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Review

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Elucidating the dual roles of apoptosis and necroptosis in diabetic wound healing: implications for therapeutic intervention

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Abstract

Wound healing is a complex and multistep biological process that involves the cooperation of various cell types. Programmed cell death, including apoptosis and necrotizing apoptosis, plays a crucial role in this process. Apoptosis, a controlled and orderly programmed cell death regulated by genes, helps eliminate unnecessary or abnormal cells and maintain internal environmental stability. It also regulates various cell functions and contributes to the development of many diseases. In wound healing, programmed cell death is essential for removing inflammatory cells and forming scars. On the other hand, necroptosis, another form of programmed cell death, has not been thoroughly investigated regarding its role in wound healing. This review explores the changes and apoptosis of specific cell groups during wound healing after an injury and delves into the potential underlying mechanisms. Furthermore, it briefly discusses the possible mechanisms linking wound inflammation and fibrosis to apoptosis in wound healing. By understanding the relationship between apoptosis and wound healing and investigating the molecular mechanisms involved in apoptosis regulation, new strategies for the clinical treatment of wound healing may be discovered.

Keywords: Apoptosis; Necroptosis; Wound healing; Inflammation; Therapeutic intervention

Highlights:

- Dual regulation of apoptosis and necroptosis is crucial for optimal diabetic wound healing.
- Hyperglycemia-induced oxidative stress alters the balance between apoptosis and necroptosis in diabetic wounds.
- MicroRNAs emerge as potential biomarkers and therapeutic targets in modulating cell death pathways during wound healing.
- Targeting the RIPK3 pathway shows promise in reducing inflammation and promoting wound repair in diabetic conditions.
- Combination therapies addressing multiple cell death pathways may offer synergistic benefits in treating diabetic wounds.

Background

Apoptosis assumes a pivotal function in the process of biological development [1]. During early development, it is used to remove redundant cells and ensure the normal development of the individual. After maturation, apoptosis remains an integral part of metabolism and is used to remove damaged and abnormal cells or organelles to keep the body's cells in dynamic equilibrium, thus maintaining homeostasis and normal functioning of the body [2]. Apoptosis is more than just a mere passive process; instead, it is an active process requiring the activation, expression, and regulation of various genes. It is not a self-injection resulting from pathological conditions but rather an active death process that enables better adaptation to the survival environment [3]. Caspase-8, crucial in cell apoptosis, can promote cell apoptosis when activated, while inhibiting its activity leads to necrotic apoptosis [4]. Necroptosis is a pro-inflammatory cell death that can initiate an uncontrolled inflammatory cascade, leading to tissue damage, chronic disease, and even tumor progression [5].

Wound healing is a multistep sequential biological process involving numerous cells and mediators [6]. Disruption of any steps can lead to delayed or poor wound healing [7]. Apoptosis, also known as programmed cell death, involves a convoluted interplay of biochemical pathways that regulate cellular events. The process of apoptosis is intricately associated with the regulation of a series of events, ranging from eradicating inflammatory cells to transforming granulation tissue into scar tissue. As such, apoptosis plays an indispensable role in the facilitation of wound healing [8]. However, the correlation between wound healing and apoptosis remains inadequately comprehended. To review recent advancements in wound healing and apoptosis research, we conducted a comprehensive literature search using databases such as PubMed, Scopus,

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and Web of Science. The keywords used included "diabetic wound healing," "apoptosis," "necroptosis," "cell death," and "inflammation." We focused on peer-reviewed articles published in English from 2000 to 2023 that were directly related to wound healing in diabetic contexts. We aim to highlight the contributions of different cell populations during each healing stage and the mechanisms of apoptosis within these populations, providing insights and strategies for clinical applications.

Review

Wound healing process

The process of wound healing is a multifaceted and intricate biological phenomenon that encompasses four distinct yet interrelated stages, namely the swift attainment of hemostasis, the requisite inflammatory response, proliferation, and, ultimately, tissue remodeling [9]. It involves soluble factors, cellular components of blood, extracellular matrix (ECM) molecules, and parenchymal cells [10]. During the process of normal wound healing, various cell types collaborate to facilitate the process, such as fibroblasts, endothelial cells, platelets, keratinocytes, and phagocytes, which are regulated by diverse growth factors [11].

After ulcer formation, vasoconstriction occurs, followed by a coagulation cascade involving platelet and fibrin formation. Hemostasis is achieved by forming a fibrin clot [12]. Neutrophils and macrophages are examples of inflammatory cells that play a role in the healing process. Neutrophils primarily function as phagocytes to prevent wound infection. Neutrophils contribute to wound healing by generating growth factors for neutrophils, such as granulocyte/macrophage colony-stimulating factor (GM-CSF) [13]. Upon differentiation into macrophages, monocytes release inflammatory cytokines, initiating a local immune response [14]. The catabolic and regenerative phases are vital steps for reversing inflammation and promoting tissue regeneration, where macrophages appear to eliminate neutrophils and apoptotic cells [15].

The commencement of the proliferative phase of repair proceeds subsequent to the conclusion of the inflammatory phase and the development of granulation tissue. Basal keratinocytes, along with residual inflammatory cells and migrating cells from both the epidermis and dermis, secrete growth factors that aid in the development of granulation tissue. This tissue aids in the formation of new epithelial cells during the wound healing process [16]. Vascular endothelial growth factor is actively produced by macrophages to elicit endothelial-mediated vascular remodeling [17]. Fibroblasts move toward the wound site, synthesizing collagen, fibronectin, and additional elements that enhance the synthesis of ECM and contribute to the formation of granulation tissue alongside new capillaries. Additionally, the re-epithelialization process, which is an essential aspect of wound healing, heavily relies on the migration and widespread growth of keratinocytes originating from the edges of the wound to the center.

This particular phenomenon is pivotal in facilitating the healing and restoration of wounds [18]. Following the completion of the healing process, a series of events known as tissue remodeling ensues, during which the skin's dermal layer reacts to injury by producing collagen and ECM proteins. Specifically, type I collagen synthesis occurs to supplant the previously formed granulation tissue. Concurrently, a distinct population of fibroblasts differentiates into myofibroblasts, a specialized contractile cell type instrumental in the approximation of wound margins.

Ultimately, the healing process reaches its conclusion as the wound progressively closes, and myofibroblasts revert to their pre-injury state [19]. Effective wound repair necessitates the orchestrated interplay of diverse cellular constituents, including neutrophils, macrophages, fibroblasts, endothelial cells, and keratinocytes. An imbalance, characterized by either an excess or premature depletion of these cells, can lead to delayed wound healing and exacerbated inflammation due to hyperactive macrophages [20].

In the instance of diabetic wounds, hyperglycemia adversely affects fibroblast differentiation and alters apoptotic pathways, thereby impairing the microenvironment conducive to myofibroblast formation, disrupting the ECM, and diminishing wound contraction [21]. Therefore, the healing of wounds is contingent upon the integrated interactions among various cell types, growth factors, and ECM components [22].

Necroptosis represents a recently identified form of programmed cell death that has gained attention in scientific research over the past few years. This particular cell death pathway plays a crucial role in the body's inflammatory responses, suggesting its significance in various physiological and pathological processes. By orchestrating specific cellular events during inflammation, necroptosis contributes to the overall immune response, highlighting its potential implications in understanding and treating inflammatory diseases. Studies have shown that necrotizing apoptosis in diabetes pathogenesis can be mitigated by inhibiting this process, potentially decreasing the occurrence of chronic microvascular complications associated with the condition. Reactive oxygen species (ROS) accumulation is the primary factor that triggers necroptosis, resulting in the impairment of cell and tissue survival near the wound, consequently causing a delay in the healing process. Receptor-interacting protein kinases (RIPK1 and RIPK3) and caspase 3 are recognized as sensitive and robust markers of necrotizing apoptosis. The research shows that SIRT3 has a protective effect on necrotizing apoptosis of diabetic skin wounds compared with the control group. SIRT3 deficiency promotes necrotizing apoptosis of skin wounds in diabetic mice, which leads to impaired wound healing [23].

Apoptosis and necroptosis

Apoptosis is a meticulously regulated process of programmed cell death that plays a crucial role in maintaining cellular homeostasis. Often characterized as a form of cellular suicide, apoptosis is marked by a specific and orderly series of events that ultimately result in the systematic elimination of cells [24]. The lysosomes present within apoptotic cells possess a unique characteristic of being impervious to destruction, setting it apart from cell necrosis. During apoptosis, cells undergo a reduction in size, chromatin condensation, detachment from neighboring tissues, and are ultimately engulfed by adjacent cells without causing inflammation [25].

The tightly controlled cellular process of apoptosis relies on a network of genes and signaling pathways. In the regulation of apoptosis through the mitochondrial pathway, the B-cell lymphoma/leukemia 2 (Bcl-2) protein family plays a role by including both pro-apoptotic and anti-apoptotic members. The apoptotic program is executed by caspases, a group of

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cysteine proteases, through the cleavage of multiple cellular substrates, which ultimately causes the recognizable morphological transformations in apoptosis [26–28].

