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Reviewing a Scarless Wound Healing: From Embryology to Post-Wound Management

Abiel Amazia Putri[1], Agastya Bayuasa Rattananda[1], Fathi Tsamara Ghufroon Rifai[1], Ahmad Fawzy[2]

[1]University of Jenderal Soedirman

[2]Department of Surgery University of Jenderal Soedirman - Margono Soekarjo County Hospital, Indonesia

ABSTRACT

Introduction: Scarring happens after trauma, injury or surgery to any tissue or organ in the body. Disturbing perceptions like pain, itchiness or tenderness from one perspective, and functional limitations in the form of contractures on the other, are ramification of problematic scars. In addition, scar esthetics can also have a negative influence on psychosocial factors. Various treatment options described in the literature include chemical, physical, and surgical methods. The purpose of physical scar treatment is primarily focused on preventing inappropriate healing of the skin

Methods: This literature review was compiled using information from numerous web databases, including NCBI, Google Scholar, Science Direct, and Pubmed. Data were analyzed.

Results: Good wound management is to reduce the incidence of scar tissue in the wound. Embryonic scarless wound healing is a form of wound healing in the embryo and results in scarless wounds. Many in vivo studies have been carried out on several experimental animals, and the molecules that play a role are examined. Molecules that play a role in scarless and scarring wound healing are TGF-β 1, 2, and 3. TGF-β 1 and 2 play a role in the formation of scar tissue, while TGF-β3 plays a role in tissue regeneration. There is a hypothesis that TGF-β3 injected into the tissue will help wound healing and increase tissue regeneration so that scarless wound healing occurs.

Conclusion: Molecules that play a role in scarless and scarring wound healing are TGF-β 1, 2, and 3. TGF-β 1 and 2 play a role in the formation of scar tissue, while TGF-β3 plays a role in tissue regeneration. Scarless and scarring wound healing is not only based on the molecules that play a role but healing time and injured tissue also have an effect on wound formation. scarring and scarless wound healing can also occur in the same individual and the same individual tissue

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INTRODUCTION

Scarring happens after trauma, injury or surgery to any tissue or organ in the body. Such scars are an outcome of a repair mechanism that replaces the incomplete normal tissue with an extracellular matrix comprimising predominantly of fibronectin and collagen types I and III, as such scarring represents a failure of tissue regeneration [1]. Physical scar management represents a significant field in science, as scars can adversely impact the quality of life of patients [2]. Disturbing perceptions like pain, itchiness or tenderness from one perspective, and functional limitations in the form of contractures on the other, are ramification of problematic scars. In addition, scar esthetics can also have a negative influence on psychosocial factors [3]. The healing process of injured skin requires a complex sequence of physiological interactions to form appropriate scar tissue and repair the dermal lesion [4]. If the wound healing process is interrupted, excessive scar tissue can form. Clinical criteria for scarring include scar color, contour, texture, and distortion. For each parameter he assigned a score from 1 to 4, with higher scores indicating more severe scarring [5]. Hypertrophic scars or keloids are the result of such abnormal wound healing [6]. Various treatment options described in the literature include chemical, physical, and surgical methods. Physical therapists focus on conservative modalities in managing scar tissue. These physical scar treatment options can be categorized into mechanical therapy, occlusive therapy and hydration therapy, and phototherapy, often used in combination [7]. The purpose

of physical scar treatment is primarily focused on preventing inappropriate healing of the skin . To date, the efficacy of physical scar treatment is still controversial in the literature. Yes, and previous reviews have focused on the treatment of post-burn hypertrophic scars and keloids [8].

METHODS

This literature review was compiled using information from numerous web databases, including NCBI, Google Scholar, Science Direct, and Pubmed. "Scarless Wound Healing", "Scarless Embryonic Wound Healing", "Molecule of Wound Healing", "Scarring Mechanism", were the keywords used in the literature search. Scientific papers were chosen by the following inclusion criteria: the journal's publication year from 1990 to 2005, the journal is open access, and the articles are matched to the subject matter covered in this literature review. Data were collected, organized, and summarized.

