necroptosis.
Abbreviations: TNF, tumor necrosis factor; TNFR1, TNF receptor 1; TRAF2, TNF receptor-associated factor 2; TRAF5, TNF receptor-associated factor 5; TRADD, TNFR1-associated death domain protein; cIAP, cellular inhibitor of apoptosis protein; RIP1, receptor interacting protein-1; RIP3, receptor interacting protein-3; Lys63-Ub, lysine-63 ubiquitinated protein; CYLD, cylindromatosis; cFLIP, cellular FLICE-like inhibitory protein; FADD, Fas-associated protein with death domain; DISC, death-inducing signaling complex; NF-κB, nuclear factor kappa-B; MAPKs, mitogen-activated protein kinases.

the transcriptional activity of solute carrier family 7 member 11 (a subunit of the system X_C^- cystine/glutamate reverse transporter), thereby sensitizing cells to ferroptosis[35,36] (Figure 1).

The necroptosis is divided into three stages: (1) the formation of complex I, (2) formation of complex IIa, and (3) formation of complex b (necrosome)[37] (Figure 2). When stimulated by internal or external necrosis signals, TNF binds to TNFR to form membrane complex I with RIPK1 to initiate necrosis. Complex I formation also involves TNF receptor-associated factor (TRAF)-2, cellular inhibitor of apoptosis protein 1/2 (clIAP1/2), and linear ubiquitin chain assembly complex (LUBAC).[38] Ubiquitination of RIPK1 by clIAP and LUBAC is the key to activating nuclear factor kappa-B (NF-kB) and suppressing apoptosis and necrosis pathways.[39,40] RIPK1 is activated after the membrane complex I formation, which initiates necrosis. Simultaneously, caspase-8, Fas-associated death domain proteins, and cylindromatosis (CYLD) combine with complex II to form complex IIa.[38] As a key regulatory factor, caspase-8 activates the downstream caspase pathway to conduct apoptosis and cleaves RIPK1 and RIPK3 to inhibit necrosis. However, when caspase-8 activity is blocked, complex IIa transforms into complex IIb (necrosome), with RIPK1 and RIPK3 as the main components. The pseudo-kinase proteins, MLKL are phosphorylated at Ser358 by RIPK3 to form oligomers, which are then transferred from the cytoplasm to the cell membrane. Thereafter, the N-terminus of these MLKL oligomers insert into the cell membrane and bind to the lipid phosphatidylinositol to form pores, thus disrupting cell membrane integrity and causing cell destruction and necroptosis.[10] Furthermore, some non-classical pathways of TLR activation in necroptosis include RIP-mediated activation of RIPK1 via TRAF and direct interaction between RIPK3 and TRAF without RIPK1.[41]

The Roles of Pyroptosis, Necroptosis, and Ferroptosis in Non-Malignant Dermatoses

Infective Dermatoses

Staphylococcus aureus (*S. aureus*) Infection

Majority of the skin infections are caused by *S. aureus*. Recurrent *S. aureus* infections cause non-healing diabetic foot ulcers (DFUs) characterized by unresolved inflammation. Additionally, intracellular *S. aureus* may induce antimicrobial resistance causing DFU recurrence.[42] In mice, perforin-2, an innate effector molecule, limits the transmission of skin infection and dissemination of *S. aureus*.[43–45] A clinical study conducted by Pastar et al[46] evaluating DFU patients receiving standardized care revealed that intracellular *S. aureus* accumulated in the DFU epidermis and triggered the activation of AIM2-inflammation and pyroptosis; however, there were no clinical infection signs owing to significant inhibition of perforin-2. *S. aureus*, that resided within the epidermis of DFU, triggered the activation of AIM2-inflammasome and pyroptosis. Furthermore, compared to healing DFUs, non-healing DFUs were characterized by increased AIM2-inflammasome and ASC-pyroptosome associated with IL-1β induction. Lastly, Pastar et al[46] found that perforin-2 inhibition, intracellular *S. aureus* accumulation and pyroptosis activation led to prolonged inflammation and inhibition of DFU healing. Liu et al[47] indicated that GSDMD may promote pathogen control and prevent tissue damage by inhibiting the chemokine ligand 1 (CXCL1)–chemokine receptor 2 (CXCR2) axis, thus having a positive effect against *S. aureus* infections. Furthermore, Kitur et al[48] found that excessive inflammatory signaling, at both systemic and local levels, contributed to morbidity and mortality in *S. aureus*-mediated infections. Studies also revealed that *S. aureus* can activate necroptosis in skin and systemic infections, suggesting that necroptosis induction during *S. aureus* infection is a key host response, necessary to promote bacterial clearance and limit inflammatory responses, especially IL-1β production.[49,50]

Group A Streptococcus (GAS) Infection

GAS (also known as Streptococcus pyogenes) can induce several acute skin infections, ranging from superficial skin infections, such as skin abscesses, to severe invasive infections.[51] LaRock et al[52] showed that GAS can secrete SpeB, a type of protease virulence factor, which initiates GSDMA-dependent pyroptosis. Considering that GSDMA is primarily expressed in skin cells, SpeB-expressing GAS-infected keratinocytes (KCs), would undergo GSDMA-dependent pyroptosis. Furthermore, LaRock et al[52] indicated that GSDMA is crucial for immunity against GAS-induced invasive skin infections. Consistently, Deng et al[53] reported that GSDMA acts as a sensor and substrate for GAS SpeB and triggers pyroptosis. Additionally, SpeB directly cleaves pro-IL-1β to produce mature IL-1β, which triggers a hyperinflammatory response to limit GAS invasion in a caspase-1-independent manner.