Apoptosis is necessary for cellular homeostasis and is involved in physiological functions such as embryonic development and immune system activity. Numerous pathological conditions are associated with dysregulation of apoptosis. For example, reduced apoptosis can cause cancer and tumor development, while excessive apoptosis may contribute to degenerative and autoimmune diseases [29, 30].

On the other hand, necroptosis means "programmed necrosis" or "inflammatory cell death." Unlike apoptosis, a necroptosis occurs when the plasma membrane is disrupted, organelles swell, and intracellular contents leak, which can provoke an inflammatory response [25]. Necroptosis is mediated by specific signaling pathways, such as those involving the RIPK1 and RIPK3 and the mixed lineage kinase domain-like (MLKL) pseudokinase. This type of cell death is implicated in several pathological conditions, such as viral infections, tissue injuries, and chronic inflammatory diseases, where it contributes to the disease pathology by exacerbating inflammation [31]. Both apoptosis and necroptosis are essential components of the cell death repertoire, with distinct roles in health and disease. Understanding these processes is essential for creating therapeutic strategies to regulate cell death in various diseases.

Roles and apoptosis of key cell types in wound healing

Neutrophils

Neutrophils are among the first responders to wound sites and have significant biological roles in the initial inflammatory phase. They exhibit bactericidal activity by releasing protein-hydrolyzing enzymes and ROS to clear pathogens and debris. Following their function, neutrophils undergo apoptosis to prevent the release of harmful enzymes that could exacerbate tissue damage. This apoptotic process typically begins within hours after injury and is essential for resolving inflammation and transitioning to the proliferative phase [13, 32].

Macrophages

Macrophages are versatile cells that can exhibit various phenotypes based on their microenvironment. Pro-inflammatory (M1) macrophages dominate early wound healing, while anti-inflammatory (M2) macrophages facilitate tissue repair and remodeling. The timely apoptosis of macrophages is critical for resolving inflammation and promoting tissue repair. Research indicates that dysregulated macrophage apoptosis in diabetic wounds contributes to chronic inflammation and delayed healing [20, 33].

Keratinocytes

Keratinocytes, the main cells in the epidermis, are crucial for re-epithelialization. Following injury, keratinocytes migrate to cover the wound defect and release growth factors and cytokines that stimulate other cells involved in wound healing. The apoptosis of stromal keratinocytes is a controlled event that helps regulate tissue remodeling and prevent overgrowth of cells, which could interfere with wound healing [34, 35].

Fibroblasts

Fibroblasts are essential granulation tissue formation and collagen deposition. During the proliferative phase, fibroblasts proliferate and produce ECM components. As the wound matures, fibroblasts undergo apoptosis to reduce cellularity and prevent excessive scarring. Dysregulation of fibroblast apoptosis can lead to hypertrophic scarring or fibrosis [36, 37].

Signal transduction pathways mediating apoptosis

The various stages of initiation in apoptosis are primarily facilitated by three main classical pathways, namely the endogenous pathway (also known as the mitochondrial pathway), the exogenous pathway (referred to as the death receptor pathway), and the endoplasmic reticulum (ER) pathway (Figure 1).

Mitochondrial pathway

Mitochondria serve as the regulatory hub for apoptosis, orchestrating the process through the release of cytochrome c (Cyt c), a protein encoded by nuclear DNA, which is integral to the apoptotic cascade modulated by the Bcl-2 family of proteins [38]. Bcl-2 antagonist X (BAX) predominantly resides in the cytosol and on the outer mitochondrial membrane in an inactive state as either dimers or monomers under non-apoptotic conditions. Conversely, Bcl-2 antagonist/killer 1 (BAK1, commonly referred to as BAK) functions as a key membrane protein that is anchored in the outer membrane of mitochondrial [39]. Apoptotic stimuli, such as DNA damage, growth factor deprivation, or deficits in hormone and cytokine signaling, trigger the activation of BAX, which leads to conformational changes [40]. Subsequently, an oligomeric complex formed by Bax/Bak infiltrates the outer mitochondrial membrane's pores, thus causing changes in the osmotic pressure within the mitochondrion and a decrease in its transmembrane potential. This disruption is a prelude to the egress of Cyt c from the mitochondria into the cytosol, which plays a crucial role in the activation of caspases [41].

Upon release, Cyt c binds to apoptotic protease activating factor-1 and ATP to assemble the apoptosome, which is an essential structure for apoptosis initiation. The apoptosome aids in transforming procaspase-9 into its active form, caspase-9, which then triggers the activation of executioner caspases, including caspase-3 and caspase-7. This activation sets off a cascade of caspase-mediated reactions, ultimately leading to the execution phase of apoptosis [42]. During apoptosis, mitochondria not only release Cyt c but also dispatch additional factors that induce cell death, such as endonuclease G and a DNA-degrading enzyme activated by caspases [43].

The Bcl-2 protein family has a dual function in the regulation of apoptosis by directly influencing the mitochondrial apoptosis-induced channel or the process of mitochondrial outer membrane permeabilization. Bax and/or Bak play a crucial role in promoting pore formation, which is an essential step for releasing pro-apoptotic factors from mitochondria [44]. In contrast, proteins like Bcl-2, Bcl-xL, and Mcl-1 work to block pore formation, thereby preventing the progression of apoptosis [45].

Death receptor pathway

The activation of cell surface death receptors, including members of the Fas/TNFR1 family, signifies the beginning of the extrinsic apoptotic pathway [46]. These receptors, which are a key component of the tumor necrosis factor receptor (TNFR) superfamily, feature an extracellular domain rich in cysteine

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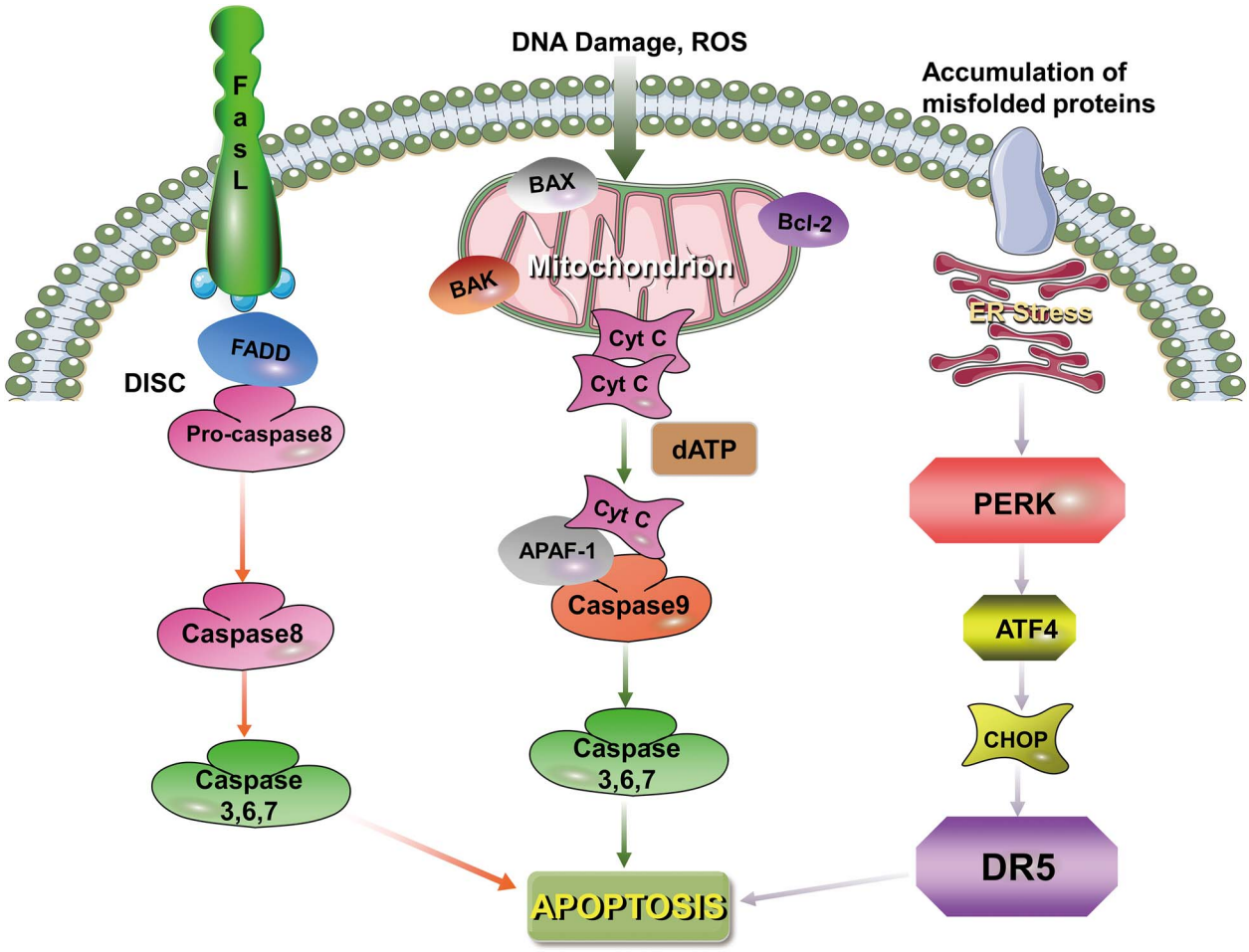

Figure 1. Diagram of apoptosis mechanism. Apoptosis can be induced through exogenous, endogenous, and ER stress pathways. Each pathway requires a specific stimulus and cystatin protease to initiate apoptosis. The activation of Caspase-3 marks the end of each initiation pathway and triggers the execution phase of apoptosis. *DISC* death-inducing signaling complex

and possess an intracellular death domain that is essential for signal transduction.