RESULTS

Scarless embryonic wound healing

There are several research papers on scarless wound healing and they contain several essence found in both humans and mammals. There is some controversies and have not been proven effective in human. Skin wounds in early mammalian embryos healed completely, with no evidence of scarring [1]. Ferguson (2004) performed systematic experiments with distinct skin wounds on mouse and sheep embryos of various gestational ages [9]. These in vivo surgical experiments demonstrate that skin wounds received during early to mid-gestation are scars in all mammalian species studied so far (mouse, rat, rabbit, sheep, pig, marsupial, and monkey). It clearly shows that it heals completely without leaving any residue. In mice, the most recent time point at which a small skin incision heals without leaving a noticeable scar is embryonic day 16 (birth time is usually embryonic day 20 or 21). The transition from non-fatal fetal wound healing to cicatricial wound healing is gradual, with abnormal organization of the neodermal tissue, primarily of the extracellular matrix composed primarily of type I and III collagen and fibronectin which characterized by deposition [1].

Mechanism of embryonic scarless healing

Mammalian embryos develop surrounded by the sterile aqueous environment of amniotic fluid, whereas adult wounds are exposed to air and many potential contaminants. Bacteria, viruses, foreign substances, etc. [1]. Some studies say otherwise. An unrelated and particularly elegant demonstration of a sterile and fluid embryonic environment for scar-free healing is an ontological study of wound healing and scarring in pouched juveniles of the marsupial Monodelphis domestica. M. domestica juvenile sacs are nevertheless regularly contaminated by the maternal urine and feces of the skin of early M. domestica pouched pups, completely scarless, despite these marked differences. It heals wounds and shows that the external embryonic environment is irrelevant for scarless healing [1]. Similarly, human fetal skin injuries during early pregnancy have been shown to heal into normal skin tissue without scarring. This may lead to techniques that minimize or eliminate many factors that are involved in fetal wound healing, including cellular elements, soluble growth factors, insoluble extracellular matrix (ECM) proteins, and tissue mechanics. A recent study found that transforming growth factor (TGF-β3) or interleukin-10 (IL-10) is insufficient for scarless wound healing when applying a single factor. Studies focusing on the process of fetal regeneration have shown that scar-free wound healing can be achieved by combining multiple cells and morphogens factors within a fetal-mimetic matrix or scaffold [10]. Fetal wounds provoke a very different inflammatory response than adult wounds. The immune system develops in the embryo and the response of these primitive immune cells to injury differs from that in adults. As a result, there are far fewer inflammatory cells in embryonic wounds (reduced numbers of neutrophils, lymphocytes, monocytes, and macrophages), less differentiation of inflammatory cells present (fewer activated macrophages), reduce time of inflammatory cells that in adult wounds [1].

Experimental manipulation of adult human wound healing

Experts have experimentally manipulated healing wounds in adult mice, rats and pigs. These manipulations were performed in transgenic animals using pharmacological or genetic approaches [1]. Healing wounds in adult rodents with neutralizing antibodies against TGF-β1 and/or TGF-β2 (preferably both) significantly improves scar formation. In contrast, exogenous addition of TGF-β3 to adult wound healing (to increase levels similar to non-scarring fetal wounds) significantly improved scar formation during adult wound healing. or disappear. It is a particularly important molecule for healing by improving scarring [1].

Transforming Growth Factor β, TGF-β signaling is required for wound healing and regeneration, as lack of TGF-β expression results in chronic non-healing wounds. Inhibition of TGF-β signaling prevents regeneration of amputated axolotl limbs. CTGF is known to be a downstream mediator of TGF-β. A single application of either CTGF or TGF-β to mouse subcutaneous tissue resulted in transient granulation tissue formation, whereas co-injection of CTGF and TGF-β resulted in long-term fibrotic tissue formation. TGF-β1 and TGF-β2 are involved in scarring, as inhibition of these isoforms by addition of exogenous antibodies reduces scarring after skin injury. Conversely, the ratio of TGF-β3/TGF-β1 was found to be higher in fetal wounds than in adults, suggesting that TGF-β3 has an antifibrotic effect. However, a phase III clinical trial based on recombinant TGF-β3 therapy to reduce scarring during wound healing failed to meet primary and secondary endpoints. The failure of the TGF-β3 clinical trial indicates a more complex role for her TGF-β family of growth factors that needs to be investigated in future studies [10]. Stimulation of fibroblast cell

migration into a healing wound results in a more organizated fibroblasts and the extracellular matrix deposition [1].