Herpes Simplex Virus (HSV) Infection

HSV, belonging to the alpha herpes virus subfamily, is a necrophagous virus that can infect the nervous system, causing the neurological diseases. It is transmitted among human body through physical contact and usually results in local mucocutaneous damage. There are two main types of HSV, HSV-1 and HSV-2; HSV-1 primarily causes oral and eye lesions, while HSV-2 causes genital lesions. Guo et al[54] revealed that HSV-1 and HSV-2 R1 proteins suppressed the association between RIP1 and RIP3 to inhibit the necroptosis in human cells. The N-terminal RIP homotypic interaction motif (RHIM) within R1 binds with the caspase-8-binding domain to activate the necroptosis-independent function of RHIM. In another study, Guo et al[55] found that Z-DNA binding protein 1 (ZBP1)-targeted antiviral response eliminated HSV-1-infected cells and limited viral replication in vitro and in vivo. During natural host infection, HSV-1 utilizes the RHIM in ICP6 to inhibit the virus-induced ZBP1/RIPK3/MLKL necrosome-like complex formation but not the TNF-induced necrosome. Wang et al[56] demonstrated that HSV-1 infection initiated RIP3-dependent necroptosis, which required MLKL but not TNFR, TLR3, CYLD, or host RIP homotypic interaction motif-containing protein DNA-dependent activator of IFN regulatory factor. HSV-1 ICP6 deletion mutant is unable to induce necroptosis of the cells infected by HSV-1. Additionally, ectopic expression of ICP6 could directly activate RIP3/MLKL-mediated necroptosis. Mice lacking RIP3 presented severely weakened control of HSV-1 replication, which was associated with severe neurological impairment of the central nervous system, including encephalitis. Hu et al[57] indicated that HSV-1 initiated GSDMD-dependent pyroptosis by activating NLRP3 inflammasomes, resulting in the mature IL-1β production and

release of active caspase-1 (p10). Consistently, suppression of the activation of NLRP3 inflammasome inhibited HSV-1-induced GSDMD-dependent pyroptosis. Xu et al[58] found that viral encephalitis was highly associated with HSV-1-induced ferroptosis and oxidative damage in microglia cells and astrocytes of murine brain and that the inhibition of ferroptosis by either ferrostatin-1 (Fer-1) or a proteasome inhibitor to prevent Nrf2 degradation alleviated HSV-1-induced encephalitis in a mouse model.

Human Papillomavirus (HPV) Infection

HPV is a sexually transmitted DNA virus that is associated with various types of skin warts. Song et al[59] found that HPV E7 could suppress double-stranded DNA transfection-induced pyroptosis and recruit E3 ligase TRIM21 to ubiquitinate and degrade the IFI16 inflammasome, thus inhibiting pyroptosis and promoting self-escaping from immune surveillance. Ma et al[60] reported that high-risk HPV (hrHPV) infection regulated the expression of (anti-)proliferative genes and RIP3 to control KC proliferation and resist necroptosis initiation, respectively, via causing the infected KCs to partly inhibit the IFN-γ/TNF-αinduced immune pressure, eventually leading to hrHPV immune escape and aggravation of hrHPV-induced infection.