Death receptors in mammals, including prominent members like Fas/Apo-1/CD95, DR-4/TRAIL-R1, and DR3/WSL-1/Ap0-3/TRAMP, exhibit structural and functional similarities to the TNFR and nerve growth factor receptor superfamilies [47]. The Fas-associated protein with death domain (FADD) interacts with various proteins via its death effector domain, engaging key apoptotic mediators such as caspase-8 [48].

Caspase-8, upon recruitment to the FADD at high local concentrations, undergoes autocatalytic cleavage into active fragments p43/41 and p20 [49]. The interaction between the Fas ligand (FasL) and its receptor triggers the formation of a death-inducing signaling complex composed of Fas, FADD, and pro-caspase-8 [50]. The resultant activation of caspase-8 acts as a nexus for the subsequent activation of effector caspases, specifically caspase-3, 6, and 7, thereby committing the cell to the apoptotic pathway [51, 52].

Endoplasmic reticulum pathway

The ER is a vital organelle that participates in various cellular functions, including protein synthesis and modification, cholesterol metabolism, maintenance of Ca^{2+} dynamic homeostasis, and initiation of apoptosis in eukaryotic cells. Under conditions such as hypoxia, disturbed calcium metabolism, and free radical attack, the ER's capacity to ensure correct protein folding—a process pivotal for cellular integrity—is challenged. Deviations from the normative protein folding pathway can have deleterious consequences for cell viability, since the build-up of incorrectly folded proteins may precipitate severe endoplasmic reticulum stress (ERS) [53].

At moderate levels, ERS can activate cytoprotective mechanisms via the unfolded protein response (UPR), aimed at restoring the functionality of the ER. However, excessive or prolonged ERS is a harbinger of apoptosis [54]. The UPR is mediated by key sensor proteins, including activating transcription factor 6, protein kinase RNA-like ER kinase (PERK), and inositol-requiring enzyme 1. These proteins signal the presence of ERS and orchestrate cellular fate through gene expression modulation, either promoting survival or inducing apoptosis through intricate signaling cascades involving the aforementioned molecular sentinels [55].

In addition, 78-kDa glucose-regulated protein (GRP78), along with C/EBP homologous protein (CHOP), is pivotal in modulating cellular responses to ERS [56]. GRP78 is instrumental in the activation of the cytoprotective arm of the UPR, whereas CHOP is implicated in the induction of apoptosis under conditions of unresolved stress [57, 58].

Activation of transcription factor 4 (ATF4) is made possible by PERK, playing a critical role in this process. ATF4, in its turn, induces the upregulation of CHOP and genes implicated

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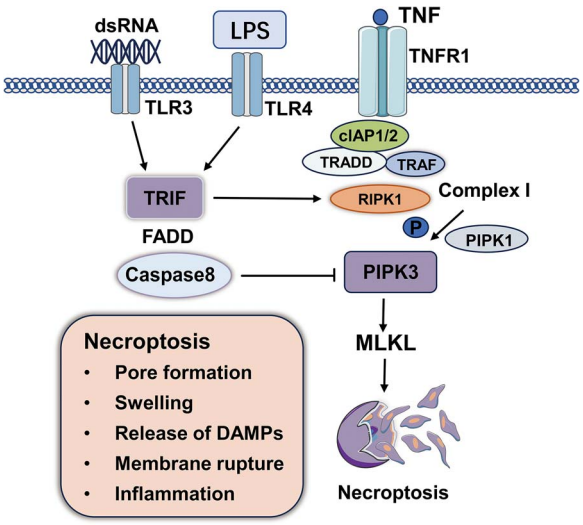

Figure 2. Diagram of necroptosis mechanism. In the absence or inhibition of caspase-8 activity, RIPK1 undergoes phosphorylation (P) and interacts with RIPK3, leading to oligomerization and phosphorylation of the pseudokinase mixed-lineage kinase domain-like (MLKL). TNF stimulation can induce necrotic apoptosis in cells expressing RIPK3, resulting in the rapid loss of cell vitality and premature termination of the TNF-induced synthesis of classical cytokines/chemokines. *dsRNA* double-stranded RNA, *PIPK* phosphatidylinositol phosphate kinases

in amino acid metabolism, protein folding, and autophagy [59]. CHOP also stimulates the upregulation of growth arrest and DNA damage-inducible protein 34, which forms a complex with phosphatase 1 to catalyze the dephosphorylation of eukaryotic initiation factor 2 alpha, thereby facilitating the resumption of protein synthesis [60].

Furthermore, during prolonged ERS, CHOP contributes to the initiation of apoptosis by upregulating pro-apoptotic molecules like Bcl-2 interacting mediator of cell death (Bim) and death receptor 5, while simultaneously downregulating the anti-apoptotic protein Bcl-2, tipping the balance toward cell death [61].

Regulation of necroptosis

Necroptosis, also known as programmed cell necrosis, is a regulated mechanism of inflammatory cell death mediated by RIPK1, RIPK3, and MLKL activation [62, 63]. When RIPK3 is activated, it phosphorylates MLKL, prompting it to translocate to the plasma membrane. This disrupts the membrane's integrity, causing cell lysis and the release of damage-associated molecular patterns, inflammatory cytokines, and chemokines [64]. This release can lead to robust inflammatory responses in the surrounding tissue.

Necroptosis can be triggered by many complicated pathways (Figure 2). The most extensively studied pathway leading to necroptosis is the one initiated by tumor necrosis factor alpha (TNFα) engaging its receptor, tumor necrosis factor receptor 1 (TNFR1) [65]. Upon TNFα stimulation, TNFR1 can form a complex that includes RIPK1 and other adapter proteins, which can then either lead to pro-survival nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling or switch toward cell death pathways, such as necroptosis. The outcome is determined by the cellular context and the presence of caspase inhibitors [66].

Toll-like receptors (TLRs) such as Toll-like receptor 3 (TLR3) and Toll-like receptor 4 (TLR4) are also key players in innate immunity, recognizing pathogen-associated molecular patterns like double-stranded RNA and lipopolysaccharide, respectively. These receptors can initiate intricate signaling cascades, ultimately resulting in the generation of type I interferons and other inflammatory mediators [67].

Interestingly, TLR3 and TLR4 can also engage in the necroptosis pathway. TLR3 can detect viral double-stranded RNA and signal through the adaptor TIR-domain-containing adapter-inducing interferon-β (TRIF), ultimately leading to the activation of RIPK3 independently of RIPK1 [68]. Similarly, TLR4 can signal through TRIF to activate RIPK3, also bypassing RIPK1, and induce necroptosis [69].

TLRs can induce necroptosis, enabling the immune system to eliminate pathogen-infected cells, particularly when other cell death pathways like apoptosis are inhibited, which is a common strategy employed by viruses to evade immune detection.

The binding of tumor necrosis factor (TNF) to its receptor, TNFR1, initiates the assembly of membrane-associated complex I. This complex is comprised of key components such as RIPK1, TNFR1-associated death domain protein (TRADD), TNF receptor-associated factor, cellular inhibitor of apoptosis protein 1 (cIAP1), and cIAP2 [70]. Within this intricate system, RIPK1 has the potential to undergo ubiquitination facilitated by cIAP1/2, a process that is reversible by the deubiquitinating enzyme cylindroma protein (CYLD) [71].

Subsequently, transforming growth factor-β-activated kinase 1, inhibitor of nuclear factor kappa-B kinase subunits α and β, and TANK-binding kinase 1/IKKε are recruited via the ubiquitin chains on RIPK1. These kinases can phosphorylate RIPK1, thereby suppressing its kinase activity and facilitating the activation of the NF-κB pathway, which plays a pivotal role in promoting cell survival [72].

