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Molecular Mechanisms of TLN2 and ZNF521 in Wound and Burn Healing – A Review

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Abstract

Chronic wound and burn infection remains an imminent public health problem, especially in developing countries, due to delayed wounds healing associated with prolonged inflammation, microbial infection, impaired vascularization, and inadequate treatment approaches. Recent advances in understanding gene regulation and mechanotransduction have improved insights into the molecular mechanisms underlying wound healing. These molecular insights are essential for identifying therapeutic targets, improving tissue regeneration, and developing effective treatment strategies for chronic wounds and burn injuries. Among the molecular regulators involved in these processes, talin-2 (*TLN2*) and Zinc Finger Protein 521 (*ZNF521*) have been shown to regulate cell adhesion, migration, and transcriptional regulation, which play essential roles in cellular regulatory mechanisms. *TLN2* is critical for integrin activation and focal adhesion formation resulting in functional cell migration and mechanical signaling during tissue repair. Variation in expression of *TLN2* can affect extracellular matrix-cell interaction and thereby impairing wound healing. On the other hand, *ZNF521* functions as a transcriptional regulator of stem cell maintenance, differentiation and inflammatory downstream pathways such as Wnt/β-catenin and BMP signaling. These functions can determine a possible important role of *ZNF521* in wound regeneration and immune responses in chronic wounds. In this review, we aim to describe the biological role of *TLN2* and *ZNF521* in the pathophysiology of wound and burn infection. Additionally, these findings show promising applications in identifying biomarkers and therapeutic targets for improving wound healing outcomes. More accurate and comprehensive study of these molecular mechanisms may yield targets for the successful clinical management.

Keywords: *TLN2*; *ZNF521*; Chronic wounds; Burn infection; Gene expression; Inflammation; Tissue repair.

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Introduction

Chronic wound and burn infection is a global health issue, particularly in developing nations, where it contributes to longer hospitalization time, higher health care cost, and increased susceptibility to microbial colonization. . These conditions increase delayed healing and persistent inflammation, which significantly impair tissue regeneration. Better clinical outcomes require an enhanced understanding of the molecular mechanisms underlying wound healing.

Wound healing is a dynamically regulated process that includes four overlapping stages - hemostasis, inflammation, proliferation & remodeling [3]. These responses require coordination among cells, extracellular matrix components, and signaling molecules highly coordinate these processes. Disruption in any of these healing processes, especially in the inflammatory phase, results in chronic non-healing wounds or some serious burn-related complications [4].

Mechanotransduction is the biological process by which cells convert mechanical stimuli into biochemical signals that regulate cellular responses. Recent studies have emphasized the importance of this process in wound healing, where the cells sense, and react to, mechanical stimuli in the form of mechanical signals from their microenvironment [5]. Thus, this process is essential for regulating cell adhesion, migration and organization of the cytoskeleton, necessary functions for tissue repair. Integrins and focal adhesion complexes are essential mediators of such a signal, connecting extracellular matrix to the intracellular cytoskeleton [6].

Talin-2 (*TLN2*) is a cytoskeletal protein involved in integrin activation and focal adhesion assembly [7]. It maintains the link between integrins and actin filaments through promoting cell adhesion and migration. Changes of *TLN2* expression/function might interfere with cellular mechanosensing and interfere with the wound healing process [8].

TLN2 also participates in the regulation of cellular responses to mechanical stress, which is crucial in injured or inflamed tissue [9]. In contrast, Zinc Finger Protein 521 (*ZNF521*) is a transcriptional regulator in maintaining, differentiation, and gene expression modulation of stem cells [10]. It modulates multiple signaling pathways such as Wnt/β-catenin and BMP pathways [11]which are critical for tissues' regeneration and repair.

ZNF521 has also been demonstrated to affect inflammatory response and cell proliferation and may involve in chronic wound disease pathogenesis [12]. Although the specific roles of *TLN2* and *ZNF521* have increasingly been established, however, an integrated role of both *TLN2* and *ZNF521* in wound and burn infections is under investigated.