Immune-Related Dermatoses

Psoriasis

Psoriasis is a chronic inflammatory skin disorder that seriously affects the quality of life of afflicted patients, especially in moderate-to-severe cases. Although the pathophysiology of psoriasis has not been fully elucidated, recent advances have contributed to investigation of the complex pathways associated with psoriatic lesions for the development of more efficient, effective and safe targeted therapies.[61] KC death is closely associated with various pathophysiological conditions which amplify the inflammatory cascade in psoriasis. Several studies have revealed that the expression of necroptosis effector molecules, RIP1, RIP3, and MLKL, is increased in psoriatic patients, as well as in psoriatic disease models. All layers of psoriatic epidermis had the upregulated expression of RIP1 and MLKL, whereas the upper epidermis had the main expression of RIP3 and phosphorylated MLKL (p-MLKL). Moreover, imiquimod (IMQ)-induced inflammatory response was inhibited and the production of inflammatory factors, including IL-1β, IL-6, IL-17A, IL-23a, CXCL1, and CCL20, was significantly downregulated through the application of RIPK1 and MLKL inhibitors in HaCaT cells and IMQ mouse models.[62] Furthermore, RIPK3 induced skin inflammation in a necroptosis-independent mode by controlling the production of neutrophil chemokines/cytokines by KCs, thus promoting psoriasis. When treated with IMQ, a significant decrease was observed in lactate dehydrogenase production between mice RIP3−/− and RIP3+/+ KCs; however, expression of IL-1β, IL-24, and CXCL2 was significantly decreased in RIP3−/− KCs, compared with that in RIPK3+/+ KCs. Moreover, there was a significant reduction in ear swelling and infiltrating neutrophil content in the skin of RIPK3−/− mice.[63] Some therapeutic drugs, such as convallatoxin and periplogenin, can potentially treat psoriasis by inducing necroptosis. These drugs induce oxidative stress and necroptotic cell death in HaCaT cells and reduce skin lesions in IMQ-induced psoriasis-like mouse models. Shou et al[64] found that the mRNA expression of ACSL4, prostaglandin-endoperoxide synthase 2, and transferrin receptor were significantly increased, while that of GPX4, ferritin light chain, and ferritin heavy chain 1 was significantly decreased in psoriatic lesions, unlike normal skin lesions. The ferroptosis in erastin-treated human primary KCs and IMQ-induced psoriasis model also observed the similar tendency. Lipid oxidation in KCs is highly associated with the Th22/Th17 response at a single-cell level, and Fer-1, an inhibitor of lipid peroxidation, suppresses ferroptosis-induced alternations in erastin-treated KCs and alleviates psoriasiform lesions in IMQ-induced models. In addition, Fer-1 reduces the production of cytokines to inhibit inflammatory responses in vitro and in vivo. Increasing evidence indicates that pyroptosis-related genes (PRGs) including GSDMD, caspase-1/2, IL-1 family genes, *NLRP1*, *NLRP3*, and *AIM2*, are differentially expressed in psoriasis. Therefore, it may be a potential therapeutic target to treat the psoriasis through the intervention in the pyroptosis-related signaling pathway. Deng et al[65] found that cycloastragenol selectively regulates macrophage function by suppressing the NLRP3 inflammasome-mediated pyroptosis, thereby ameliorating psoriatic skin inflammation induced by IMQ in mice. Additionally, Miglio et al[66] revealed that fumaric acid esters mediated therapeutic effects by inhibiting the NLRP3 inflammasome-mediated and ATP-triggered pyroptosis of different THP-1 cells.

Vitiligo

Vitiligo is a common depigmentation disorder that is histologically characterized by melanocyte destruction, which may be caused by various mechanisms, including apoptosis and autoimmune damage. Li et al[67] found that necroptosis markers, like phosphorylated RIP3 and p-MLKL, were upregulated in melanocytes of vitiligo perilesional skin samples, while RIP1 was significantly upregulated in hydrogen peroxide-treated melanocytes. Furthermore, they confirmed that necroptosis significantly promoted oxidative-stress-induced death of melanocytes via the RIP1 signaling pathway. Wu et al[68] observed that human epidermal melanocytes (HEMs) were sensitive to ferroptosis and suggested its role in vitiligo pathogenesis. An in vitro study found that erastin could induce ferroptosis, while N-acetyl-L-cysteine could inhibit ferroptosis in HEMs. Yang et al[69] also suggested a potential role of ferroptosis in vitiligo pathogenesis and proposed that baicalein could inhibit melanocyte ferroptosis by upregulating GPX4. Altogether, these studies suggest that ferroptosis can be a potential therapeutic target for vitiligo treatment.

Other Immune-Related Dermatoses

Alopecia areata (AA) is a chronic and recurrent immune-mediated inflammatory condition of hair follicles that leads to non-cicatricial alopecia. Previous studies on AA have revealed the occurrence of three distinct patterns of cell degeneration at variable frequencies, including "dark cell" transformation, apoptosis, and necrosis. Jang et al[70] investigated the role of necroptosis in AA and found that RIP3 and RIP1 were not associated with the pathogenesis of AA. Therefore, further large-scale studies are required to clarify the role of necroptosis in the pathogenesis of AA. Bumiller-Bini et al[71] found that the associated variants involved in apoptosis and necroptosis, including TNF, TRAF2, protein activated kinase 2 (PAK2), and pro-inflammatory cytokines with pemphigus foliaceus, suggested that the death receptor pathway acted as a specific role in this condition. Lauffer et al[72] investigated the overlap of two interface dermatitis (ID)-positive cutaneous diseases, including lupus erythematosus (LE) and lichen planus (LP), and detected a significant increase in the epidermal expression of RIP3, which is a key regulator of necroptosis. Furthermore, they also found that TCS stimulated KCs to induce phosphorylation of RIP3 and MLKL, depending on the presence of IFN-γ or TNF-α in the TCS and short hairpin RNA knockdown of RIP3 can prevent KC cell death stimulated by IFN-γ. Generally, type I immunity is related to the two diseases and induces KCs necroptosis.

