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Co-stars for Wound Healing and Novel interacting Partners in the Frontier of Burn Wound Healing Process

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Abstract

Skin is a composite organ with functional coordination between various cell types. Trauma injuries disrupt the skin architecture and in response to the injury, fibroblasts, macrophages, platelets, keratinocytes mobilize to seal the damage. However, in many cases, trauma causes a serious problem. Effective chronic non-healing wounds in burns are still a challenge. There is no infallible solution available that can overcome the various complexities in burn wound healing and its management. Hence, there is a need to develop suitable technologies that could solve burn wound related complexities. An ideal intervention for wound care must involve components that act at different steps in the process of burn wound healing. In this article, we would like to review the role MMPs (Matrix Metalloproteinase in modulating the extracellular matrix proteins (ECM) proteins in burn wound healing. In addition, a clear understanding of molecular interaction among growth factors, cytokines, MMPs, and other ECM proteins may provide a suitable platform to bring precise solutions for the life of suffering burn patients. To build up a wide-scale for therapeutic strategies, co-stars of this review might help in aiming at stimulating the tissue regeneration process.

Keywords: Burn wound healing; MMPs; Collagens; Extracellular Matrix.

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Introduction

According to the World Health Organization, the highest mortality rates are observed in low and middle income countries with most cases seen in Southeast Asia. The mortality rate among low income countries is 11 times higher than in high income countries. For example: In India, over 1000 000 people are moderately or severely burnt every year. Globally, burns related trauma is the fourth most common type of trauma worldwide, following traffic accidents, falls, and interpersonal violence.

The largest organ of our body that is the skin, makes the integumentary system, prevents fluid loss and provides barriers against microorganisms. When there is a wound, after dressings wound does not get healed. Most current treatment options such as laser therapy, cryotherapy, skin grafts, pressure garments, dressings have not yielded significant results. We need to understand the mechanism of burn wound healing and the regulation by ECM and co-stars, which may be able to provide appropriate treatment. Fibroblast cells synthesize and secrete ECM proteins that will guide for new skin tissue to form. Signalling pathways such as TGF β, WNT, NOTCH, SONIC HEDGEHOG play a crucial role during organogenesis as well as maintain homeostasis in adult organisms. The ECM and MMPs function at the molecular level

in every signalling pathway in human and most importantly during the process of burn wound healing. The multi step complex wound healing process comprises of homeostasis, inflammatory stage, Proliferative stage, Remodelling Stage.[1] The epidermal layer guards underlying tissues and dermal layer offers tensile strength and provide cushions for skin through the support of ECM.[2,3] Once haemostasis is attained, interleukins (IL) and other cytokines modulate the inflammatory response and recruit other immune cells to take part together in the inflammatory stage. The proliferative stage is characterized by angiogenesis, collagen deposition, and granulation tissue. Fibroblasts grow and produce a new extracellular matrix by secreting collagen.[4,5] After the proliferation phase, the last stage is the remodelling phase, which takes a longer period. In this phase, collagen production predominantly happens, and previously disorganized collagen fibers are rearranged and cross linked to provide tensile strength.[6] The complex healing process of burn wounds, the cascade of molecular overlapping events happens during healing, finely controlled biological process involving a series of complex cellular interactions and is interrupted by local and systemic factors.

When the right environment created in wound bed and body works in a sensible way, accumulation of collagen and ECM restores tensile strength. The functions of cells participating in the healing process are controlled by cytokines and growth factors and interactions with ECM components, mediated by integrin receptors and adhesive molecules.[7,8] The fundamental role in the healing process is played by extracellular matrix components.

Extracellular Matrix in Wound Healing

Fibroblasts are present within the dermal extracellular matrix, and it appears that within an ECM, crosstalk happens between keratinocytes and fibroblasts. The communication occurs between ECM, Keratinocyte and fibroblast are rapid during wound healing. An increase of all dermal extracellular matrices and growth factors happens significantly along with increase of type IV collagen. Type I collagen and elastin increased. A dramatic induction of MMP 1 and MMP 9 was observed shortly after wounding.[9] The increased expression of VEGF, bFGF are critical to angiogenesis, occurred early with peak at days 1 and 4, respectively. Expression of basic fibroblast growth factor (bFGF) strongly promote both fibroblast cells and endothelial cells. To improve the burn wound healing, several developing strategies developed in which correlation between growth factor expression and dermal matrix deposition have been associated.[10] The effects of ECM proteins impact two major signal transduction pathways, intracellular calcium and cyclic adenosine monophosphate (cyclic AMP). The Matrix Metalloproteinase (MMPs) play specific role in wound healing. MMPs are group of enzymes responsible for the degradation of ECM proteins. They are also known as matrixins and can degrade all kinds of extracellular matrix proteins, also can process a number of bioactive molecules. The essential MMPs which play a significant role in wound healing are MMP1, MMP2, MMP3, MMP7, MMP9, MMP12, MMP13.[11] The connection between the cells and extracellular matrix components are integral part of burn wound healing, interacting with cells and growth factors in a dynamic give and take that eventually results in wound closure. Hence it is essential to know the role of ECM in healthy skin.