This review presents a broad overview of the mechanisms of molecular functions of both *TLN2* and *ZNF521*, and the possible roles they play in inflammation, tissue remodeling or incomplete repair-associated inflammation/resorption and/or impaired healing. Knowledge about these mechanisms may give insights into the design of targeted therapeutic interventions for treatment of chronic wounds or burn infections. This review provides an integrative overview of *TLN2* and *ZNF521* mediators in wound and burn infections by integrating mechanotransduction with transcriptional regulation associated with tissue repair.

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Role of Skin as a Barrier against Wounds:

The human skin is the largest organ of the body and functions as a multidimensional protective barrier between the body's internal and external environments [13]. It comprises three major layers: the epidermis, dermis, and hypodermis, which contribute to structural integrity and physiological homeostasis [13]. The epithelial lining of the skin consists primarily of keratinocytes, which are constantly turned over to assemble the protective stratum corneum that acts as a barrier to water loss, chemical, physical, and biological stresses [14].

Moreover, specialized epidermal cells, including melanocytes, Langerhans cells, and Merkel cells, contribute to pigmentation, immune defense, and sensory functions [3]. The hypodermis, formed mainly by adipose tissue, provides insulation, mechanical protection, and energy storage. Along with its biological function, the skin is an active immune organ that houses immune cells that keep abreast and respond to germs. It also plays a part in sensing, thermoregulation processes, and the body´s endocrine activities. This includes vitamin D synthesis [15]. As a result, the functioning of the skin barrier is critical for a healthy physiological equilibrium, and an impaired barrier increases the risk of infection and impaired wound healing.

Etiology and epidemiology of wound and burn injuries:

Wound and burn etiology is a set of causal mechanisms resulted from tissue injury and damage to skin integrity. Wound pathogenesis is mainly caused by external trauma or internal pathologies that compromise normal healing pathways. This has led to traumatic wounds, mostly from mechanical forces (lacerations, abrasions, and penetrating injuries).

In contrast, during chronic wound conditions resulted from pathological processes does not allow the repair of tissue. For instance, diabetic foot ulcers are related to peripheral neuropathy and vascular insufficiency (reduced sensation and blood flow, which postpones healing [4]).

Likewise, pressure injuries occur during the persistent pressure of soft tissues between a bony prominence and an external surface leading to ischemia and necrosis of tissues [16]. Burn injuries are tissue damage from energy transfer (for instance thermal sources, flame, scalds and others), which are a major global morbidity [5]. Complex systemic responses that include capillary leak and inflammatory cascades leading to organ dysfunction are associated with significant burns and are recognized globally as a risk factor for severe burns [6].

Other types of wound and burns etiology may resulted from chemical burns due to corrosive agents, electrical burns leading to significant damage to tissue, radiation burns, most commonly due to ultraviolet. Understanding these various etiological factors is critical to enhancing preventive measures and care of both wound and burn injuries.

The epidemiological patterns of wound and burn injuries vary across geographic regions according to demographic characteristics, healthcare accessibility, environmental conditions, and population-related risk factors. Burn injuries occur more frequently in low- and middle-income countries and remain important public health concerns in Middle Eastern and North African regions [17].

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Chronic wounds, including pressure injuries and diabetic-related wounds, also contribute substantially to healthcare challenges because of prolonged healing duration, increased healthcare demands, and impaired quality of life [16]. Epidemiological characteristics differ among populations according to healthcare systems, socioeconomic conditions, and environmental influences. Vulnerable populations, particularly children and elderly individuals, remain at increased risk of wound- and burn-related complications [17].