On the contrary, ubiquitination of RIPK1 also facilitates the release of TRADD and RIPK1 from complex I, potentially resulting in cell death via apoptosis or necrosis [73]. During apoptosis, FADD and caspase-8 are assembled into the complex comprising TRADD and RIPK1, ultimately leading to the activation of caspase-8 and the subsequent induction of apoptosis [74].

In the absence of caspase-8, necrosis ensues, characterized by the phosphorylation and ensuing activation of RIPK3. Upon activation, RIPK3 catalyzes the phosphorylation of the mixed lineage kinase domain of MLKL, prompting a series of conformational changes within it. These modifications enable MLKL to facilitate the transfer and disruption of the integrity of the plasma membrane, ultimately leading to its destruction [75].

Following the assembly of the necrosome, RIPK1's kinase domain facilitates RIPK3 activation via cis-autophosphorylation. Activated RIPK3 then phosphorylates MLKL, precipitating the disruption of the plasma membrane. Intriguingly, studies have confirmed that homodimerization of RIPK3 alone is sufficient to activate MLKL [76].

RIPK1 and CYLD, two key upstream mediators of necrotizing apoptosis, are substrates for caspase-8 proteolytic cleavage [77]. Although RIPK3 was first discovered as a mediator of necrotizing apoptosis, recent research suggests its role in caspase-8 activation and apoptosis regulation. It operates downstream of RIPK1 in death receptor-mediated signaling pathways that govern both necrosis and apoptosis [78, 79].

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Apoptosis and necroptosis in normal wound healing

Apoptosis in normal wound healing

Apoptosis, also called programmed cell death, plays a vital role in normal wound healing. It ensures the timely removal of cells, promoting proper resolution of inflammation and scar tissue formation. During the initial phase of inflammation, neutrophils are recruited to the wound site to clear pathogens and debris. Once their function is fulfilled, neutrophils undergo apoptosis and are phagocytosed by macrophages, preventing the release of harmful enzymes that could exacerbate tissue damage [80]. Macrophages also undergo a phenotypic shift from M1 to M2 state, which is crucial for tissue repair and regeneration [20].

Necroptosis in normal wound healing

Necroptosis, a regulated form of necrosis, is characterized by its inflammatory nature and can serve as a defense mechanism against infections by creating a hostile environment for pathogens [79]. However, excessive necroptosis can lead to uncontrolled inflammation and tissue damage. In normal wound healing, a delicate balance between apoptosis and necroptosis is necessary to ensure proper wound repair. The inhibition of necroptosis pathways, such as RIPK3, has been demonstrated to enhance wound healing by decreasing inflammation and encouraging cell migration [78].

Apoptosis and necroptosis in diabetic wound healing

Apoptosis in diabetic wound healing

In diabetic wound healing, the regulation of apoptosis is often disrupted due to hyperglycemia and other metabolic imbalances. This disruption can lead to prolonged inflammation and impaired resolution, contributing to chronic wounds and delayed healing [7]. Diabetic wounds exhibit a delayed pattern of apoptosis, resulting in persistent inflammation and reduced clearance of apoptotic cells [24]. This imbalance can hinder the transition to the proliferative phase, leading to poor wound healing outcomes.

Necroptosis in diabetic wound healing

Diabetic wound healing is also greatly influenced by necroptosis. The pro-inflammatory nature of necroptosis can exacerbate chronic inflammation and tissue damage in diabetic wounds. Studies have shown that the inhibition of necroptosis pathways, such as RIPK3 and FADD-caspase-8, can enhance wound healing by mitigating inflammation and facilitating tissue repair [81]. However, a delicate balance is required, as excessive inhibition of cell death pathways can lead to uncontrolled cell proliferation and hypertrophic scarring.

Interplay between apoptosis and necroptosis in wound healing

The delicate equilibrium between apoptosis and necroptosis is pivotal for effective wound healing. Both forms of cell death play distinct roles, yet they are interconnected in regulating inflammation, tissue repair, and regeneration. Understanding their interplay can offer insights into the mechanisms of normal and impaired wound healing, particularly in chronic conditions such as diabetes.

Interplay in normal wound healing

In the context of normal wound healing, apoptosis plays an essential role in promoting the resolution of inflammation and facilitating the transition from the inflammatory phase to the proliferative phase. Macrophages efficiently clear apoptotic cells, contributing to the limitation of pro-inflammatory mediators release and promotion of tissue repair [82]. On the other hand, necroptosis, characterized by its inflammatory nature, can act as a defense mechanism against infections by creating a hostile environment for pathogens [79]. However, excessive necroptosis can lead to uncontrolled inflammation and tissue damage, highlighting the need for a balanced regulation of these cell death pathways.

Interplay in diabetic wound healing

In diabetic wound healing, the balance between apoptosis and necroptosis is often disrupted. Hyperglycemia and other metabolic imbalances can impair apoptotic pathways, leading to prolonged inflammation and delayed wound resolution [7]. Studies have shown that diabetic wounds exhibit reduced apoptosis of inflammatory cells, such as macrophages, resulting in sustained inflammation and impaired healing [24]. Additionally, the pro-inflammatory nature of necroptosis can exacerbate chronic inflammation and tissue damage in diabetic wounds. Wound healing has been shown to be improved by reducing inflammation and promoting tissue repair through the inhibition of necroptosis pathways [81].

Interplay in molecular interactions

The molecular interactions between apoptosis and necroptosis involve various signaling pathways and regulatory proteins. For instance, caspase-8 is a key regulator that can promote apoptosis when activated, but its inhibition can lead to necroptosis [78]. The interplay between these pathways is further modulated by factors such as TNF-α, which can trigger either apoptotic or necroptotic cell death based on the cellular context and specific signaling molecules [79].

Interplay in therapeutic implications

Understanding the interplay between apoptosis and necroptosis has significant therapeutic implications. Targeting these pathways can help to modulate the inflammatory response and promote effective wound healing. For example, the use of necroptosis inhibitors, such as Nec-1, has shown promise in enhancing wound healing by reducing excessive inflammation [81]. Similarly, promoting apoptosis of inflammatory cells at appropriate stages of wound healing can help to resolve inflammation and facilitate tissue repair.

The interaction between apoptosis and necroptosis plays a crucial role in wound healing. A delicate balance between these forms of cell death is necessary to ensure effective resolution of inflammation and tissue repair. Disruptions in this balance, as seen in diabetic wounds, can lead to chronic inflammation and impaired healing. Future research should elucidate the molecular mechanisms underlying this interplay and develop targeted therapies to modulate these pathways for improved wound healing outcomes.

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Apoptosis and wound healing

Role of apoptosis in wound healing

Wound healing is a highly coordinated process involving various cellular events and interactions. It is critical for preserving the integrity of the skin and other tissues following injury [81]. During wound healing, cell death is responsible for inflammatory cell shedding and granulation tissue scar formation [82]. Delayed healing of wounds poses a significant impediment to the well-being of diabetic patients. The root cause of this issue is believed to be the perturbation of blood glucose levels, which impairs cell death mechanisms during the wound healing process. It has been established that cell death is closely linked to various stages of tissue regeneration, as supported by empirical evidence.

In the initial phase of inflammation, neutrophils demonstrate a bactericidal effect by releasing protein-hydrolyzing enzymes, which serve to clear wounds and uptake expired bacteria and interstitial debris. Following the fulfillment of their function, neutrophils typically undergo apoptosis and are subsequently phagocytosed by macrophages [80]. This process is crucial as it prevents the release of potentially damaging enzymes and contents from dying neutrophils, which could exacerbate inflammation and tissue damage [83].

Macrophages are versatile cells that can exhibit different phenotypes depending on the microenvironment. The M1 macrophages are pro-inflammatory and crucial in early wound healing by removing pathogens and releasing inflammatory cytokines. As the healing process progresses, the macrophage phenotype often shifts toward the M2 type, which has anti-inflammatory properties and supports tissue repair and remodeling by dampening the immune response [84, 85].

The removal of apoptotic cells by macrophages, also known as efferocytosis, is a critical step in resolving inflammation and promoting the transition to the healing phase of wounds. Failing to clear apoptotic cells efficiently can lead to a prolonged inflammatory response, ultimately impeding the healing process [86]. Studies in animal models, such as rats, have demonstrated that apoptosis of inflammatory cells in the wound area begins within hours after injury. The pattern of apoptosis observed in these studies provides insights into the dynamics of cell turnover and the importance of timely cell death and clearance in the healing process [87].

Researchers have elucidated that apoptosis of stromal keratinocytes is a pivotal event initiating the reparative response following corneal injury [88]. This process of programmed cell death precipitates a series of biological events, including the infiltration of myeloid-derived cells, the proliferation and migration of residual keratinocytes, and, infrequently, the generation of myofibroblasts [89]. Hyperglycemia-induced apoptosis in streptozotocin-treated diabetic rats disrupts normal wound healing due to the attenuated expression of the anti-apoptotic Bcl-2 protein [90].

