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Novel Strategies to Accelerate Wound Healing via Wound Healing-Related Pathways

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Abstract

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Introduction

According to the World Health Organization, approximately 180,000+ deaths per year are a result of burns, with the majority taking place in low and middle income countries. The leading cause of morbidity is non-fatal burn injuries, leaving both infants and older adults at the greatest risk for burn injury4. According to Johns Hopkins, the leading causes of burn injury for adults are smoking and open flame, while the leading cause of burn injury for children is scalding[5].

Depending on the cause of the burn injury itself, there are four defined degrees of burn wounds that increase in severity6. Though treating first or second degree burns may be more manageable and not require intensive therapies, third and fourth degree burns may cause trauma to both the external surface and the internal environment[7]. Therefore, it is important to learn more about molecular pathways that currently exist in order to treat burn wound injuries at all levels.

Current therapeutics focus on topical treatment and management, especially when it comes to keeping the injury clean and reducing the severity of scars as a result. In terms of assessing whether novel treatments are effective, there are several factors to identify that have been proven to indicate efficient burn wound repair. These factors include the reduction of healing rates and inflammatory infiltration, scar scores, an increase in collagen deposition, and other markers that will define successful treatment execution. Novel targets of therapy including LncRNA XIST, IL-33, and miR-19b, are proven to be efficient mechanisms of accelerating burn wound healing through the enhancement of cell proliferation, extracellular matrix synthesis, and the inhibition of fibroblast apoptosis. Several clinical trials were reviewed with their respective results contributing to the understanding of novel approaches in treating burn wound injury[8]. Scientific literature was necessary in order to gather more information on the background of burn wound injury, its pathological course of events, and current treatment effectiveness.

1.1 Pathophysiology of burn wound injury

Burn wounds can be classified into four stages: hemostasis, inflammation, tissue proliferation, and tissue maturation/remodeling[9–11]. Each stage involves a complex interplay of molecular mechanisms, growth factors, and signaling pathways.

Hemostasis is the first stage of the wound healing process, which stops bleeding and prevents further damage[12]. This stage is composed of several processes that occur simultaneously. Primary hemostasis involves the formation of a platelet clot, where platelets attach to damaged tissue and activate to attract more platelets. Vasoconstriction, the narrowing of blood vessels by small muscles, slows blood flow. Secondary hemostasis involves the activation of coagulation factors in the blood, which amplify the clotting effect. Fibrin is then formed, which acts as a stable blood clot. Fibrin clot remodeling or fibrinolysis occurs when the temporary seal is removed, and the blood clot is remodeled into the tissue that was there before the injury. Growth factors involved in this process include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor-beta (TGF-β), insulin-like growth factor-1, and platelet factor-IV.

The second stage of wound healing is inflammation, where platelets aggregate to block bleeding and release a chemoattractant to activate inflamed cells for wound healing. Edema, or swelling and inflammation, occurs in the first phase after the secretion of histamine/leukotrienes. Vasodilation and increased capillary permeability lead to fluid leaking from blood vessels. The second phase involves fluid penetration through capillaries and activation of cytokines, enhancing cellular immune response. White blood cells are driven into the interstitial space surrounding the wound, and protease enzymes degrade dead cells. Macrophages defend against dead cells and bacteria. Growth factors stimulate the generation of new capillaries and promote the synthesis of fibroblasts[13].

The third stage of wound healing is tissue proliferation, where cells of the epidermis and dermis migrate to the wound site. Fibroblasts migrate to the wound site and synthesize collagen and elastin. Collagen causes the wound to adhere, and keratinocytes cause re-epithelialization. Angiogenesis occurs, and

new blood vessels form within the healing tissue. Burns that affect deep layers of the skin heal slower because they don't have as many helper cells, and new skin can only grow after the dead tissue is removed. New blood vessels initially form densely, but later reduce to levels similar to the surrounding skin.

The final stage of wound healing is tissue maturation/remodeling, which is the formation of new epithelium and scar tissue. Fibroblasts degrade protein and realign collagen fibers. Apoptosis of fibroblasts and myofibroblasts prevent excessive scarring. Realignment of collagen fibers transforms the initial collagen matrix into a highly organized collagen matrix whose structure mimics that of the native tissue. New tissue with a high tensile strength and a minimal number of cells and vascularization is formed. A visual diagram of the four burn wound stages is displayed in Figure 1.