Talin (*TLN2*): Structure and functions

Talin-2 (*TLN2*) is a large cytoplasmic adaptor protein that functions as a molecular linker connecting integrins to the actin cytoskeleton, thereby facilitating cell adhesion, signal transduction, and cytoskeletal organization essential for integrin-mediated cellular functions. It is one of the two talin family members, Talin-1 (*TLN1*) is an additional member, however its expression is more limited, mainly in mechanically active tissues like muscle and certain neuronal populations [18-19].

The distribution suggests that *TLN2* has a specialized role in force-bearing cellular environments. On top of that structural construction *TLN2* has an N-terminal FERM domain binding β-integrin cytoplasmic tails and a C-terminal rod domain, which interacts with actin and vinculin. This complex allows *TLN2* to act as a mechanical bridge between the ECM and the actin cytoskeleton by linking the former to form stable adhesion complexes [20–21].

Crucially *TLN2* also is a mechanotransducer that transforms mechanical forces into intracellular biochemical signals. Conformational changes in the rod domain expose vinculin-binding sites under mechanical tension, reinforcing adhesion complexes and facilitating cytoskeletal organization [22-23]. This mechanosensitive behavior is crucial to regulate cell adhesion, migration, and the transmission of mechanical force.

TLN2 is critical for several specific mechanisms related to wound healing including keratinocyte migration, fibroblast activation, and ECM remodeling. These mechanisms are critical for tissue replacement and closure of the wound, especially at the proliferative and remodeling stages [7-8].

Through the stabilization of integrin mediated adhesions, *TLN2* promotes more active cellular responses to mechanical cues in the wound space.

TLN2 function is thought to be dysregulated by pathological states such as impaired tissue repair, fibrosis, or tumor growth, indicating TLN2's function as a regulator of cellular mechanics and signaling [24-25].

Upon integrin activation, *TLN2* promotes vinculin and more actin-binding proteins through its C-terminal rod domain which has its own vinculin-binding sites (VBS). Mature adhesion complexes (focal adhesions and costameres) are formed and stabilized by this process [21], therefore reinforcing the mechanical connection between actin and integrins.

TLN2 is a central mechanosensitive protein for force transduction over the integrin–actin axis, in addition to its involvement in adhesion. Mechanical tension allows ligand conformational translation into *TLN2* and exposes hidden vinculin-binding sites that promote adhesion in dynamic force-driven fashion [22].

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TLN2 also has important cytoskeletal organization role through actin interaction and signals, such as FAK (focal adhesion kinase), that modulate cell migration and the organization of structure [8]. *TLN2* is important in wound repair by allowing for keratinocyte and fibroblast migration, promoting extracellular matrix remodeling, and stimulating cellular response to mechanical signals in the wound site [7]. *TLN2* dysregulation or function can lead to disrupted tissue repair, delayed wound closure or excessive fibrosis [25].

Role of *TLN2* in wound healing:

Successful wound healing, especially in the context of major injuries like burns, constitutes a highly orchestrated, multi-stage biological evolution that necessitates accurate temporal orchestration of cellular migration, adhesion, proliferation, and ECM remodeling.

In this complex reparative milieu, Talin-2 (*TLN2*) serves as an important mechanotransducer and integrin activator that plays a major role in tissue repair and structural restoration. Keratinocytes migrate across the provisional ECM for resumption of the epidermal barrier in the latter of its re-epithelialization stages.

TLN2 stabilizes integrin-mediated adhesions, especially when they consist of fibronectin-binding integrins, allowing sustained traction forces essential for coordinated cell migration. Impaired re-epithelialization and ultimately delayed wound closure may be the consequences of dysregulation of *TLN2* [27].

During proliferative stages, *TLN2* is crucial for fibroblast activation as well as for the deposition of extracellular matrix. Support for stability-promoting adhesion complexes for both forces transferred by the wound cells and contraction of the tissue, and for granulation formation, and to assist tissue regeneration [28].

Angiogenesis is another vital procedure under the healing process in which *TLN2* promotes endothelial cell adhesion and stabilizes fresh blood vessels. This results in better vascular integrity and nutrient provision in the healed tissue [28].