Fibroblasts are the most important cell type in the wound healing process. Connective tissue deposition after skin injury was shown to be due to a unique lineage of fibroblasts in the lower dermis (reticular layer) [11]. Phylogenetic tracing by Rinkevich et al. This led to the identification of a single fibroblast lineage (Engrailed-1) as a major effector cell in wound healing in mouse dorsal skin and in the production of ECM during embryonic development [12]. This unique fibroblast lineage, identified by the cell surface marker adenosine deaminase complex protein 2 (CD26), accounted for 1% of skin fibroblasts in early pregnancy, a proportion that was lower in postnatal skin in which needed increased by more than 75%. Furthermore, this fibroblast lineage was found to play an important role in the switch from scarless to scar wound healing in the second trimester. The skin is anatomically composed of three layers: epidermis, dermis, and hypodermis, which is further divided into epidermis (papillary) and deep (reticular) dermis. In an in vitro tissue culture system, we investigated the properties of isolated fibroblasts from superficial and deep layers of human normal dermis and HTS tissues. They found that deep dermal fibroblasts were larger, proliferated more slowly, and had higher levels of TGF-β1, connective tissue growth factor (CTGF), a-SMA, and collagen compared to superficial fibroblasts. reported low levels of collagenase. They further reported that deep dermal fibroblasts and fibroblasts isolated from HTS tissue have similar properties [13]. Therefore, deep dermal fibroblasts may be responsible for scarring in relatively deep skin injuries [10].

The ideal time of intervention

The final result of a wound healing, however, are scars. Scars typically don't become stable and mature in rodents until 80 days after the wound. Similar to women, scars in men often take at least six months to grow and become stable. Therefore, scarring has been considered a late event in wound healing that primarily involves extracellular matrix remodeling [14,15]. Why, then, is it necessary to deliver a therapeutic drug soon after surgery or an injury in order to reduce scarring? There are numerous rationales that could apply. Within seconds of wounding, degranulating platelets at the wound site produce active molecules, primarily TGF-β1 and PDGF, which act as the initial trigger in the healing of a wound. Gene transcription or translation do not cause this first response; rather, a large number of stored active molecules are released. These early triggers quickly cause a number of cytokine and cellular cascades that are redundant and overlap. Early intervention at the time of, or soon after, wounding has two major consequences: (i) a small alteration in the early mediators, such as a reduction in TGF-β1, can have a major long-term effect due to alteration and reduction of these autoinductive regulatory cascades; and (ii) early in the healing process, there are only a few major signaling molecules. Additional cytokines and growth factors are triggered or produced as wound healing advances quickly, and numerous overlapping and interconnected cytokine cascades are generated. These cascades have undergone evolutionarily enhanced robustness and redundancy, enabling them to resist significant variations in the number and kind of molecules present.

A different repertoire of receptors and responses can also be induced on the target cells by the early application of master regulatory cytokines like TGF-β3. This results in a noticeably different response to the various factors released during subsequent stages of healing and, consequently, a noticeably better scar. Early use of therapeutic medicines may also change inflammatory (monocyte, macrophage, lymphocyte, etc.) or fibroblast populations' recruitment and persistence throughout subsequent healing phases [16].

Therefore, the timing of an experimental or therapeutic intervention is crucial for producing adult scar-free recovery. This timing is helpful and not a concern in clinical practice. According to science, many regenerating systems share this long time lag between experimental intervention and phenotypic effect, such as lung regeneration caused by retinoic acid [17] and neuronal restitution of the central nervous system after stem-cell application [18]. In fact, this lag is a distinguishing feature of axolotl limb regeneration, where the early stages of blastema formation, cellular de-differentiation [19].