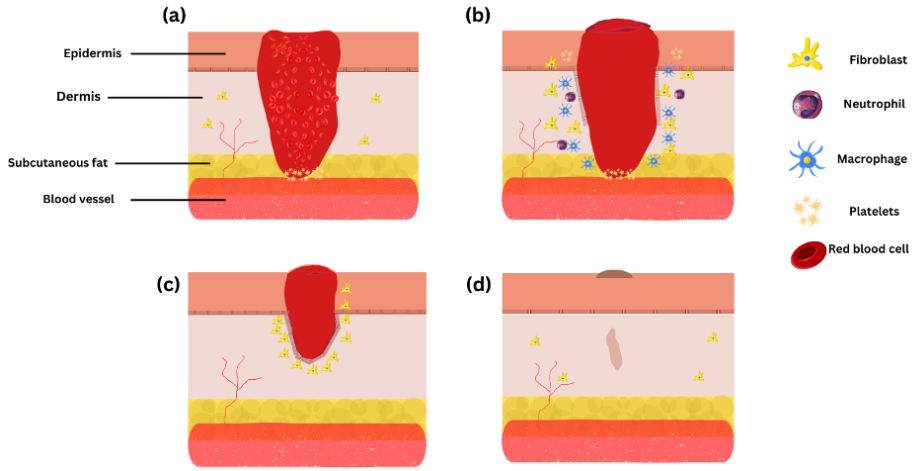

Figure 1: The four stages of wound healing. *(A) Hemostasis: Clotting factors such as platelets aggregate to form a blood clot. (B) Inflammation: White blood cells like neutrophils and macrophages fight off potential infection by clearing bacteria. They also prepare the area for fibroblast proliferation. (C) Tissue proliferation: Fibroblasts begin the process of epithelialization. (D) Remodeling: There is a build up of collagen and scar tissue becomes visible while the new tissue is stronger and flexible.*

1.2 Molecular Mechanisms of Treatment

Wound healing is a complex process involving numerous molecular mechanisms. Recently, long non-coding RNA (LncRNA) XIST, interleukin-33 (IL-33), and microRNA-19b (miR-19b) have been identified as key regulators in wound healing-related pathways. This section will discuss

how LncRNA XIST binds to miR-19b, which binds to IL-33 and activates M2 macrophages in burn injury healing in human skin fibroblast (HSF) cells (Figure 2)[14]. It will also explore how these molecules contribute to the proliferation, migration, and extracellular matrix (ECM) production of HSFs, and their role in the regulation of wound healing.

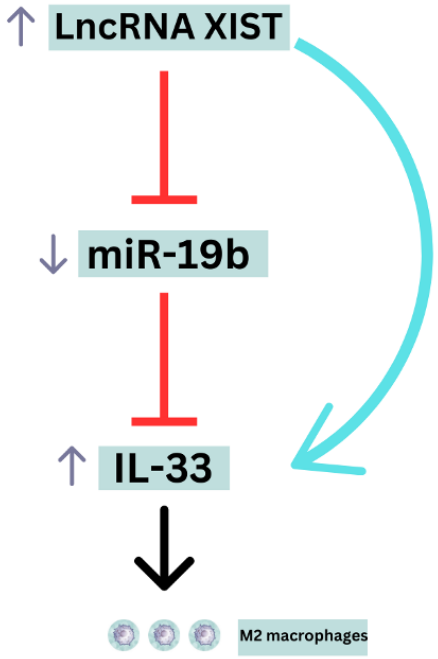

Figure 2: Molecular pathways of LncRNA XIST and miR-19b. *In the process of wound healing, LncRNA XIST binds and inhibits miR-19b, which in turn binds and inhibits IL-33. The binding of LncRNA XIST to miR-19b decreases the amount of miR-19b that is available freely, leading to an increase in IL-33. Thus, LncRNA-XIST indirectly activates IL-33, leading to M2 macrophage activation*