The extracellular matrix of skin consists of a large number of distinct components, and the predominant ones are collagens (type I, type III, type IV, V, VI, and VII), anchoring fibrils, elastinfibers, fibrillin, heparan-sulphate proteoglycan, basement membranes, laminin and fibronectin which provide various functions. Almost 30 percent of total protein mass of ECM is collagen.[12] In normal human dermis, among several types of collagen, collagen types I and III are considered to be the major interstitial fiber-forming collagens.[13,14] Matrix metalloproteinase belongs to family of proteinases that have been increasingly implicated in normal and pathologic extracellular matrix remodelling.[15] The MMPs are a gene family of enzymes that are produced as inactive zymogens, zinc-dependent for catalytic activity, different in substrate specificity, and inhibited by tissue-derived inhibitors (TIMPs).[16] In the healing process of chronic wounds, MMPs act as a novel target for therapeutic intervention. The production of MMPs results due to the interaction of ECM and growth factors.

In humans, currently, at least 24 known MMPs are there[17] different MMPs are explained. Wound healing is the dynamic biological process that involves many complex interactions at the molecular level. MMPs can cleave laminin to release a fragment that binds EGF receptor on fibroblasts

and stimulates migration and proliferation of keratinocytes. Among many growth factors and cytokines, TGF-ßs play critical roles in regulating the development of the ECM. There are three isoforms (TGF-ß1–3) in humans, with each playing distinct roles in regulating synthesis of the ECM components, and even cellular proliferation or cellular death.[18,19] TGF-ßs are produced in latent forms that need to be activated by cleavage of their pro-peptides, before exerting their activities on the ECM, which include stimulation of cellular production of ECM components.[20] The most well known is TGF-ß1, which can control production and degradation of many constituents involved in wound healing.[21] Once TGF-ß1 binds to its receptor, this interaction stimulates the synthesis of ECM components such as collagen, fibronectin, and hyaluronic acid in many types of cells, including fibroblasts.[21]

In the process of wound healing, MMP and their inhibitors TIMP play a great role. Interaction between Collagen 1, 2, 3 and MMP1 COL1A1 (Collagen type 1) is shown in figure 1, in which inter molecular interactions occuramong MMP1, MMP3 MMP9 and their functional partners such as TIMP1, COL1A2, PLG (Plasminogen), COL3A1 and JUN . TIMP1 interacts with the MMP partners and inactivates them by finding their catalytic zinc co-factors and these interactions regulate cell differentiation, migration.

In figure 2, the interaction of Matrix Metallopro -teinases (MMP1, MMP3 & MMP9) and Collagens 1, 2 & 3 MMP1 cleaves collagens and do proteolysis of extracellular matrix (ECM). MMP9 cleaves collagen type IV and play an essential role in cell migration, degrading Fibronectin. This signalling helps in wound healing process.

The functional predicted partners of collagens and MMP are TIMP1, JUN, CD44, COL6A3. CD44 interacts with HA (hyaluronic acid) and mediate cell-cell, cell-matrix interaction and it has affinity for collagens and MMPs. These interactions helps for activation of lymphocytes and haematopoiesis. Also, TIMP1 act as a growth factor that regulates functional signalling pathway for wound healing. TIMP1 interacts with the MMP partners (MMP1, MMP2, MMP3 & MMP9) and inactivates them by finding their catalytic zinc co-factors and these interactions regulate cell differentiation, migration.

Observation from Burn Wound

Authors examined type I and III collagen content and expression of Fibronectin in fibroblasts isolated from normal and hypertrophic skin tissue of the burn patients. Also elucidated possible mechanisms of hypertrophic scar through the software interaction study. Normal human skin and hypertrophic scar specimens were obtained from burn patients of with informed consents and fibroblasts were isolated from the skin tissues using standard protocol. The results indicated that collagen I, expression in scar fibroblast increased in comparison to normal. Collagen III expression also checked quantification indicated that level of collagen III expression slightly higher in hypertrophic scar than the normal. Fibronectin expression was also indicated that expression of cells is greater in the hypertrophic scar than the normal. To predict the interacting partners of ECM proteins, "STRING" software has been used and interaction among ECM proteins were discussed. The software analysis is being done which shows the interacting partners of Collagens. The MMP are found to be an active partner involved in it. MMP are present with their inhibitors TIMP and helps in the wound healing process.