TLN2 also acts as a mechanosensor in the remodeling step that becomes increasingly stiff with increasing matrix compaction. By means of mechanotransduction it modulates cytoskeletal arrangement and signals related to tissue maturation signaling. Yet, abnormalities in this process may cause excessive fibrosis and abnormal scar formation [25].

TLN2 gene expression and regulation:

TLN2 is a cytoplasmic adaptor protein involved in integrin-mediated adhesion, cytoskeletal organization, and mechanotransduction. It plays a central role in force transmission between the extracellular matrix and actin cytoskeleton, thereby contributing to cell stability, mechanical signaling, and maintenance of cell–matrix adhesion in mechanically stressed tissues. Unlike *TLN1*, which is broadly expressed across multiple tissues, *TLN2* exhibits tissue-specific expression patterns and is predominantly enriched in cardiac muscle, skeletal muscle, and selected neuronal regions. The human *TLN2* gene is located

on chromosome 15q22.31, and its tissue-specific distribution reflects specialized functional roles in force-bearing cellular environments [30–31].

TLN2 expression is tightly regulated during cellular growth and differentiation and contributes to maintaining force-resistant cell–matrix adhesions in mechanically stressed tissues [32]. During myogenesis, myogenic regulatory factors, including MyoD and myogenin, upregulate *TLN2* expression, leading to its predominance in mature muscle fibers where it supports sarcomere assembly and maintenance of myotendinous junctions [33]. In the nervous system, *TLN2* expression increases during neuronal maturation, reflecting its contribution to cytoskeletal organization and cellular stability. Additionally, alternative splicing generates distinct *TLN2* isoforms that enable tissue-specific functional adaptation.

TLN2 expression is also influenced by extracellular stimuli, including mechanical stress and signaling pathways such as transforming growth factor-β (TGF-β), which contribute to tissue remodeling and mechanotransduction-related processes [8]. Dysregulation of *TLN2* expression has been associated with several pathological conditions. Loss-of-function mutations have been linked to muscular disorders and cardiomyopathy, whereas abnormal upregulation may contribute to pathological fibrosis and cancer progression [34–35]. Given the established role of *TLN2* in mechanotransduction, tissue remodeling, and cellular stability, disturbances in its regulation may impair wound repair processes and contribute to abnormal healing responses, highlighting its potential relevance in wound and burn healing.

Zinc finger protein 521 (*ZNF521*):

ZNF521, also known as Early Hematopoietic Zinc Finger (EHZF), is a C2H2-type zinc finger transcription factor that primarily functions in transcriptional regulation, stem cell maintenance, cellular differentiation, and tissue homeostasis [36]. As a transcriptional regulator, *ZNF521* participates in chromatin remodeling, RNA metabolism, and modulation of biological pathways essential for cellular development and physiological regulation [36].

ZNF521 is predominantly localized within the nucleus, where it regulates transcriptional activity according to cellular context and differentiation status. It is highly expressed in stem and progenitor cell populations, particularly hematopoietic stem cells, where it contributes to maintenance of stemness and prevention of premature differentiation [12,37].

Structurally, *ZNF521* is encoded by the *ZNF521* gene located on chromosome 18q11.2 and produces a large protein (~1,296 amino acids) containing multiple tandem C2H2 zinc finger domains that mediate DNA binding and protein–protein interactions required for transcriptional control [38–39]. These conserved zinc finger domains facilitate interactions with chromatin modifiers and transcriptional co-regulators involved in cellular regulation [38–39].

At the molecular level, *ZNF521* regulates gene expression through promoter and enhancer binding, recruitment of histone deacetylases (HDACs), and interactions with transcriptional regulators including RUNX and EBF1 [36]. Furthermore, *ZNF521* integrates multiple developmental signaling pathways, including BMP, Wnt/β-catenin, and Notch signaling, thereby influencing cell fate determination and differentiation processes [40].