Old Belief and Evolutionary Considerations of Scar

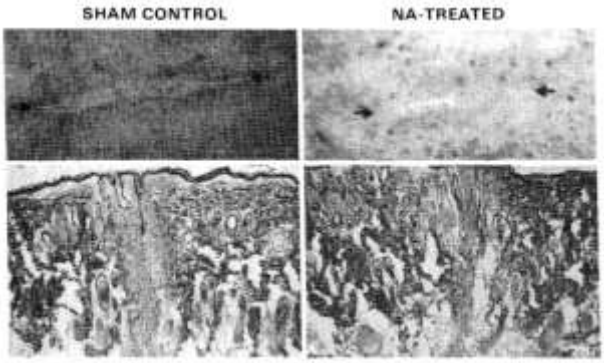
Most people think that scarring is an inevitable result of injury and, thus, an evolutionarily preferred outcome. This widely held belief conflicts logically with the outcomes of our experimental manipulations and frequently prompts inquiries regarding the potential drawbacks of being scar-free. No such drawbacks were found in experiments. Despite how it may appear morphologically, a skin scar is really weaker than healthy skin [20].

While prenatal wounds heal without scarring and with a reduced inflammatory and cytokine response, adult wounds heal with the creation of scar tissue. We administered transforming growth factor beta neutralizing antibodies (NA) to adult rats' healing cutaneous wound edges (TGF-β). All of the control wounds (irrelevant antibody, TGF-β, or no injection) healed with scarring, however the wounds that were treated with NA did not generate any scar tissue. Compared to the other wounds, NA-treated wounds showed more typical dermal architecture, fewer macrophages and blood vessels, and lower collagen and fibronectin concentrations. A novel strategy for the management of scarring may involve early modulation of the concentrations of particular cytokines [16].

Transforming growth factor (TGF-β), one of the numerous cytokines associated with wound healing, has an impact on all stages of the healing process, including the inflammatory response and extracellular matrix accumulation. TGF-β is also implicated in the development of glomerulonephritis and causes scarring in neonatal

wounds. Although cytokine therapy can hasten wound healing, it is likely that wound healing will be slowed down if cytokine levels fall. Skin scarring was significantly affected by the ratio of NA to TGF-β, and NA-treated wounds had less macrophages than controls. Additionally, wounds that have received NA have much less blood vessels. A week after wounding, wounds treated with NA had much less collagen than untreated wounds in the same animals, according to immunocytochemical and biochemical analyses [20].

However, normal extracellular matrix orientation was present in wounds treated with NA, permanently reducing the amount of scar tissue [21]. Collagen fiber orientation in all NA-treated wounds showed a more typical, regenerative pattern of dermal architecture compared to control or TFG-treated wounds, which exhibited a significant amount of improperly oriented collagen fibers in the scar. Surprisingly, there was no delay in healing or loss of wound strength together with the favorable effect on scar tissue in NA-treated wounds. According to research, NA against TGF-β applied in small doses right away after wounding is effective because it blocks the autocatalytic and autoinductive cascade of TGF-β amplification at the wound site, lowering the final growth factor concentration. TGF-β is angiogenic and chemotactic for monocytes and macrophages, which release their stores of TGF-β. This regulates TGF-synthesis beta when NA is first applied to TGF-β, the autoinductive action is lessened and there are fewer blood vessels, macrophages, and monocytes at the wound site [22].



Picture 1. Macroscopic and microscopic appearances of NA-treated wounds

Factor of Wound Size and Type

The natural continuum of mammalian tissue repair comes to a halt with scars. Total regeneration with new tissue with the same structural, esthetic, and functional qualities as the old, unharmed skin would be the ideal outcome. Early mammalian embryos have scarless skin healing, and lower vertebrates like salamanders and invertebrates have complete regeneration.[22]

Researcher propose that a particular sort of wound, which is not commonly seen now, served as the target of evolutionary selection on various wound-healing mechanisms (scarring or regeneration). Due to the fact that huge mammals simply die quickly after suffering an injury, its hypothesize that there have been few evolutionary selection forces on large mammals. Additionally, its contend that only a few number of particular, selective pressures act on extremely small mammalian wounds, such as those that may be brought on, for instance, by a plant's thorn.[24] The primary survival pressure in such small wounds will be to reduce wound infection and facilitate the removal of the foreign body. When this occurs, the evolutionary selective factors acting on the healing response will favor a scarring effect (an aberrant arrangement of extracellular matrix), also known as a fibrotic walling-off effect.[22]