Allergic Dermatoses

Atopic Dermatitis (AD)

AD is a common chronic inflammatory skin disorder that is mediated by T helper (Th)2 and has a relapsing course. AD pathogenesis is mediated by multiple factors, including skin barrier damage, microbial dysbiosis and immune dysregulation.[73] Han et al[74] found that epigallocatechin-3-gallate nanoparticles (EGCG-NPs), extracellular signal-regulated kinase (ERK)-1, and ERK2 significantly inhibited the overexpression of RIP1, RIP3, and MLKL in the entire epidermal layer, suggesting EGCG-NPs can serve as a promising necroptosis-targeting drug-delivery system for AD treatment. Additionally, inhibition of dynamin-related protein 1 (Drp1) is a potential therapeutic strategy for treating inflammatory skin conditions. Li et al[75] investigated the effect of Drp1 inhibitor, mitochondrial division inhibitor-1 (mdivi-1), on experimental AD and found that mdivi-1 suppressed the activation of NLRP3 inflammasome and pyroptosis, as evidenced by the downexpression of NLRP3, ASC, cleavage of caspase-1, GSDMD-NT, IL-1β, and IL-18 in KCs under AD-like inflammation.

Urticaria

Urticaria is a common allergic skin disease, characterized by a sudden onset of wheal, angioedema, or both. Presently, studies investigating urticaria and the associated cell death mechanisms are limited. A study by Kambe et al[76] revealed that abnormal activation of NLRP3 inflammasome in mast cells, associated with IL-1β production in cryopyrin-associated periodic syndromes, led to pathogenesis of histamine-independent urticaria. A bioinformatics study on the molecular mechanism of PRGs in chronic spontaneous urticaria (CSU), by Peng et al,[77] found that IL-β, a PRG, and its related molecules might be potential biomarkers associated with CSU occurrence and development.

Drug Reaction

Both Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are lethal cutaneous adverse drug reactions (CADRs), primarily induced by KC death. Saito et al[78] demonstrated that the binding of annexin A1 to the formyl peptide receptor 1 (FPR1) triggers necroptosis in TEN. Additionally, Kim et al[79] demonstrated the role of necroptosis in TEN pathogenesis based on the upregulation of *RIP3* expression and positive staining for p-MLKL in the tissue sections obtained from TEN patients. Additionally, Kinoshita et al[80] suggested another mechanism of neutrophil-triggered inflammation in the early stage of SJS/TEN, which proposed that the infiltrating CD8+ T cells in the skin produce lipocalin-2 in a drug-specific manner, which triggers the formation of neutrophil extracellular traps in early lesions. Neutrophils undergoing NETosis release IL-37, an antimicrobial peptide, which induces FPR1 expression in KCs. FPR1 expression increases KC sensitivity to necroptosis, further triggering release of IL-37 and expression of FPR1 in the surrounding KCs, thus amplifying the necroptotic reaction. Studies found that the NET-necroptosis axis is a unique process in adverse CADRs (SJS/TEN) but not in mild CADRs, autoimmune diseases, or neutrophil-associated disorders; therefore, further studies are required to investigate the effect of necroptosis in the pathogenesis of TEN, with a particular focus on necroptosis-triggering factors.

Benign Proliferative Disease

Keloid

Keloid is an excessive tissue response of the human body to dermal injury characterized by local fibroblast proliferation and excessive collagen production. Keloid is the growth of fibers beyond the initial area of injury, invading the adjacent normal skin tissue. Lee et al[81] confirmed an autophagy defect, via the IL-17-STAT3-HIF-1a axis, in the keloid tissues, which was associated with enhanced fibrosis and necroptosis; however, the autophagy defect, necroptosis, and fibrosis were diminished after the application of HIF-1a inhibitor. Li et al[82] investigated the effects hydrogen sulfide (H_2S) on skin fibroblast proliferation and found that H_2S production was impaired in the plasma and skin of keloid patients; however, exogenous H_2S supplementation could inhibit the proliferation of fibroblasts in keloid tissues and TGF-β1-stimulated fibroblasts in the normal skin tissues, which may be associated with oxidative stress alleviation and necroptosis inhibition.