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The highly conserved structural organization of *ZNF521* across vertebrate species emphasizes its biological importance in development and cellular regulation [37]. Given its central role in cellular differentiation, transcriptional regulation, and tissue homeostasis, dysregulation of *ZNF521* may contribute to impaired tissue repair processes. Since wound and burn healing require tightly coordinated regulation of cellular proliferation, differentiation, and tissue remodeling, alterations in *ZNF521* regulatory activity may influence healing responses and tissue regeneration outcomes.

Functions of *ZNF521*:

ZNF521 has several functions in cellular differentiation, stem cell maintenance, and gene expression in many biological environments. This is particularly critical in the regulation of the balance between stemness and differentiation; this balance is affected by its interaction with the major signaling pathways and transcriptional networks. In hematopoietic tissues as well, it plays a negative regulator role in HSC differentiation.

ZNF521 regulates the hematopoietic system to maintain stability and preservation of quiescence of stem cells and proliferation in the basal state of differentiation and self-renewal by modulation of the

BMP, Wnt, and Notch signaling pathways. Increased expression of *ZNF521* can be found in primitive stem cells, which diminish with lineage commitment [10-11].

ZNF521 also plays important roles in neuronal differentiation and neural development in the nervous system by both maintaining progenitor cells and determining lineage specification. It modulates oligodendrocyte maturation and neural plasticity, emphasizing its centrality in the development of the central and peripheral nervous system [41]Additionally, *ZNF521* prevents osteogenic differentiation via the suppression of RUNX2 function in mesenchymal stem cells, further promoting their undifferentiated state. It is for this function that bones are shaped and maintain their shape in the course of development by using their bone [12].

In pathological situations, especially in AML, *ZNF521* is also an oncogenic regulator in that it promotes self-renewing leukemic stem cells, increases resistance to apoptosis, and also plays a role in progression to disease. High *ZNF521* expression is correlated with poor clinical outcome in certain leukemia subtypes [42].

At the molecular level, *ZNF521* controls gene expression by direct DNA binding, binding HDACs, and binding to chromatin remodeling complexes. It also incorporates signals from major pathways, BMP/Smad and Wnt/β-catenin, permitting it to act as transcriptional activator or repressor depending on cellular context [43].

Due to its dual role in normal development and pathology, *ZNF521* presents a promising therapeutic approach. Its regulation is currently being experimentally developed, most especially for use in cancer therapy or regenerative medicine based on stem cells [41].

The role of *ZNF521* in wound healing:

ZNF521 is a well-characterized transcriptional regulator in blood vessels and other tissue. Expression inside dermatological stem cell spaces most importantly in the hair follicle bulge region and the dermal papillae clearly means that this gene is involved in regenerating injured body tissue. By providing the

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balance between stem cell self-renewal and differentiation, *ZNF521* sets out to be a crucial controller that manages coordinated cellular responses for thorough wound closure. And when wound tissue forms are intact this is when structures go straight back over-the-horizon: back into the proper fold.

ZNF521 gene expression is upregulated in periwound regions of wound cells during the pre-wound stages and acts to regulate stem and progenitor cell dynamics. *ZNF521* preserves these cells in a primed but undifferentiated manner to prevent premature differentiation and promote adequate cellular reservoir for return to epithelialization.

This regulation is largely mediated by critical signaling pathways, such as Wnt/β-catenin and bone morphogenetic protein (BMP) signaling, critical for determining stem cell fate at the cutaneous repair stage [41]. It is *ZNF521* role in modulating the inflammatory phase is also significant. In this way, appropriate regulation of inflammation is vital for clearing pathogens from an organism while limiting the extent of tissue damage. *ZNF521* helps maintain that balance by helping to promote macrophage polarization, thus facilitating the shift from a pro-inflammatory M1 type to an anti-inflammatory M2 type of cell. This is conducive to transition towards tissue regeneration and diminishes the danger of chronic inflammation and compromised healing [45].