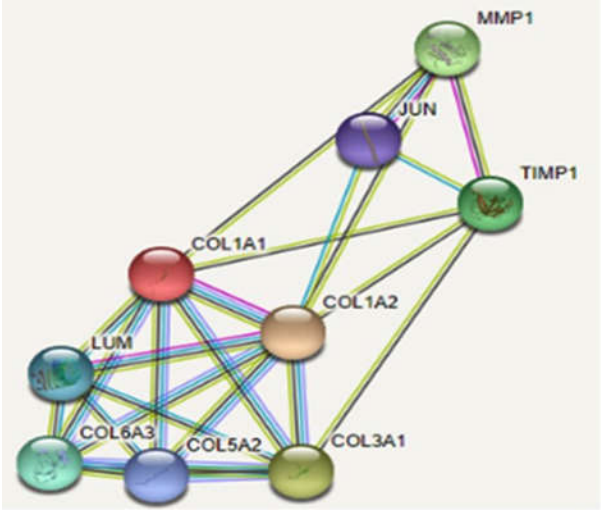

Fig. 1: Interaction between Collagen 1, 2, 3 and MMP1.

COL1A1(Collagen type 1) interacts with MMP1, MMP3 MMP9 and their functional partners are TIMP1, COL1A2, PLG (Plasminogen), COL3A1 and JUN . TIMP1 interacts with the MMP partners and inactivates them by finding their catalytic zinc co-factors and these interactions regulate cell differentiation, migration and plays a role in integrin signalling pathways.

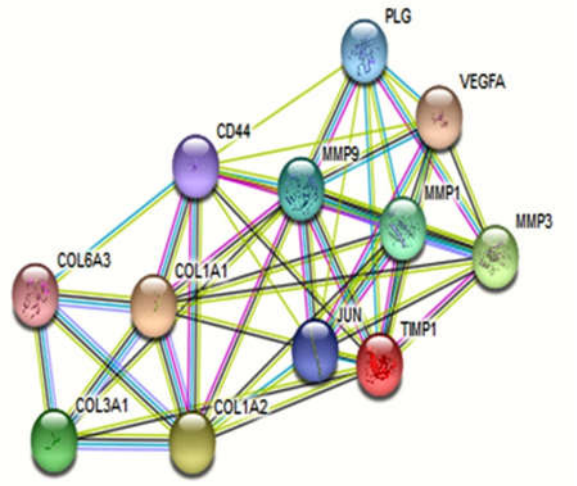

Fig. 2: Interaction of Matrix Metalloproteinases (MMP1, MMP3 & MMP9) And Collagens 1, 2 & 3

MMP1 cleaves collagens and do proteolysis of extracellular matrix (ECM). MMP9 cleaves collagen type IV and play essential role in cell migration, degrades Fibronectin. The functional predicted partners of collagens and MMP are TIMP1, JUN, CD44, COL6A3. CD44 interacts with HA (hyaluronic acid) and mediate cell-cell, cell-matrix interaction and it has affinity for collagens and MMPs. These interactions helps in lymphocyte activation, recirculation and haematopoiesis. Also, TIMP1 act as a growth factor that regulates functional signalling pathway for wound healing. TIMP1 interacts with the MMP partners (MMP1, MMP2, MMP3 & MMP9) and inactivates them by finding their catalytic zinc co-factors and these interactions regulate cell differentiation, migration and plays a role in integrin signalling pathways.

Discussion

Wound healing involves various cellular events, secreted growth factors and cytokines. This complex process involves interaction among extracellular matrix components which are essential for wound repair phenomenon. ECM creates a provisional matrix, providing structural integrity with various types of cells. The delicate balance between repair system and Extracellular components play key role in proliferation, differentiation and remodelling of tissue. Moreover, ECM components such as Fibronectin, proteoglycans, vitronectins, and collagen all together bring together a state of healing of wound. The ECM elements such as Collagen-I, Collagen-III, Fibronectin and Matrix Metalloproteinase have indispensable role and the "scaffolding" created by ECM provide the structural integrity during the stages of wound healing. Since wound healing is a dynamic process of the molecular interaction among cytokines, growth factors, MMPs, ECM full fill a function of signal transduction and the interactive sequence of biological reactions are connected with the healing process. Scaring in burns and contracture formation inversely proportional to the dermal tissue component available for healing, which is directly related to the support of fibroblast infiltration, new vascularization and epithelialization. Therefore the interaction of MMPs, and other essential components make significant contribution in dermal tissue remodelling and burn wound healing.[22,23,24] In fig. 3, Model showing, Factors Associated with Burn wound healing which provide future prediction to target the molecule for better understanding for healing of burn wound scar.

Fig. 3: Model showing, Factors Associated with Burn wound healing.

Summary

The precise balance between the restoration system and ECM components plays a key role in tissue repair. Regardless of all recent advances in burn wound healing, burn wound represents a major challenge throughout the world. Basic needs of specific types of wounds and degree of burns such as nutritional optimization and advanced suitable burn wound healing agents need to be focused on. ECM proteins and MMPs could open a better avenue. Thorough knowledge of understanding of the molecular intervention is required for better understanding of healing of burn wound scar.

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