Effectively this is a selective pressure to rapidly form granulation tissue and to rapidly remodel that granulation tissue into some form of scar tissue, such that the injured body part, e.g. limb can function at least partly so as to preserve the life of the organism. hypothesize that the most common wound injury seen in contemporary man or animals, heals by inappropriate and suboptimal cellular and molecular mechanisms that have been phylogenetically selected over a long time period for the healing of a different type of wound (bite, blow, contusion, etc.) with different degrees of tissue damage, wound infection, widespread impalement of foreign bodies and different wound morphology (no approximation of the wound margins). The result of this evolutionary mismatch is a scar that can be excessive and debilitating even after minor injury.[22]

Scarring, we submit, is essentially an evolutionary response to wall off foreign bodies and infection and to rapidly reconstitute semi-functional missing tissue. We hypothesize that the normal healing response in these sharp, clean, margin approximated wounds is excessive, with inappropriate levels of inflammatory cells and mediators, inappropriate stimulation of granulation tissue and inappropriate fibrotic differentiation signals resulting in walling off and scarring.[25]

There is a hypothesise that wound healing is evolutionarily optimised for speed of healing under dirty conditions, where a multiply redundant, compensating, rapid inflammatory response with overlapping cytokine and inflammatory cascades allows the wound to heal quickly to prevent infection and future wound breakdown. A scar may therefore be the price we pay for evolutionary survival after wounding.[22]

A wide range of scar forms are produced as a result of skin tissue healing, including "typical" fine lines, extensive scars, atrophic scars, scar contractures, hypertrophic scars, and keloid scars.[23]

The fine lines of surgical scars gradually enlarge and broaden, which typically takes place three weeks following surgery, resulting in widespread (stretched) scars. They are normally asymptomatic, pale, flat scars that are frequently observed following knee or shoulder surgery. Stretch marks (abdominal striae) are variations of common scars in which the dermis and subcutaneous tissues have been injured but the epidermis has not been penetrated. In contrast to hypertrophic scars, mature widespread scars do not have elevation, thickening, or nodules.[23]

Flat and depressed beneath the surrounding skin, atrophic scars are visible. They typically appear after chicken pox or acne and are typically tiny, spherical, with an indented or inverted center.

Scar contractures – Scars that intersect joints or skin folds at a straight angle are more likely to shrink or contract. When a scar is not fully developed, it can contracture; these hypertrophic contractures are often painful and dysfunctional. They frequently occur following burn injury to joints or skin concavities.

Hypertrophic or keloid scars are the terms used to describe raised skin scars. In general, hypertrophic scars regress naturally after the first injury and are elevated scars that remain within the limits of the original lesion. Scars from hypertrophy are frequently painful, itchy, red, and inflammatory. They frequently happen following burns to the trunk and extremities.[23]

Keloid scars are raised scars that are site-specific in their invasion of the surrounding normal skin and extend past the original wound's edges. A keloid almost always returns after a straightforward excision since it doesn't spontaneously retreat over time and keeps growing. Although there is no specific time frame, it is challenging to use the term "keloid" until a scar has been present for at least a year. Histologically, collagen fibers form a swirling, nodular pattern in keloids.[26]

For diagnosis, as well as for launching, monitoring, and assessing a therapy approach for scar management, accurate scar assessment is crucial. It's crucial to consider the origin and progression of scarring—is it becoming better or worse? Scar assessment tools like the Vancouver scar scale provide for a quantitative evaluation of scar severity, which is frequently determined by eye. Abnormal scarring is linked to a number of factors, including the presence of a favorable family history, prior abnormal scarring in the same or different anatomical sites, a poor response to treatment or recurrence of scarring, certain anatomical locations (such as the sternum), large size, protracted inflammation, and severe symptoms.[22]

Fact that Regeneration and Scarring May Occur in The Same Species and Even in the Same Soft Tissue

Regeneration and scarring can occur in the same species and can occur in the same tissue. Regeneration and scarring can be influenced by several things, such as the location or tissue that is being repaired, the molecules that play a role, and how the wound occurs. This was proven by a study by Cowin et al (1886) who compared the healing of skin incision wounds in fetal rats and adult mice. The results prove that fetal rats experience scarless healing while adult rats experience scar-forming healing. Differences in wound healing are due to differences in molecules that play a role between embryonic tissue and adult tissue. The number of inflammatory molecules that play a role will affect the outcome of wound healing, such as the occurrence of a scar or scarless wound[28].