Angiogenesis is also crucial in wound healing and is particularly associated with burn injury with widespread vascular damage. *ZNF521* mediates neovascularization through its action on angiogenic mediators like VEGF. By this action, it increases proliferative and migratory endothelial cell proliferation, migration (and) vascular network formation through vascular network formation of endothelial cells, improving tissue perfusion thus promoting tissue perfusion and helping regrowing processes [46].

During the transition phase, *ZNF521* controls the organisation of ECM organization and formation of scar morphology of extracellular spaces during remodeling of the extracellular matrix (ECM). It also modulates collagen formation and matrix remodeling via the regulation of matrix metalloproteinases (MMPs) and their inhibitors. Moreover, it also engages in TGF-β signaling in fibroblast differentiation into myofibroblasts and wound contraction, thus resulting in myofibroblasts assisting in wound contraction and tissue maturation. Balanced activity of *ZNF521* elicits organized collagen design and enhanced mechanical integrity of the healed tissue (reduced pathologic scarring risk) [47].

Taken together, these observations demonstrate *ZNF521* as a multifunctional regulator of stem cell homeostasis, inflammation alleviation, angiogenesis, and extracellular matrix reorganization during. wound and burn healing. Its tightly controlled expression is therefore essential for effective tissue repair and regenerative outcomes.

ZNF521 gene expression and regulation:

ZNF521 gene expression is tightly regulated in a tissue-specific and developmentally controlled manner due to its important functions in stem cell regulation and differentiation. It is highly expressed in stem and progenitor cell populations including hematopoietic, neural, and mesenchymal tissues, where it is involved in preserving cellular immaturity and regulating lineage commitment [10].

ZNF521 expression is elevated in early progenitor cells during development, but gradually decreases with differentiation. This pattern demonstrates its involvement as a key regulator of stemness and an

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inhibitor of premature differentiation, preventing differentiation and maintaining the self-renewal abilities of stem cells [11].

At a molecular level, *ZNF521* is regulated by multiple signaling pathways implicated in tissue regeneration and repair. The Wnt/β-catenin pathway has also been found to be a positive regulator of *ZNF521* transcription and involved in proliferative and regenerative pathways.

ZNF521 may also participate in regulatory feedback loops that play a role in influencing mesenchymal and osteogenic differentiation [41] through bone morphogenetic protein (BMP) signaling. Epigenetic mechanisms are also important in the modulation of *ZNF521* gene expression.

DNA methylation and histone modifications regulate transcriptional activity of this gene, in which active chromatin marks correspond to high expression in stem cell populations, and repressive marks lead to downregulation of the gene during differentiation [43].

In pathological contexts, dysregulation of *ZNF521* expression has been observed in certain diseases including leukemia and solid tumors, where it leads to abnormal proliferation and impaired differentiation.

Conversely, decreased levels of gene expression are correlated with diminished regenerative potential in some tissues [42]. Essentially, dynamic regulation of *ZNF521* gene expression is critical for sustaining the balance between stem cell maintenance and differentiation and coordination of appropriate tissue repair and regeneration.

Integrated role of *TLN2* and *ZNF521* in wound healing:

Wound healing requires coordinated regulation of mechanical signaling and transcriptional programs to maintain tissue repair and regeneration. *TLN2* and *ZNF521* contribute to this process through interconnected but functionally distinct mechanisms. *TLN2* mediates mechanotransduction by linking integrins to the actin cytoskeleton, enabling cells to sense and respond to mechanical cues within the wound microenvironment. This process is essential for cellular adhesion, migration, extracellular matrix remodeling, and tissue repair [22–23] as shown in figure 1.

In parallel, *ZNF521* functions as a transcriptional regulator involved in stem cell maintenance, cellular differentiation, inflammatory responses, and regenerative pathways relevant to tissue healing [10,12]. Through interactions with signaling pathways including Wnt/β-catenin and BMP signaling, ZNF521 contributes to regulating cellular programs required for effective tissue regeneration [41].