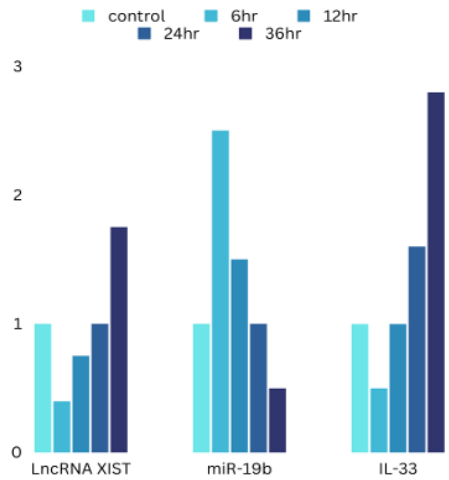

Figure 3: Relative expression of LncRNA XIST & miR-19b. *In the process of wound healing, regulator expression is time dependent and varies throughout the process. LncRNA XIST & IL-33 increase while miR-19b decreases. LncRNA XIST and IL-33 expression are proportional because XIST activates IL-33.*

LncRNA XIST is a key regulator in wound healing-related pathways[15]. Studies have found that LncRNA XIST expression increases during the healing process after a burn injury in a time-dependent manner[14]. LncRNA XIST contributes to the proliferation and migration of HSFs by inhibiting miR-19b and enhancing fibroblast ECM production by promoting the transformation of macrophages into the M2 phenotype. In this way, XIST can promote the repair of the injured dermis. Moreover, LncRNA XIST targets miR-29b-3p/COL1A1[16] and can also inhibit miR-29a and promote LIN28A expression, effectively contributing to the synthesis of HSFs[14,17]. Finally, XIST is also crucial in alleviating pain behavior as it suppresses cytokines that cause inflammation[14,18]. These results suggest that LncRNA XIST may be a promising therapeutic target for promoting wound healing.

IL-33 is an immune cytokine that plays a critical role in wound healing. IL-33 participates in the pathological process of many diseases and acts as an alarm to alert the immune system when released by epithelial barrier tissues during injury, effectively it acts as a link between the skin and the immune system[14,19].

A study shows that IL-33 is not detected in healthy, undamaged human skin cells, but its expression increases when there is a wound and the immune system is alerted. It is not normally produced and is only synthesized when needed. IL-33 promotes the repair of skin damage and enhances wound healing through mucosal healing and epithelial restoration and repair[14,20]. It further plays a role in the regulation of wound healing by upregulating the expression of M2 macrophages, which are the proliferative, anti-inflammatory form compared to the M1 macrophages. These findings suggest that IL-33 may be a potential therapeutic target for wound healing[21].

miR-19b is a microRNA that has been implicated in wound healing-related pathways. Studies have found that miR-19b expression decreases during the healing process after a burn injury in a time-dependent manner[14]. It can be concluded that miR-19b has roles that are more important at the beginning of the healing process. Studies show that miR-19b increases the proliferation and migration of cardiac fibroblasts[14,22,23] and inhibits the apoptosis of endothelial cells[24]. miR-19b also promotes the activation of M1 macrophages, TLR3-mediated NF-κB activation by targeting SHCBP1, and reducing the production of inflammatory chemokines and cytokines by keratinocytes. To account for the decrease in expression, studies have shown that overexpression of miR-19b may inhibit the expression of CGTF[25], which is a connective tissue growth factor. CGTF plays a crucial conducive role in wound healing so its decreased expression due to the overexpression of miR-19b is detrimental to the healing process. These results suggest that targeting miR-19b may be a promising therapeutic pathway for promoting wound healing.

1.3 Treatments of Interest and Measurement of Efficacy

The treatment of patients who experience difficulty and obstacles during burn wound healing is a significant hurdle in clinical practice[26]. Therefore, gaining a deeper comprehension of the molecular mechanisms underlying burn wounds can facilitate the development of more efficacious treatments, which can ultimately enhance patients' life quality. The main ways LncRNA XIST, miR-19b, and IL-33 have been used treatment-wise is through expression modulation via gene knockdowns, small molecule inhibitors, and RNA interference[27].