Conclusion and Perspectives

Several studies have reported that the recently identified modes of PCD (necroptosis, pyroptosis, and ferroptosis) play significant roles in the occurrence and development of skin diseases. In this study, we reviewed and summarized the existing literature on the roles of necroptosis, pyroptosis, and ferroptosis in non-malignant dermatoses. Compared with pyroptosis and necroptosis, studies on the role of ferroptosis in dermatoses are limited, possibly owing to its relatively recent discovery. Additionally, research on PCD in some non-malignant dermatoses, such as urticarial and pemphigus, is still in the preliminary stages. Therefore, further investigations are needed to develop a deeper understanding of the specific roles, molecular mechanisms, and regulation of necroptosis, pyroptosis, and ferroptosis and to determine prevention and therapeutic strategies for these non-malignant dermatoses.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

References

1. Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases. *Signal Transduct Target Ther*. 2021;6(1):128. doi:10.1038/s41392-021-00507-5

2. Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. *Cell Mol Immunol*. 2021;18(5):1106–1121. doi:10.1038/s41423-020-00630-3
3. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–1072. doi:10.1016/j.cell.2012.03.042
4. Chen X, Kang R, Kroemer G, Tang D. Ferroptosis in infection, inflammation, and immunity. *J Exp Med*. 2021;218(6). doi:10.1084/jem.20210518
5. Cookson BT, Brennan MA. Pro-inflammatory programmed cell death. *Trends Microbiol*. 2001;9(3):0–114. doi:10.1016/S0966-842X(00)01936-3
6. Brennan MA, Cookson BT. Salmonella induces macrophage death by caspase-1-dependent necrosis. *Mol Microbiol*. 2000;38(1):31–40. doi:10.1046/j.1365-2958.2000.02103.x
7. Robinson N, Ganesan R, Hegedűs C, Kovács K, Kufer TA, Virág L. Programmed necrotic cell death of macrophages: focus on pyroptosis, necroptosis, and parthanatos. *Redox Biol*. 2019;26:101239. doi:10.1016/j.redox.2019.101239
8. Kovacs SB, Miao EA. Gasdermins: effectors of Pyroptosis. *Vaccine*. 2017;35:35.
9. Fang Y, Tian S, Pan Y, et al. Pyroptosis: a new frontier in cancer. *Bio Pharmacot*. 2020;121:109595. doi:10.1016/j.biopha.2019.109595
10. Grootjans S, Vanden Berghe T, Vandenabeele P. Initiation and execution mechanisms of necroptosis: an overview. *Cell Death Differ*. 2017;24(7):1184–1195. doi:10.1038/cdd.2017.65
11. Zhang YY, Liu H. Connections between various trigger factors and the RIP1/ RIP3 signaling pathway involved in necroptosis. *Asian Pac J Cancer Prev*. 2013;14(12):7069–7074. doi:10.7314/APJCP.2013.14.12.7069
12. Liu Y, Liu T, Lei T, et al. RIP1/RIP3-regulated necroptosis as a target for multifaceted disease therapy (Review). *Int J Mol Med*. 2019;44(3):771–786. doi:10.3892/ijmm.2019.4244
13. Tonnus W, Meyer C, Paliege A, et al. The pathological features of regulated necrosis. *J Pathol*. 2019;247(5):697–707. doi:10.1002/path.5248
14. Galluzzi L, Kepp O, Chan FK, Kroemer G. Necroptosis: mechanisms and Relevance to Disease. *Annu Rev Pathol*. 2017;12:103–130. doi:10.1146/annurev-pathol-052016-100247
15. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol*. 2021;22(4):266–282. doi:10.1038/s41580-020-00324-8
16. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. *Cell Res*. 2021;31(2):107–125. doi:10.1038/s41422-020-00441-1
17. Yang WS, Stockwell BR. Ferroptosis: death by Lipid Peroxidation. *Trends Cell Biol*. 2016;26(3):165–176. doi:10.1016/j.tcb.2015.10.014
18. Xu T, Ding W, Ji X, Molecular mechanisms of ferroptosis and its role in cancer therapy. *J Cell Mol Med*. 2019;23(8):4900–4912. doi:10.1111/jcmm.14511
19. Lei Q, Tao YI. Research progresses of the effective mechanism of pyroptosis and its related diseases. *J Med Postgrad*. 2017;2017:648–652.
20. Man SM, Karki R, Kanneganti TD. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. *Immunol Rev*. 2017;277(1):61–75.
21. Mitchell PS, Sandstrom A, Vance RE. The NLRP1 inflammasome: new mechanistic insights and unresolved mysteries. *Curr Opin Immunol*. 2019;60:37–45. doi:10.1016/j.coi.2019.04.015
22. Robinson KS, Teo DET, Tan KS, et al. Enteroviral 3C protease activates the human NLRP1 inflammasome in airway epithelia. *Science*. 2020;370:6521.
23. Broz P, Pelegrín P, Shao F. The gasdermins, a protein family executing cell death and inflammation. *Nat Rev Immunol*. 2020;20(3):143–157.
24. Ding J, Wang K, Liu W, et al. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature*. 2016;535(7610):111–116. doi:10.1038/nature18590
25. Wang K, Sun Q, Zhong X, et al. Structural mechanism for GSDMD targeting by autoprocessed caspases in pyroptosis. *Cell*. 2020;180(5):941–955.e920. doi:10.1016/j.cell.2020.02.002
26. Stowe I, Lee B, Kayagaki N. Caspase-11: arming the guards against bacterial infection. *Immunol Rev*. 2015;265(1):75–84. doi:10.1111/imr.12292
27. Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell*. 2017;171(2):273–285. doi:10.1016/j.cell.2017.09.021
28. Kagan VE, Mao G, Qu F, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. *Nat Chem Biol*. 2017;13(1):81–90. doi:10.1038/nchembio.2238
29. Doll S, Proneth B, Tyurina YY, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol*. 2017;13(1):91–98. doi:10.1038/nchembio.2239
30. Yuan H, Li X, Zhang X, Kang R, Tang D. Identification of ACSL4 as a biomarker and contributor of ferroptosis. *Biochem Biophys Res Commun*. 2016;478(3):1338–1343. doi:10.1016/j.bbrc.2016.08.124
31. Gao M, Yi J, Zhu J, et al. Role of Mitochondria in Ferroptosis. *Mol Cell*. 2019;73(2):354–363.e353. doi:10.1016/j.molcel.2018.10.042
32. Gao M, Monian P, Quadri N, Ramasamy R, Jiang X. Glutaminolysis and transferrin regulate ferroptosis. *Mol Cell*. 2015;59(2):298–308. doi:10.1016/j.molcel.2015.06.011
33. Chu B, Kon N, Chen D, et al. ALOX12 is required for p53-mediated tumour suppression through a distinct ferroptosis pathway. *Nat Cell Biol*. 2019;21(5):579–591. doi:10.1038/s41556-019-0305-6
34. Zhang Y, Koppula P, Gan B. Regulation of H2A ubiquitination and SLC7A11 expression by BAP1 and PRC1. *Cell Cycle*. 2019;18(8):773–783. doi:10.1080/15384101.2019.1597506
35. Bi J, Yang S, Li L, et al. Metadherin enhances vulnerability of cancer cells to ferroptosis. *Cell Death Dis*. 2019;10(10):682.
36. Piani D, Fontana A. Involvement of the cystine transport system xc- in the macrophage-induced glutamate-dependent cytotoxicity to neurons. *J Immunol*. 1994;152(7):3578–3585. doi:10.4049/jimmunol.152.7.3578
37. Seo J, Nam YW, Kim S, Oh DB, Song J. Necroptosis molecular mechanisms: recent findings regarding novel necroptosis regulators. *Exp Mol Med*. 2021;53(6):1007–1017.
38. Pasparakis M, Vandenabeele P. Necroptosis and its role in inflammation. *Nature*. 2015;517(7534):311–320. doi:10.1038/nature14191
39. Dondelinger Y, Delanghe T, Priem D, et al. Serine 25 phosphorylation inhibits RIPK1 kinase-dependent cell death in models of infection and inflammation. *Nat Commun*. 2019;10(1):1729. doi:10.1038/s41467-019-09690-0
40. Wang X, Yousefi S, Simon HU. Necroptosis and neutrophil-associated disorders. *Cell Death Dis*. 2018;9(2):111. doi:10.1038/s41419-017-0058-8