Wound regeneration and healing are also affected by the location or tissue that is injured. Healing of wounds on the lens tissue of the eye, liver, and gums. Several other tissues have limited ability to regenerate, there are even tissues that cannot regenerate, such as the retina in the eye[29]. Regeneration is influenced by how the wound occurs in a tissue. Injury to the liver caused by partial hepatectomy can result in a scarless wound, while an injury due to a stab will cause a scar-forming wound in the tissue [30].

Fact that Regeneration and Scarring May Occur in The Same Adult Human Skin

Scarring formation and wound regeneration can occur in all parts of the human skin. Skin exposed to a light injury can regenerate well, and the mechanism is similar to scarless healing in embryos. Light injuries also have a minimal molecular response compared to large injuries. Large injuries will cause scarring and involve several molecules such as TGF-β 1,2,3, monocytes, macrophages, fibronectin, and collagen. Scarring can occur due to an increase in TGF-β 1 and 2, as well as an increase in immune responses such as monocytes, macrophages, fibronectin, and collagen. Scar reduction in wounds can be done by performing endogenous reduction in the form of TGF-β1 and 2 with the exogenous injection of neutralizing antibodies. Increasing specific endogenous TGF-β3 which is specified as an anti-scarring to help reduce the occurrence of scarring. The endogenous reduction will have the effect of decreasing the number of monocytes and macrophages around the wound [27].

Molecular Similarities of Scarring and Regeneration

Scarring and wound regeneration have molecules that play a role in it, one of which is TGF-β 1,2,3, as well as the immune response. Scarring in the form of wound healing with fibrous tissue repair will result in wound closure in the form of a scar. The main molecules that play a role in fibrous tissue repair and scar formation are TGF-β 1 and 2. Regeneration takes the form of wound healing with the formation of normal skin. The main molecule that plays a role in regeneration is TGF-β3. Both mechanisms have the same molecular form of TGF which mechanically plays a role by controlling the balance of the number of roles, namely scarring and anti-scarring [16].

TGF has a concept of balance in the body and will affect the immune response circulating the wound. The type

of TGF that will circulate will be adjusted to the shape of the wound, such as a wound in a tissue that must regenerate, so TGF-β3 will play a large role in its healing. While wounds that are exposed to the outside, or wounds that occur with contamination, scars will form, and TGF-β 1 and 2 play a lot of roles around the wound [16].

Molecular and Clinical Variables

The form of wound healing is influenced by several things. Variables that influence the form of wound healing are based on three things; the molecules involved, the tissues that are injured, and how the injury occurs. The molecules that play a role greatly affect the determination of the shape of the wound. Clinical factors that affect the number of molecules are the location and type of tissue, age, gender, race, and wound contamination during healing. The location of the tissue determines the number of circulating molecules such an injury to the gums will trigger regeneration, but an injury to the deltoid area can inhibit regeneration and trigger scar formation. The younger the patient, the worse the scar formation is compared to old age. Gender will affect the amount of circulating TGF due to the hormone estrogen. Race becomes a precipitating factor because racial differences trigger differences in circulating molecules. Wound contamination will inhibit regeneration and trigger scar formation in wounds [16].

CONCLUSION

Good wound management is to reduce the incidence of scar tissue in the wound. Embryonic scarless wound healing is a form of wound healing in the embryo and results in scarless wounds. Many in vivo studies have been carried out on several experimental animals, and the molecules that play a role are examined. Molecules that play a role in scarless and scarring wound healing are TGF-β 1, 2, and 3. TGF-β 1 and 2 play a role in the formation of scar tissue, while TGF-β 3 plays a role in tissue regeneration. There is a hypothesis that TGF-β 3 injected into the tissue will help wound healing and increase tissue regeneration so that scarless wound healing occurs. Scarless and scarring wound healing is not only based on the molecules that play a role but healing time and injured tissue also have an effect on wound formation. scarring and scarless wound healing can also occur in the same individual and the same individual tissue.

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