The measurement of efficacy of LncRNA XIST can be assessed through several methods, including *in-vitro* and *in-vivo* studies. *In-vitro* studies can be executed using HSF cells or other appropriate cell lines to assess LncRNA XIST effects. These in-vitro studies use techniques like western-blotting, quantitative polymerase chain reaction (qPCR) and immunofluorescence to detect changes in gene and protein expression[28]. For example, in a clinical trial involving 25 burn patients[16], total RNA was extracted from HSF cells and reversely transcribed to cDNA followed by qPCR. A western blot was then applied for protein identification. Using these methods, the researchers were able to demonstrate that upregulation of XIST expression boosts fibroblast proliferation and migration via mIR-29b-3p/COL1A1 pathway[16], which regulates collagen synthesis, resulting in improved wound healing. Other in-vitro studies that use qPCR and western blotting include a study where results show that overexpression of LncRNA XIST in HSF cells significantly increased cell proliferation and migration with a decrease in apoptosis, suggesting a possible for XIST in burn injury wound healing[28].

Fewer studies have been conducted in-vivo to investigate the role of LncRNA XIST in burn wound healing. These studies use animal models of burn injury to evaluate the effects of LncRNA XIST on wound healing and scar formation. These studies use techniques such as immunohistochemistry, histological analysis, and mechanical testing to evaluate changes in wound healing parameters[29]. For example, in a study involving mice[6], burn wounds were induced and the wound tissues were processed for histological analysis, immunohistochemistry, and qPCR data. The results reveal that LncRNA XIST targets the IL-33/miR-19b axis to promote wound healing. Results from other in-vivo experiments include seeing an increase in HSF proliferation and ECM synthesis when XIST is overexpressed[7] and inhibition of XIST leads to a decrease in wound healing acceleration[29].

Through *in-vitro* and *in-vivo* studies, IL-33 has been shown to accelerate wound closure, help reduce scar formation in animal models, and aid in fibroblast proliferation, which are cells that help form new tissue[30-32]. In addition to the techniques mentioned in the previous paragraphs, cytokine and chemokine levels are measured to evaluate IL-33's role in regulating

inflammation and immune response. Some examples are using histological analysis on wound tissue samples to evaluate the degree of inflammation and tissue repair and qPCR to measure gene expression levels, in which it was found that IL-33 recruits group 2 innate lymphoid cells (ILC2s) to promote wound healing via re-epithelization[30].

Using a full-thickness skin wound model on mice, where the wound extends below the epidermis and dermis layers, researchers assessed wound healing at four time points (days 0, 1, 3, and 14)[31]. They also researched how autophagy, or the clearance of damaged or old cells, is involved in wound closure rate by looking at the YAP/IL-33 pathway. The yes-associated protein (YAP) has been shown to regulate inflammation[33], specifically, it increases the articulation of proinflammatory cytokines[34]. The researchers utilized an autophagy inhibitor (3-MA) as well as verteporfin, a YAP inhibitor, and anti-IL-33, an IL-33 inhibitor to observe wound healing results. Their results reveal that with autophagy inhibition, there is an upregulation of IL-33 along with a suppression of tumor necrosis factors. Verteporfin decreased the expression of YAP while increasing the expression of IL-33, in which the upregulation of IL-33 contributed to wound healing in both cases. Anti-IL-33 downregulated IL-33 leading to no promotion of wound healing. Thus, IL-33 can increase wound closure and help decrease wound size.

There is limited research specifically investigating the role of miR-19b in burn wound healing, however, some studies show that miR-19b could be a potential therapeutic target[35-37]. In an *in-vitro* experiment, the researchers investigated the potential of exosomes derived from human adipose-derived mesenchymal stem cells (ADSCs) containing miR-19b[35]. Their results reveal that treatment with miR-19b enhanced cell proliferation and migration, and in a mouse model, miR-19b increased the deposition of collagen and blood vessel formation. In a clinical trial, 18 human samples were collected and results show that miR-19b is an important factor in wound healing by reducing inflammation while an absence of miR-19 reduces wound healing capabilities. Their methods involve qPCR, Western blotting, miR-19 antisense inhibitors and luciferase reporter assay[36].