Prior research has demonstrated that apoptosis represents the most cogent mechanism for eliminating cells, as it obviates the need for cellular migration and does not incite inflammation [91]. Effective wound healing is critical and requires both the resolution of inflammation and scar tissue formation. During tissue repair, apoptosis plays a crucial role in balancing cell proliferation to prevent excessive growth. Clearance of inflammatory cells is a prerequisite for the commencement of the next phase of wound healing, and failing to clear inflammatory cells causes persistent inflammation that culminates in non-healing wounds. Additionally, the reduction of granulation tissue is a necessary step for the proper architectural reconstruction of cellular structures (Figure 3) [92].

Overall, the regulation of cell death and immune response during wound healing is interconnected and essential for successful tissue repair. Imbalances or dysfunctions in these processes can lead to chronic wounds or excessive scarring, both of which are complications often observed in diabetic patients (Table 1).

Apoptosis mediates wound inflammation

Wounds associated with diabetes exhibit a persistent invasion of pro-inflammatory macrophages, while wounds in normal skin display an anti-inflammatory phenotype [17]. Apoptosis is intricately linked with the modulation of inflammatory processes and plays a crucial role in the inflammatory dimension of wound healing [93]. The hemostatic phase commences promptly following wound formation, aiming to impede the uncontrolled blood release to the wound and conferring transient safeguarding measures to the affected region [94]. Platelets release an array of pro-inflammatory mediators, including serotonin, bradykinin, prostaglandins, prostacyclin, thromboxane, and histamine. These mediators function to widen blood vessels and encourage the proliferation and movement of cells toward the site of injury [95]. Furthermore, platelets aid in attracting inflammatory cells, including leukocytes, neutrophils, and macrophages, which are essential for clearing microbes and debris from the wound through the secretion of proteases and antimicrobial ROS [96].

Concurrently, neutrophils exude detrimental enzymes that may damage surrounding healthy tissue. To curtail further inflammation, neutrophils are phagocytized by macrophages as part of their apoptotic pathway [97]. Macrophages are pivotal scavengers that resolve inflammation and stimulate tissue regeneration [98].

Apoptosis is indeed integral to the wound healing process, especially in the context of removing inflammatory cells and facilitating scar formation. The eradication of inflammatory cells is imperative for advancing through the stages of wound healing, and failure to clear these cells efficiently can result in persistent inflammation and chronic, non-healing wounds [99]. In diabetic wounds, macrophages exhibit a diminished ability to phagocytose dead cells due to impaired clearance activity, which can lead to increased apoptotic cell death in the wound area [33]. This heightened level of apoptosis may then lead to a rise in pro-inflammatory cytokines, further aggravating wound inflammation [100].

The present investigation suggests that the occurrence of apoptosis among immune cells represents a crucial factor in the cessation of inflammation and the commencement of the healing process [32]. Previous studies have highlighted the role of the antiproliferative protein p53 in mediating the apoptosis of inflammatory cells throughout the wound healing process, as evidenced by its expression in the healing of porcine skin injuries [101]. Additionally, research involving human umbilical vein endothelial cells (HUVECs) has shown that intermittent hyperglycemia can induce apoptosis, which is indicated by increased DNA fragmentation, decreased Bcl-2 expression, and elevated Bax expression [102]. These findings point to the complex interplay between apoptosis, inflammation, and cellular proliferation that is essential for proper

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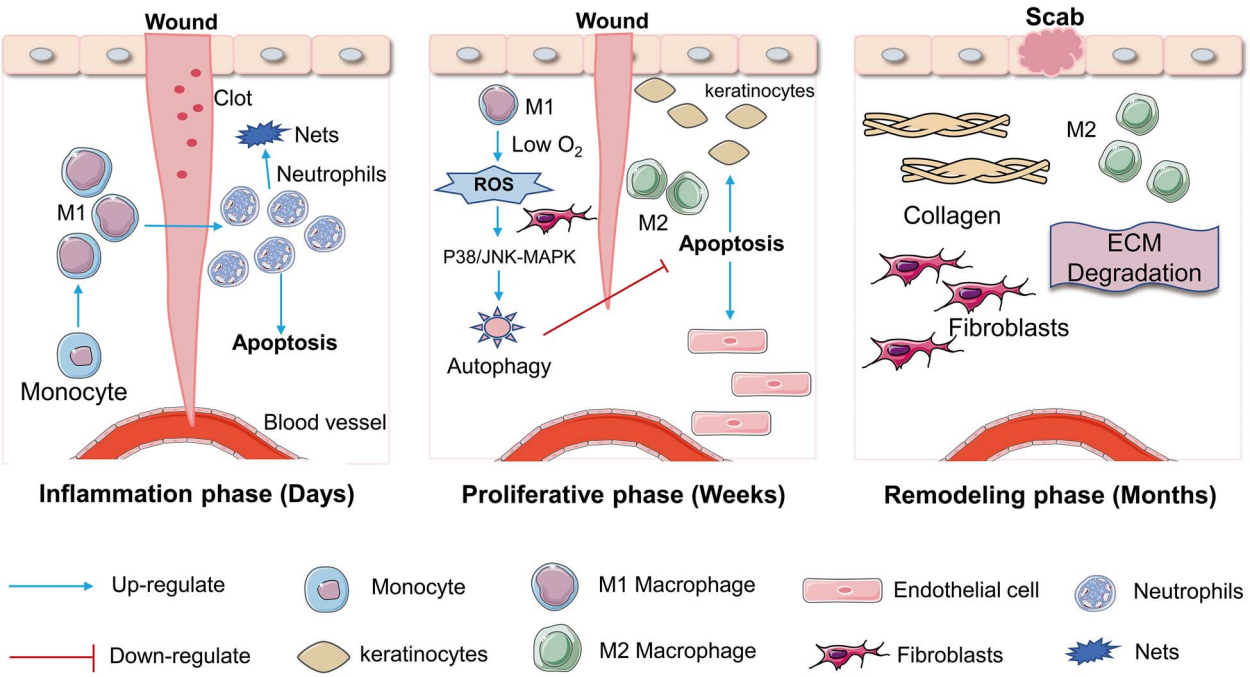

Figure 3. The role of apoptosis in skin wound healing. Apoptosis plays a vital role in the process of wound healing, specifically in the regulation of various phases such as inflammation (**a**), proliferation (**b**), and remodeling (**c**). By controlling the proliferation and migration of neutrophils, macrophages, endothelial cells, keratinocytes, and fibroblasts, apoptosis actively promote the healing of wounds. M1, pro-inflammatory macrophages; M2, anti-inflammatory macrophages

Table 1. The overview of apoptosis and necroptosis in diabetic wound healing

Classification	Target cells	Mechanism of effect	Wound healing results	References
Necroptosis	Macrophage	Decreased necroptosis	Wound healing is promoted	[150]
Apoptosis	Fibroblast	Apoptosis inhibition in late stage of wound healing	Scar formation	[131]
	Fibroblast	Apoptosis increased in the late stage of wound healing	Wound healing is promoted	[131]
	Neutrophil	Increased apoptosis	Inflammation subsides and promotes healing.	[83]
	Macrophage	Impaired apoptosis	Impaired healing	[85]
	Endothelial	Increased apoptosis	Impaired healing	[37]
	Keratinocyte	Increased apoptosis	Impaired healing	[88]

wound healing, and how this balance can be disrupted in pathological conditions such as diabetes.

Apoptosis promotes wound proliferation

The shift from the inflammatory stage to the proliferative stage marks a significant juncture in the process of wound healing. Once inflammation has subsided, the body can begin to build new tissue—known as granulation tissue—to fill in the wound and restore structural integrity.

Keratinocytes, the primary cell type in the epidermis, play a pivotal role immediately after an injury. They begin migrating to cover the wound defect, moving along or beneath the fibrin clot that forms as an initial response to tissue injury [35]. The interaction between epidermal keratinocytes and dermal fibroblasts is crucial for regulating tissue balance and repair. During migration, keratinocytes release growth factors and cytokines that stimulate fibroblasts and endothelial cells to proliferate, forming collagen-rich granulation tissue with ECM components. This granulation tissue provides a scaffold for new tissue to develop and is essential for the subsequent re-epithelialization, where new epithelial cells form to cover the wound [103].

During the healing process, the apoptosis of certain cells, such as stromal keratinocytes, is a controlled and necessary event. The programmed cell death of keratinocytes is essential in corneal wound healing as it regulates tissue remodeling and prevents cell overgrowth, which can compromise cornea transparency and function [34].