41. Buchrieser J, Oliva-Martin MJ, Moore MD, et al. RIPK1 is a critical modulator of both tonic and TLR-responsive inflammatory and cell death pathways in human macrophage differentiation. *Cell Death Dis*. 2018;9(10):973. doi:10.1038/s41419-018-1053-4
42. Ramirez HA, Pastar I, Jozic I, et al. Staphylococcus aureus triggers induction of miR-15B-5P to diminish DNA repair and deregulate inflammatory response in diabetic foot ulcers. *J Invest Dermatol*. 2018;138(5):1187–1196. doi:10.1016/j.jid.2017.11.038
43. McCormack R, de Armas L, Shiratsuchi M, Podack ER. Killing machines: three pore-forming proteins of the immune system. *Immunol Res*. 2013;57(1–3):268–278. doi:10.1007/s12026-013-8469-9
44. McCormack R, de Armas LR, Shiratsuchi M, Ramos JE, Podack ER. Inhibition of intracellular bacterial replication in fibroblasts is dependent on the perforin-like protein (perforin-2) encoded by macrophage-expressed gene 1. *J Innate Immun*. 2013;5(2):185–194. doi:10.1159/000345249
45. Strbo N, Pastar I, Romero L, et al. Single cell analyses reveal specific distribution of anti-bacterial molecule Perforin-2 in human skin and its modulation by wounding and Staphylococcus aureus infection. *Exp Dermatol*. 2019;28(3):225–232. doi:10.1111/exd.13870
46. Pastar I, Sawaya AP, Marjanovic J, et al. Intracellular Staphylococcus aureus triggers pyroptosis and contributes to inhibition of healing due to perforin-2 suppression. *J Clin Invest*. 2021;131:24. doi:10.1172/JCI133727
47. Liu ZZ, Yang YJ, Zhou FH, et al. GSDMD contributes to host defence against Staphylococcus aureus skin infection by suppressing the Cxcl1-Cxcr2 axis. *Vet Res*. 2021;52(1):71. doi:10.1186/s13567-021-00937-7
48. Kitur K, Wachtel S, Brown A, et al. Necroptosis promotes staphylococcus aureus clearance by inhibiting excessive inflammatory signaling. *Cell Rep*. 2016;16(8):2219–2230. doi:10.1016/j.celrep.2016.07.039
49. Wen SH, Lin LN, Wu HJ, et al. TNF-α increases Staphylococcus aureus-induced death of human alveolar epithelial cell line A549 associated with RIP3-mediated necroptosis. *Life Sci*. 2018;195:81–86. doi:10.1016/j.lfs.2018.01.008
50. Wong Fok Lung T, Monk IR, Acker KP, et al. Staphylococcus aureus small colony variants impair host immunity by activating host cell glycolysis and inducing necroptosis. *Nat Microbiol*. 2020;5(1):141–153. doi:10.1038/s41564-019-0597-0
51. Cole JN, Barnett TC, Nizet V, Walker MJ. Molecular insight into invasive group A streptococcal disease. *Nat Rev Microbiol*. 2011;9(10):724–736. doi:10.1038/nrmicro2648
52. LaRock DL, Johnson AF, Wilde S, Sands JS, Monteiro MP, LaRock CN. Group A Streptococcus induces GSDMA-dependent pyroptosis in keratinocytes. *Nature*. 2022;605(7910):527–531. doi:10.1038/s41586-022-04717-x
53. Deng W, Bai Y, Deng F, et al. Streptococcal pyrogenic exotoxin B cleaves GSDMA and triggers pyroptosis. *Nature*. 2022;602(7897):496–502. doi:10.1038/s41586-021-04384-4
54. Guo H, Omoto S, Harris PA, et al. Herpes simplex virus suppresses necroptosis in human cells. *Cell Host Microbe*. 2015;17(2):243–251. doi:10.1016/j.chom.2015.01.003
55. Guo H, Gilley RP, Fisher A, et al. Species-independent contribution of ZBP1/DAI/DLM-1-triggered necroptosis in host defense against HSV1. *Cell Death Dis*. 2018;9(8):816. doi:10.1038/s41419-018-0868-3
56. Wang X, Li Y, Liu S, et al. Direct activation of RIP3/MLKL-dependent necrosis by herpes simplex virus 1 (HSV-1) protein ICP6 triggers host antiviral defense. *Proc Natl Acad Sci U S A*. 2014;111(43):15438–15443. doi:10.1073/pnas.1412767111