1.4 Practical Applications

In the case of LncRNA XIST, IL-33, and miR-19b, although they show promising burn wound healing results in preclinical studies, more research is needed to determine the safety and efficacy of these molecules in practical settings. They are currently not commonly used as a clinical treatment for burn wounds, but ongoing clinical trials are exploring its potential use[38,39]. For more severe injuries, like third and fourth degree burns, more intensive treatment is required, particularly at the molecular-level, to restore healing related pathways[40]. However, for minimal burn wounds requiring repair at a superficial level, such as first degree burns, minimally invasive treatments may be more appropriate, including holistic applications.

Holistic treatments for burn injuries include a combination of traditional and medical treatments and alternative therapies to promote physical, mental and emotional healing. Some holistic approaches that have been explored include: acupuncture, eating a good and healthy diet, massages, and herbs[41,42]. Acupuncture helps decrease pain and shock after a burn injury and may also decrease infection[43,44]. As for a diet, with the right amounts of vitamins and nutrients, as well as sufficient protein and calorie intake, the body can promote new skin and tissue in a timely manner[37]. In a review paper, the authors suggest that burn patients may have increased requirements for certain micronutrients, and that supplementation with these nutrients may help improve outcomes[45]. Like acupuncture, massages help decrease pain and itching[46, 47]. Several herbs have been traditionally used for their potential wound healing and anti-inflammatory properties, for example, aloe vera and calendula can help reduce pain and inflammation in first and second-degree burns[48, 49].

1.5 Prevention Strategies

Burns are preventable, especially when considering the majority of burns take place in the home and workplace. In order to strategize prevention plans, it is important to address impactful factors that heighten/lessen burn wound injuries. These factors include knowledge regarding the hazards related to specific burn injuries, access to education for vulnerable populations, and first aid training in case of an emergency. It is insightful to study which populations

are most affected, especially as it was mentioned previously that the majority of burn wound injuries occur in low and middle income countries. After considering the following factors, an effective prevention procedure can be produced and include several initiatives. Initiatives such as heightened awareness within the community, efficient policy enforced in order to safely prevent burn wounds if possible, prioritized research endeavors committed to learning more about not only prevention plans but also treatment options available, and the revaluation of current burn care therapeutics in order to ensure success alongside verifying new treatments being studied currently are all necessary to research when prevention strategies are organized[50]. As initial strategies have targeted more physical and pathophysiological consequences, research has also suggested significant mental health outcomes, especially for the parents of burn wound victims[51], that should be studied further in order to provide the necessary resources. According to Stanford Children's Health, burn injuries and fatalities have significantly decreased throughout the last 20 years[52]. This is promising when addressing the effect that increasing public awareness may result in more adequate resources, further pushing the importance of fire safety and burn wound injury research. Though these statistics suggest the harm is not as intense as it might have been in the past, it is still just as important to continue studying both the medical and sociological factors to enhance burn wound injury healing.

1.6 Future Directions

LncRNA XIST, IL-33, and miR-19b all contribute to burn wound healing repair and their results thus far should permit them to be treatment options to be further studied. It is still important to compare the effectiveness between these novel therapeutic options and other standard treatments for burn wound healing in order to identify any gaps or contrasting ideas that might exist and inhibit efficiency. By studying the molecular pathways in which these treatment options interact with, other factors that are also present in the repair mechanism may also come to light in terms of promising targets, as well as targeting other related or unrelated biological pathways. Studying the association between LncRNA XIST in particular, and burn wound repair presents promising results, though an exact mechanism is unclear. By studying

its role in depth, it is possible to specifically investigate the network of cell proliferation and extracellular matrix synthesis, accelerating repair further.

Conclusion

The investigation of novel therapeutic options for burn wound injury has advanced in the last 20 years, and continues to produce promising results the more the scientific literature is discussed. Targets of therapeutic strategies including LncRNA XIST, IL-33, and miR-19b as well as more standard and holistic approaches to burn wound healing have proven to be effective options for the acceleration of burn wound repair as it results in cell proliferation, extracellular matrix synthesis, and an inhibition of fibroblast apoptosis, all resulting in overall healing on a molecular and more surface level. The combination of both topical and standard products that serve as treatments for less severe wounds, as well as the incorporation of molecular acceleration via targeting key receptors collectively aid repair. Due to the lack of substantive results, more diversified and inclusive trials are necessary to solidify their role as viable treatment options for long-term use.

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