Inflammatory cytokines are crucial in the proliferative phase by regulating angiogenesis. Angiogenesis involves endothelial cells migration, capillary tubes formation, and new blood vessels maturation. These new vessels are crucial for delivering oxygen, nutrients, and immune cells to the wound site, which supports tissue growth and resistance to infection [104]. A well-vascularized wound is more likely to heal efficiently because the increased blood supply facilitates cells migrate and multiply, which is vital for tissue repair [105]. Overall, the proliferative phase is a highly coordinated effort that involves multiple cell types and biological processes working together to restore skin and tissue integrity following injury. miR-21 enhances keratinocyte differentiation, proliferation, and migration during wound re-epithelialization. It accomplishes this by simultaneously reducing apoptosis and oxidative stress, thereby promoting the survival of HUVECs and angiogenesis [106].

Apoptosis promotes wound remodeling

Tissue remodeling represents the final phase of wound healing, involving the modification or repair of preexisting tissue.

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Within the wound site, fibroblasts proliferate and synthesize the ECM, contributing to the development of granulation tissue enriched with new blood vessels [107]. During the phase of remodeling, ECM reorganization occurs, type III collagen is converted to type I collagen, and scar formation is terminated in the granulation tissue [108].

As healing progresses, selective cell populations are eliminated. Fibroblasts undergo programmed cell death, resulting in scar tissue with tensile properties similar to intact skin. Previous studies have identified apoptosis as a critical process for the removal of myofibroblasts, with endothelial cells also participating in this phenomenon. The miR-29 family, inclusive of miR-29a, miR-29b, and miR-29c, is crucial in modulating cellular proliferation and apoptosis [109]. Overexpression of miR-29b at injury sites has been associated with decreased wound contraction and an increased collagen III/I ratio.

Additionally, previous studies have shown that miR-29b inhibits the transforming growth factor-β1 (TGF-β1)/Smad signaling pathway, thus reducing wound scar formation, as evidenced by previous studies [110, 111]. Research has further demonstrated that miR-98 assumes a noteworthy function in wound healing via its ability to augment fibroblast proliferation and regulate scar formation [112]. In diabetic patients, the wound healing process involves a complex interplay of signals related to apoptosis and inflammation, which are integral to the tissue remodeling facilitated by gap junctions. Although existing studies have emphasized the regulatory significance of apoptosis in promoting proliferation and remodeling, more exhaustive research is warranted to elucidate these mechanisms fully.

Apoptotic signaling in wound healing

Neutrophils, the foremost cells to be mobilized from the circulatory system, are promptly recruited into damaged human skin and wounds in experimental murine models. The predominant population of neutrophils that migrate to the wound area accomplishes their fundamental task of eliminating microbes and experiencing apoptosis. They are rapidly and efficiently engulfed by macrophages through a non-inflammatory mechanism, as evidenced by existing literature [80, 113].

The elucidation of neutrophil apoptosis mechanisms has been initiated. Empirical studies have revealed that TNF-α partakes in the signaling of neutrophil apoptosis. The interaction with these granulocytes in the b2 integrin (CD11b/CD18) accentuates apoptosis [114]. These discoveries imply that the binding to a specific protein (integrin) or mere migration through capillaries could instigate the apoptotic pathway [115].

In an investigative comparison between *db/db* mice and their non-diabetic counterparts, the miRNA expression profiles of neutrophils derived from bone marrow exhibited distinct patterns. Notably, miR-129-2-3p, linked to caspase-6 and CCR2—key players in inflammation and apoptosis—was differentially expressed. In *db/db* mice, increased miR-129-2-3p expression at wound sites was associated with faster healing compared to controls, indicating miR-129-2-3p's role in modulating neutrophil function in diabetic conditions [116].

Macrophages dominate the inflammatory response and are rapidly lost through apoptosis [117]. The influx of monocytes and macrophages (Mo/MΦ) into cutaneous wounds is rapid post-injury but diminishes as healing progresses. In non-diabetic mice, this decline in Mo/MΦ parallels wound healing. However, in diabetic mice, decreased Mo/MΦ apoptosis contributes to their sustained presence, fostering chronic inflammation and delayed wound resolution [118]. This pattern implies that systemic macrophage reduction in the subacute healing phase may attenuate scar formation, highlighting the pro-fibrotic role of macrophages in skin fibrosis [119].

Post-inflammation, macrophages facilitate the clearance of immune cells and apoptotic debris, a critical step in the transition to active tissue repair during wound inflammation [120]. Macrophages utilize various signals to identify apoptotic neutrophils for phagocytosis. The versatile growth factor TGF-β orchestrates a broad spectrum of cellular responses to cutaneous injury, encompassing inflammation, stromal development, re-epithelialization, and remodeling [121]. Intriguingly, the acceleration of wound re-epithelialization is observed in transgenic mice with inhibited TGF-β signaling in keratinocyte, leading to increased keratinocyte proliferation at the wound periphery [122].

As the wound healing process advances, the regulation of cell populations is critical. The downregulation of fibroblasts aligns with the reduction in vascularity, suggesting a tailored decline in these cells as the need for tissue repair subsides [123]. Growth factors, especially insulin-like growth factor-I, are involved in stimulating fibroblast proliferation and can also inhibit the apoptotic pathways, thus extending the survival of these cells during wound repair [124].

In contrast, certain growth factors, such as TGF-β1, can downregulate wound fibroblast activity. The signaling pathway of TGF-β1 involves ROS, contributing to fibronectin production and the expression of growth factors that promote fibroblast proliferation and migration, essential steps in tissue repair [125].

The *TP53* gene encodes the p53 protein, a crucial cell cycle regulator and tumor suppressor, playing a significant role in preventing cancer. p53 is frequently referred to as the "guardian of the genome" due to its function in maintaining stability by safeguarding against genome mutation. It is renowned for inducing apoptosis, the programmed cell death that eliminates damaged or unnecessary cells [126].

In *TP53* knockout mice, where the gene is inactivated, research has shown that apoptosis can still occur through alternative pathways, indicating that there are compensatory mechanisms in place that allow for cell death even in the absence of functional p53 [127]. During the healing process, the dynamics of p53 expression seem to be complex. In the case of pig skin wounds, p53 expression is downregulated during the rapid proliferation phase of healing. This makes sense as p53 can induce cell cycle arrest and apoptosis, which would be counterproductive during a phase when cell division is necessary for repair. Conversely, when the proliferation needs to slow down in the later stages of healing, p53 expression increases, which could help in terminating the proliferative process and removing cells that may have sustained DNA damage during the rapid division phase. This pattern is inversely correlated with the expression levels of platelet-derived growth factor (PDGF), which is known to stimulate cell growth and proliferation [101].

Further investigation of how growth factors influence the regulation of inflammatory cell apoptosis is deemed imperative [128]. Such research provides insights into the equilibrium between cell proliferation and apoptosis during wound healing. For instance, in normal and diabetic mice, the expression of p53 and Bcl-2, a gene associated with inhibiting

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apoptosis, and their proteins, can give clues about how the healing process is managed at the molecular level [129]. The observed pattern, with p53 being upregulated at the wound periphery and Bcl-2 within the epithelium, aligns with the need to regulate cell survival and proliferation carefully. As inflammation resolves, characterized by decreased Bcl-2 and increased p53, it suggests a shift toward a state where cell proliferation is unnecessary. This facilitates tissue remodeling and the elimination of cells that are no longer required [130, 131].

Apoptosis is a common way to eliminate unwanted cells and tissues during phagocytosis without causing an inflammatory reaction. After removing invasive organisms and inactive tissues, inflammatory cells are expected to undergo apoptosis and be removed without causing more inflammation. Similarly, when enough collagen is deposited (at the end of the proliferation period), fibroblasts will begin to apoptosis. Finally, after the wound matures, the endothelial cells and the remaining fibroblasts will disappear silently [132].

Apoptosis and scar proliferation

Apoptosis is integral to the regulated diminution of cellular constituents during the transition of granulation tissue to scar tissue. Granulation tissue, emerging from the connective tissue surrounding the impaired area, is principally composed of small blood vessels, inflammatory cells, fibroblasts, and myofibroblasts [133]. Subsequently, as the injury site heals and transforms into a scar, there is a substantial decrease in the number of cells, including the disappearance of characteristic myofibroblasts [134].

At the proliferative phase's termination, fibroblasts initiate apoptosis following adequate collagen deposition [37]. With the wound's maturation, both endothelial cells and residual fibroblasts undergo programmed cell death, leading to their eventual elimination [135]. Hyperplastic scarring is characterized by the aberrant proliferation of dermal fibroblasts and consequent anomalous ECM remodeling [36]. The perturbation of apoptotic pathways during the development of atypical scars, such as hypertrophic scars or fibrosis, may critically influence the granulation tissue's architecture and its healing trajectory [136].

An imbalance in apoptosis within granulation tissue can significantly impact wound healing. Excessive apoptosis may impede healing, leading to protracted recovery, whereas insufficient apoptosis can result in hypertrophic or keloid scarring, typified by an overabundance of cells. Therapeutically, the induction of apoptosis in hypertrophic scar fibroblast cells offers a promising strategy for managing hypertrophic scars [137].