57. Hu X, Zeng Q, Xiao J, et al. Herpes simplex virus 1 induces microglia gasdermin D-dependent pyroptosis through activating the NLR family pyrin domain containing 3 inflammasome. *Front Microbiol*. 2022;13:838808. doi:10.3389/fmicb.2022.838808
58. Xu XQ, Xu T, Ji W, et al. Herpes simplex virus 1-induced ferroptosis contributes to viral encephalitis. *mBio*. 2022;14:e0237022. doi:10.1128/mbio.02370-22
59. Song Y, Wu X, Xu Y, et al. HPV E7 inhibits cell pyroptosis by promoting TRIM21-mediated degradation and ubiquitination of the IFI16 inflammasome. *Int J Biol Sci*. 2020;16(15):2924–2937. doi:10.7150/ijbs.50074
60. Ma W, Tummers B, van Esch EM, et al. Human papillomavirus downregulates the expression of IFITM1 and RIPK3 to Escape from IFNγ- and TNFα-mediated antiproliferative effects and necroptosis. *Front Immunol*. 2016;7:496. doi:10.3389/fimmu.2016.00496
61. Ruggiero A, Picone V, Martora F, Fabbrocini G, Megna M. Guselkumab, risankizumab, and tildrakizumab in the management of psoriasis: a review of the real-world evidence. *Clin Cosmet Investig Dermatol*. 2022;15:1649–1658. doi:10.2147/CCID.S364640
62. Duan X, Liu X, Liu N, et al. Inhibition of keratinocyte necroptosis mediated by RIPK1/RIPK3/MLKL provides a protective effect against psoriatic inflammation. *Cell Death Dis*. 2020;11(2):134. doi:10.1038/s41419-020-2328-0
63. Honda T, Yamamoto O, Sawada Y, et al. Receptor-interacting protein kinase 3 controls keratinocyte activation in a necroptosis-independent manner and promotes psoriatic dermatitis in mice. *J Allergy Clin Immunol*. 2017;140(2):619–622.e616. doi:10.1016/j.jaci.2017.02.027
64. Shou Y, Yang L, Yang Y, Xu J. Inhibition of keratinocyte ferroptosis suppresses psoriatic inflammation. *Cell Death Dis*. 2021;12(11):1009. doi:10.1038/s41419-021-04284-5
65. Deng G, Chen W, Wang P, et al. Inhibition of NLRP3 inflammasome-mediated pyroptosis in macrophage by cycloastragenol contributes to amelioration of imiquimod-induced psoriasis-like skin inflammation in mice. *Int Immunopharmacol*. 2019;74:105682. doi:10.1016/j.intimp.2019.105682
66. Miglio G, Veglia E, Fantozzi R. Fumaric acid esters prevent the NLRP3 inflammasome-mediated and ATP-triggered pyroptosis of differentiated THP-1 cells. *Int Immunopharmacol*. 2015;28(1):215–219. doi:10.1016/j.intimp.2015.06.011
67. Li B, Yi X, Zhuang T, et al. RIP1-mediated necroptosis facilitates oxidative stress–induced melanocyte death, offering insight into vitiligo. *J Invest Dermatol*. 2021;141(12):2921–2931.e2926. doi:10.1016/j.jid.2020.06.042
68. Wu X, Jin S, Yang Y, et al. Altered expression of ferroptosis markers and iron metabolism reveals a potential role of ferroptosis in vitiligo. *Pigment Cell Melanoma Res*. 2022;35(3):328–341. doi:10.1111/pcmr.13032
69. Yang M, Li X, Li H, Zhang X, Liu X, Song Y. Baicalein inhibits RLS3-induced ferroptosis in melanocytes. *Biochem Biophys Res Commun*. 2021;561:65–72. doi:10.1016/j.bbrc.2021.05.010
70. Jang YH, Jin M, Moon SY, et al. Investigation on the role of necroptosis in alopecia areata: a preliminary study. *J Am Acad Dermatol*. 2016;75(2):436–439. doi:10.1016/j.jaad.2016.03.015
71. Bumiller-Bini V, Cipolla GA, Spadoni MB, et al. Condemned or Not to Die? Gene polymorphisms associated with cell death in pemphigus foliaceus. *Front Immunol*. 2019;10:2416. doi:10.3389/fimmu.2019.02416
72. Lauffer F, Jargosch M, Krause L, et al. Type I immune response induces keratinocyte necroptosis and is associated with interface dermatitis. *J Invest Dermatol*. 2018;138(8):1785–1794. doi:10.1016/j.jid.2018.02.034