The integration of *TLN2*-mediated mechanical signaling with *ZNF521*-dependent transcriptional regulation may establish a coordinated molecular framework linking extracellular mechanical stimuli to intracellular gene regulation during wound healing [43]. Disruption of these regulatory processes may contribute to impaired tissue repair, chronic inflammation, fibrosis, and delayed wound healing outcomes [42]. Therefore, understanding the functional relationship between *TLN2* and *ZNF521* may provide insight into potential therapeutic strategies for improving wound healing and tissue regeneration.

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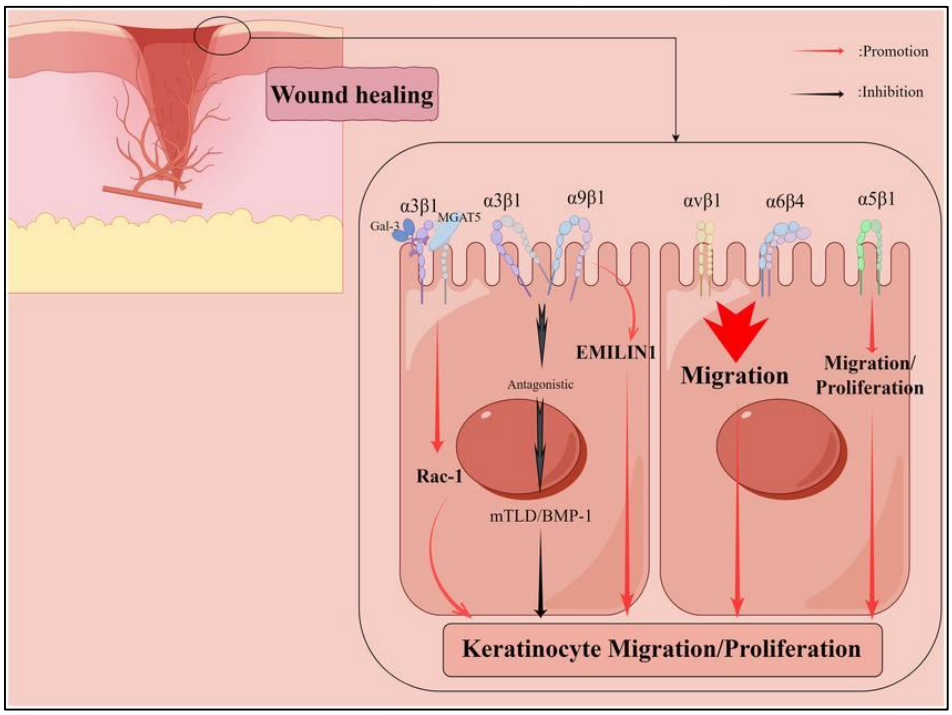

Figure 1: Integrin-mediated signaling pathways involved in keratinocyte migration and proliferation during wound healing (Adapted from Yu et al., 2024).

Conclusion

TLN2 and *ZNF521* represent functionally distinct but potentially interconnected molecular regulators involved in wound and burn healing. *TLN2* contributes to mechanotransduction, cellular adhesion, and cytoskeletal organization, whereas *ZNF521* regulates transcriptional programs associated with stem cell maintenance, cellular differentiation, and tissue regeneration. Coordinated interactions between mechanical signaling and gene regulatory pathways may influence tissue repair outcomes, while dysregulation of these mechanisms may contribute to impaired healing, chronic inflammation, and fibrosis. Further investigation into *TLN2–ZNF521* interactions may improve understanding of wound pathophysiology and support the development of targeted therapeutic strategies for chronic wounds and burn injuries.

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Authors' Declaration

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Authors' Contribution Statement

Dina A. Aziz performed the literature review and wrote the manuscript. Dr. Sahar M. hussaien supervised and revised the manuscript.

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