The available evidence suggests that TGF-β is of utmost importance in suppressing inflammation while concurrently augmenting collagen deposition through the upsurge in synthesis and the reduction in collagenase activity [138]. The aforementioned discoveries elicit a prospective conjecture aimed at elucidating the development of abnormal scar tissue. A prolonged inflammatory reaction is frequently observed when wounds or tissues are subjected to microorganisms or external agents. Although inflammation is healthy and necessary in the short term, prolonged exposure increases TGF-β production, activating the apoptotic pathways of leukocytes and fibroblasts and ultimately controlling the inflammatory response [139, 140].

However, the activity of inflammatory cells leads to an increased production of TGF-β and PDGF, which may interfere with apoptotic processes. Excess TGF-β fosters a dysregulation of collagen homeostasis, culminating in enhanced accumulation. Understanding these aberrant processes is essential for devising therapeutic strategies to curb excessive scarring [141].

TGF-β exhibits a dichotomous function, acting as both an anti-inflammatory agent and a critical mediator in the onset of fibrosis [142]. In rodent models, TGF-β1 inhibition has been shown to reduce scar formation. Intriguingly, TGF-β3 has demonstrated antifibrotic effects, suggesting its potential significance in ameliorating pathological scarring.

Additionally, miRNA-9-5p has been identified as being upregulated in dermal fibroblasts and has a close relationship with collagen regulation. It has been demonstrated that miRNA-9-5p can suppress the growth of fibroblasts from hypertrophic scars and promote apoptosis [143]. The precise mechanisms instigating this pathologic scarring remain elusive, marking a critical area for in-depth research to inform the management of pathological fibrosis (Figure 4) [144].

Targeting apoptosis and necroptosis

Apoptosis, an intrinsic cellular process, is pivotal in wound healing, as it mitigates prolonged inflammation and excessive scarring [145]. Recently, there has been a demonstration of the efficacy of bee venom (BV) treatment in hastening the process of wound closure in diabetic mice. The healing rate in BV-treated diabetic mice parallels that of non-diabetic counterparts and surpasses that in diabetic mice without treatment. BV mitigates the diabetes-induced impairments in keratinocyte dynamics and apoptosis, which are exacerbated by oxidative stress, by safeguarding macrophages from apoptosis and augmenting the signaling pathways of Nrf2, Ang-1, and Tie-2 [146].

Dysregulated apoptosis can hinder wound repair, leading to protracted recovery periods. Stem cell-derived extracellular vesicles (EVs) show promise for cutaneous wound management. Studies have shown that EVs can potentiate the growth and motility of skin fibroblasts, thus potentially expediting the healing of severe frostbite injuries [147]. Additionally, recent findings indicate that sesquiterpene therapy can enhance the proliferative, adhesive, migratory, and angiogenic capabilities of cells *in vitro*. Specifically, sesquiterpene has been observed to significantly attenuate apoptosis in human umbilical vein endothelial cells (HUVECs). HUVECs challenged with *tert*-butyl hydroperoxide, suggesting its therapeutic efficacy.

Furthermore, an *in vivo* study has shown that sesamin administration can accelerate granulation tissue renewal and collagen matrix deposition and remodeling. These findings confirmed that sesamin has a beneficial effect on wound healing, at least partly due to its anti-apoptotic effect on endothelial cells at the site of injury. Consequently, sesamin shows promise as a treatment candidate for vascular damage-related wounds [148].

A prior study has elucidated that incorporating hydroethanolic extracts of Trypanosoma's pratense into commercial ointments may accelerate wound healing. This acceleration is achieved by upregulating Bcl-2, decreasing p53 and Bax levels, and supporting the proliferative phase of the healing process [149].

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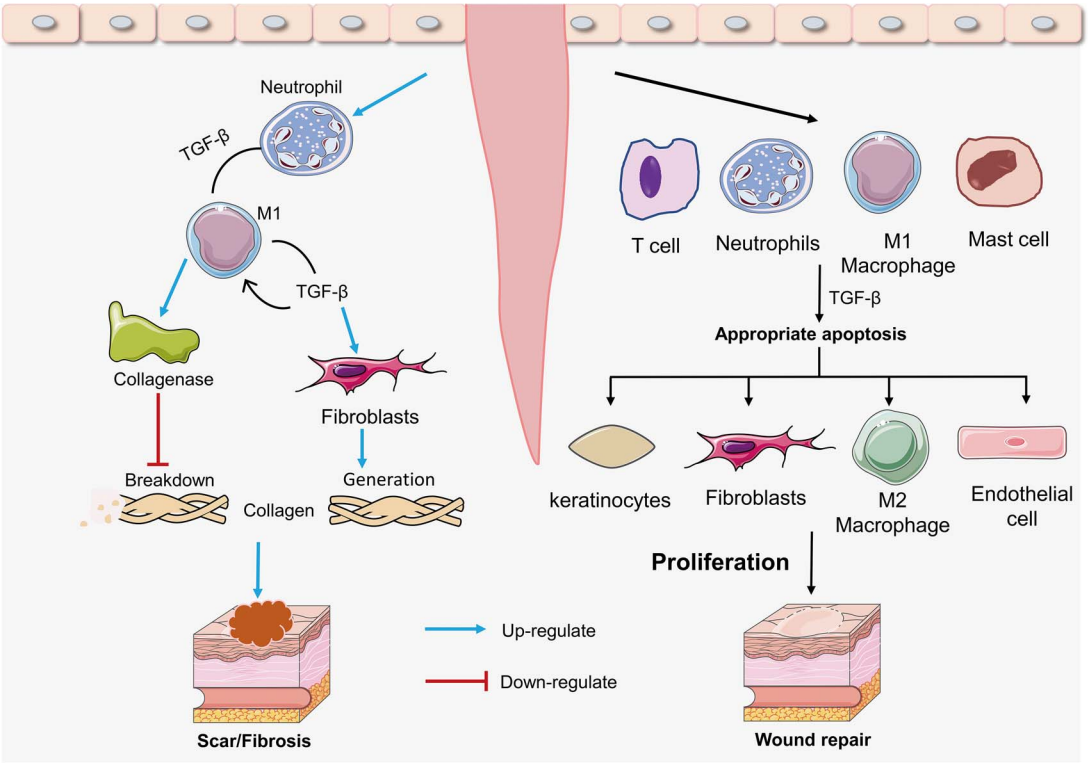

Figure 4. Apoptosis and wound scarring. TGF-β plays a crucial role in downregulating the inflammatory response. Prolonged upregulation of TGF-β following trauma hampers fibroblasts' ability to regulate their collagen synthesis activity effectively. As a consequence, an imbalance arises between collagen synthesis and degradation, leading to the formation of scars or keloids. Apoptotic immune cells are closely associated with wound healing. However, proper apoptosis of cells, including fibroblasts, helps inhibit excessive collagen synthesis and promotes normal wound healing. M1, pro-inflammatory macrophages; M2, anti-inflammatory macrophages

Furthermore, existing research indicates that denatured collagen can modulate fibroblast activity, prompting their differentiation into myofibroblasts. Unlike the effects of native collagen, denatured collagen stimulates autophagy and suppresses apoptosis in fibroblasts, thereby enhancing cell viability and influencing wound healing outcomes [150].

The role of various cellular mechanisms in wound healing is a complex and nuanced field of study. Vimentin, an intermediate filament protein often released in exosomes from adipocyte progenitor cells, has been shown to enhance wound healing. It does so by safeguarding fibroblasts from osmotic stress and preventing apoptosis induced by such stress. This suggests that vimentin could be a target for therapeutic strategies aimed at improving wound healing [151].

Monotropein is another compound that has potential therapeutic benefits for wounds related to endothelial injury. It appears to exert its effects by diminishing macrophage infiltration and promoting angiogenesis. Angiogenesis is crucial for providing nutrients and oxygen to healing tissue and restoring blood flow to the damaged area [152].

Regulated cell death, such as necroptosis, is distinct from apoptosis and is characterized by its inflammatory nature. This form of cell death acts as a defense mechanism against various infections by creating a hostile environment for pathogens [153]. High glucose (HG) levels can enhance the production of ROS, trigger necrotic apoptosis, and worsen inflammation, resulting in a range of complications including diabetic nephropathy, diabetic cardiomyopathy, and impaired healing of diabetic wounds. Thus, the promotion of healing in diabetic wounds can be achieved by inhibiting necrotizing apoptosis [154]. However, necroptosis can also have negative implications for diseases such as cancer. For instance, blocking the signal transduction pathways involved in necroptosis can enhance the wound-healing capabilities and migration of breast cancer cells, as evidenced by the effects of necroptosis inhibitor Nec-1 [155] (Table 2).