73. Napolitano M, Fabbrocini G, Martora F, Picone V, Morelli P, Patruno C. Role of aryl hydrocarbon receptor activation in inflammatory chronic skin diseases. *Cells*. 2021;10:12. doi:10.3390/cells10123559
74. Han M, Wang X, Wang J, et al. Ameliorative effects of epigallocatechin-3-gallate nanoparticles on 2,4-dinitrochlorobenzene induced atopic dermatitis: a potential mechanism of inflammation-related necroptosis. *Front Nutr*. 2022;9:953646. doi:10.3389/fnut.2022.953646
75. Li L, Mu Z, Liu P, Wang Y, Yang F, Han X. Mdivi-1 alleviates atopic dermatitis through the inhibition of NLRP3 inflammasome. *Exp Dermatol*. 2021;30(12):1734–1744. doi:10.1111/exd.14412
76. Kambe N, Nakamura Y, Saito M, Nishikomori R. The inflammasome, an innate immunity guardian, participates in skin urticarial reactions and contact hypersensitivity. *Allergol Int*. 2010;59(2):105–113. doi:10.2332/allergolint.09-RAI-0160
77. Peng S, Zhang T, Zhang S, Tang Q, Yan Y, Feng H. Integrated bioinformatics and validation reveal IL1B and its related molecules as potential biomarkers in chronic spontaneous urticaria. *Front Immunol*. 2022;13:850993. doi:10.3389/fimmu.2022.850993
78. Saito N, Qiao H, Yanagi T, et al. An annexin A1-FPR1 interaction contributes to necroptosis of keratinocytes in severe cutaneous adverse drug reactions. *Sci Transl Med*. 2014;6(245):245ra295. doi:10.1126/scitranslmed.3008227
79. Kim SK, Kim WJ, Yoon JH, et al. Upregulated RIP3 Expression Potentiates MLKL phosphorylation-mediated programmed necrosis in toxic epidermal necrolysis. *J Invest Dermatol*. 2015;135(8):2021–2030. doi:10.1038/jid.2015.90
80. Kinoshita M, Ogawa Y, Hama N, et al. Neutrophils initiate and exacerbate Stevens-Johnson syndrome and toxic epidermal necrolysis. *Sci Transl Med*. 2021;13:600. doi:10.1126/scitranslmed.aax2398
81. Lee SY, Lee AR, Choi JW, et al. IL-17 induces autophagy dysfunction to promote inflammatory cell death and fibrosis in keloid fibroblasts via the STAT3 and HIF-1α dependent signaling pathways. *Front Immunol*. 2022;13:888719. doi:10.3389/fimmu.2022.888719
82. Li L, He Z, Zhu Y, Shen Q, Yang S, Cao S. Hydrogen sulfide suppresses skin fibroblast proliferation via oxidative stress alleviation and necroptosis inhibition. *Oxid Med Cell Longev*. 2022;2022:7434733. doi:10.1155/2022/7434733