Moreover, the simultaneous suppression of RIPK3-induced necroptosis and FADD-caspase-8-driven apoptosis in macrophages has been shown to significantly delay wound healing [156]. This indicates that a delicate equilibrium among various types of cell death is crucial for optimal wound repair. More and more evidence shows that necrotizing apoptosis will lead to endothelial dysfunction in diabetes. Exposure of HUVEC to HG was found to induce cell damage, increase ROS production, cause loss of mitochondrial membrane potential, and lead to increased expression of RIPK3. However, treatment with hydrogen sulfide significantly alleviated necrotizing apoptosis in HUVEC simulated by HG [154].

Advancements in understanding of the molecular mechanisms and biochemical functions of cell death forms like apoptosis and necroptosis hold promise for novel clinical applications. The latest research shows that H_2S regulates the polarization and necroptosis of macrophages, which helps accelerate the healing of diabetic wounds. These data provide a new approach for treating diabetic wounds. Given that MLKL, RIPK1, and RIPK3 are crucial regulators of necrotizing apoptosis, targeting these molecules with drugs could be valuable for treating diabetic endothelial dysfunction [157]. These could potentially lead to more effective treatments for

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Table 2. Potential drugs or compounds targeting apoptosis or necroptosis for the treatment and management of wound healing

Drug/Compounds	Mechanism of effect	Wound healing results	References
MicroRNA-9-5p	Inhibiting the proliferation of HS fibroblasts and induce apoptosis	Preventing abnormal wound healing after skin injury	[143]
BV	By protecting functional macrophages from apoptosis and enhancing Nrf2, Ang-1, and Tie-2 signaling	Immune enhancement in improving the healing process of diabetic wounds	[146]
EVs	By promoting fibroblasts proliferation and inhibiting apoptosis	Wound healing is promoted	[147]
Sesamin	By alleviating TBHP-induced apoptosis in human umbilical vein endothelial cells	Wound healing is accelerated	[148]
Hydroethanolic extract of *Trifolium pratense*	Upregulating the expression of Bcl-2 and reducing the levels of p53 and Bax	Wound healing is promoted	[149]
Denatured collagen	By increasing autophagy and inhibiting apoptosis of the fibroblasts	Promoting cell survival and influence wound healing	[150]
Vimentin	By protecting fibroblasts from osmotic stress and inhibiting stress-induced apoptosis	Wound healing is accelerated	[151]
Mtp	By protecting against apoptosis and autophagy by suppressing the AMPK/mTOR pathway	Wound healing in rats is accelerated, as indicated by reduced healing times	[152]
Nec-1	Blocking the signal transduction of necrotizing apoptosis	Wound closing and migrating are significantly increased.	[155]

a range of conditions, including chronic wounds, vascular injuries, and even cancer.

Future directions in apoptosis and necroptosis for diabetic wound healing

Given the intricate roles of apoptosis and necroptosis in wound healing, particularly in the context of diabetic wounds, future research should focus on several key areas to advance therapeutic strategies.

Elucidation of molecular pathways and mechanisms

A comprehensive understanding of the molecular pathways regulating apoptosis and necroptosis is paramount. This includes detailed studies on the roles of key proteins, such as caspase-8, RIPK1, RIPK3, and MLKL, and their interactions with other signaling molecules. Investigating how hyperglycemia and other diabetic conditions influence these pathways will provide critical insights into the dysregulation observed in diabetic wounds. For instance, the switch from apoptosis to necroptosis mediated by caspase-8 inhibition and the pro-inflammatory nature of necroptosis underscores the need for targeted molecular interventions.

Identification of biomarkers for cell death pathways

The identification of specific biomarkers for apoptosis and necroptosis can significantly aid in the early detection and monitoring of wound healing processes. These biomarkers could be utilized to assess the efficacy of therapeutic interventions and to tailor treatments to individual patients based on their specific cellular responses. For example, the role of miR-21 in reducing apoptosis and promoting angiogenesis highlights the potential of microRNAs as biomarkers and therapeutic targets.

Development of therapeutic inhibitors and activators

Developing specific inhibitors and activators for apoptosis and necroptosis pathways holds significant therapeutic potential. For instance, necroptosis inhibitors such as Necrostatin-1 (Nec-1) have shown promise in reducing inflammation and promoting wound healing [158]. Similarly, modulating the activity of caspase-8 to favor apoptosis over necroptosis could enhance the resolution of inflammation and facilitate tissue repair. The dual roles of apoptosis in mediating wound inflammation and promoting wound remodeling further emphasize the need for precise modulation of these pathways.

Exploration of combination therapies

Exploring combination therapies that target multiple cell death pathways simultaneously may offer synergistic benefits. For example, combining necroptosis inhibitors with agents that promote apoptosis could provide a balanced approach to managing inflammation and promoting tissue regeneration in diabetic wounds. The interplay between apoptosis and necroptosis, and their respective roles in inflammation and tissue repair, necessitates a multifaceted therapeutic approach.

Investigation of the wound microenvironment

The wound microenvironment, including factors such as oxygen levels, pH, and the presence of inflammatory cytokines, significantly influences cell death pathways. Investigating how these microenvironmental factors modulate apoptosis and necroptosis will help in designing targeted therapies that can adapt to the dynamic conditions of the wound site. For instance, the role of macrophage phenotypes (M1 and M2) in wound healing highlights the importance of the microenvironment in regulating cell death and inflammation.

Performing thorough preclinical and clinical research

It is crucial to perform thorough preclinical and clinical research to evaluate the safety and efficacy of novel therapeutic agents targeting apoptosis and necroptosis, which is essential. These studies should include diverse patient populations to ensure the generalizability of the findings and to identify any potential adverse effects. The complexity of wound healing, involving multiple cell types and biological

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processes, necessitates a thorough evaluation of new therapeutic strategies.

Advancing personalized medicine approaches

Integrating genetic, epigenetic, and proteomic data can enhance personalized medicine by identifying patients most likely to benefit from targeted apoptosis and necroptosis. Personalized treatment plans can optimize therapeutic outcomes and minimize side effects. For instance, targeting DNA methylation and demethylation in diabetic foot ulcers exemplifies the potential of personalized approaches in wound healing [11].

Both excessive and insufficient cell death can lead to pathological conditions. Excessive inhibition of apoptosis could lead to chronic inflammation and fibrosis, while excessive enhancement could impair tissue regeneration. Chronic inflammation is a significant concern because it can result in prolonged wound healing times and the development of fibrotic tissue, which can compromise the functional and aesthetic outcomes of wound repair [99]. On the other hand, excessive apoptosis can deplete essential cell populations needed for tissue regeneration, thereby hindering the healing process [37].

The underlying reasons for altered cell death in diabetic conditions include hyperglycemia-induced oxidative stress and inflammation. Hyperglycemia is known to induce oxidative stress by generating ROS, which can damage cellular components and trigger apoptosis [159]. Additionally, the chronic inflammatory state observed in diabetes can exacerbate cell death and impede wound healing [33]. By understanding these mechanisms, we aim to develop balanced therapeutic strategies that carefully modulate cell death to avoid adverse effects. For example, antioxidants that reduce oxidative stress have shown promise in mitigating hyperglycemia-induced apoptosis and improving wound healing outcomes [125].

Preclinical studies using animal models of diabetes are crucial for assessing the potential adverse effects of therapies that modulate cell death. These studies can provide insights into the optimal dosing and timing of interventions to achieve a balance between promoting cell survival and preventing excessive cell death [81]. Furthermore, preclinical research can help identify biomarkers that predict therapeutic responses and adverse effects, thereby guiding the development of personalized treatment strategies for diabetic wounds.

Conclusions

Significant progress has been made in understanding apoptosis and necroptosis to promote wound healing, yet the complexity of cell death in diabetic wounds remains underexplored. Apoptosis is vital for resolving inflammation and scar formation, but its imbalance can lead to complications like hypertrophic scars and chronic wounds. The interplay between apoptosis and other forms of regulated cell death, such as necroptosis, pyroptosis, ferroptosis, and cuproptosis, is not well understood, complicating therapeutic interventions. A holistic approach that considers these diverse cell death pathways, alongside systemic and local factors, is essential. Combinatory therapies that include antioxidants, antimicrobial agents, and treatments to improve blood flow and modulate the immune response hold promise for better outcomes. Future research should elucidate molecular mechanisms, identify biomarkers, and explore innovative strategies such as nanoparticle delivery systems and CRISPR-Cas9 gene editing technologies. These advancements could enhance the body's regenerative capabilities and improve healing in chronic and non-healing wounds.

Author contributions

Xingqian Wu and Rifang Gu are the main writers of the review, completing the collection and analysis of relevant literature and writing of the first draft of the paper. Xingqian Wu, Ming Tang, Xingrui Mu, and Wenjie He participated in the analysis and collation of literature. Xuqiang Nie reviewed the manuscript, making a substantial, direct, and intellectual contribution to the work, and approved it for publication (supervisor).

Xingqian Wu (Software [Equal], Visualization [Equal]).

Conflict of interest

None declared.

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