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Review Article

The Fetal Wound Healing: A Review

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Fetal wound healing has drawn the attention of many researchers from diverse background and specialties. Fetal wound healing is unique and differs from postnatal healing in that fetal skin wounds heal rapidly without scar formation. If the mechanism underlying such phenomenon can be elucidated, it will be serve as a significant milestone in the study of wound healing. Furthermore, the implications for therapeutic applications in wound management and in diseases where scarring is the basic pathogenetic mechanism would be immense. Rather than to list the results and conflicting data of numerous studies, this article hopes to provide a general overview of the recent developments.

Key Words: Fetal wound healing, scar formation, overview

Unraveling the mechanism of scarless fetal wound healing has been an intriguing subject of research in plastic surgery for some time. Although numerous study models and methodologies have contributed pieces of valuable knowledge in the jigsaw puzzle, none has been able to clearly define the mystery behind this phenomenon. It may well be that not only one critical step or key characterizes it, but an array of myriad yet subtle differences that lead to a totally different outcome. Nevertheless, researchers have made some important progress in finding out these potential elements that may later add up to obtaining our ultimate goal as clinicians in its therapeutic application.

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ANIMAL MODEL

Among the different fetal animal and wound implant models used in the study of fetal wound healing, exists inherent differences in the animal model itself that limit universal interpretation of results. A good example would be that excisional skin wounds contract and heal in fetal lambs, whereas this does not happen in fetal rabbits.[1,2]

The first animal model for fetal surgery was developed in the guinea pig, but difficulties in obtaining reliably time-dated pregnancies have made this model not very popular.[3] Although limited by a relatively short gestational age (31 days) which confines studies to the third trimester, the rabbit has gained wide acceptance as an animal model for fetal wound healing.

The sheep model has a sufficiently long gestation (145 days) to permit comparison of fetal wound healing at different gestational ages, is of adequate size to permit surgical manipulation and provide ample tissue for extensive analysis.[4] Burrington was the first to study fetal wound healing in the sheep.[5] He demonstrated that unlike the fetal rabbit excisional open wounds that do not contract or heal, same wound in the fetal rapid showed rapid contraction and healing. This has been attributed to the presence of myofibroblasts in the excisional wound in the fetal lamb demonstrated by both anti-muscle actin antibody and transmission electron microscopy. The role of wound collagen in fetal wound healing was extensively studied in the fetal lamb, and it has been firmly established that organization of collagen within the fetal wound matrix is the key factor in wound scarring pattern.

ORGAN SPECIFICITY

How different fetal organs possess different regenerative patterns have posed another variable in the study of fetal wound healing. Apart from skin and bone tissue, other tissue organs systems, including nerve, stomach, trachea, myocardium and diaphragm failed to regenerate scarlessly even in early gestation.[6,7] Therefore, fetal wound healing is an organ specific response.

THE FETAL ENVIRONMENT

There are numerous intrinsic and extrinsic differences between the fetus and adult that may influence wound healing. The fetal wound is continuously bathed in warm, sterile amniotic fluid rich in growth factors and ECM components such as hyaluronic acid and fibronectin.[8-10] Amniotic fluid could modulate fetal skin wound repair by application of HA and fibronectin directly onto fetal skin wounds, and by providing growth factors to stimulate fetal wound cells to make a unique environment. However, both amniotic fluid environment and perfusion by fetal blood failed to prevent scar formation in the wounded adult skin graft experiment, suggesting that other more important factors are in play.[11]

One intrinsic difference includes fetal tissue oxygenation. The fetus has a very low pO2 since there is a large transplacental oxygen gradient between maternal arterial and umbilical venous blood. It is still to be explained how the fetus can heal so efficiently in the relatively hypoxemic environment.

THE FETUS

The fetal fibroblast

The fetal fibroblast differs from the adult cells in that it is capable of achieving local wound repair without the presence of macrophages. Therefore, instead of inflammatory reaction required in the adult skin wound, the fetal milieu is able to signal local fibroblasts to begin the repair process. This is also related to the fact that the fetus is significantly neutropenic and lacks self/nonself immunologic identity. Thus the fetal wound lacks the typical inflammatory response seen in the adult tissue repair. This minimal fetal inflammatory response may play a pivotal role in the unique fetal repair process.

A significant difference lies in the regulation of collagen production, having a much greater prolyl hydroxylase enzyme activity, a critical limiting step in collagen synthesis.[12] A greater amount of hyaluronic acid synthesis and a fourfold greater density of hylauronic acid receptors also characterize the fetal fibroblasts. ASMA (alpha-smooth muscle actin) expression in the fetal fibroblasts also coincide with the onset of wound contraction and scar formation in the fetal wound.[13,14]

THE EXTRACELLULAR MATRIX

Hyaluronic acid, an important structural and functional component of the ECM, is laid down early in the matrix of both adult and fetal wounds. It has been shown that sustained deposition of hyaluronic acid is unique to fetal wound healing.[15]

The significance of hyaluronic acid was demonstrated initially in a PVA sponge experiment in the rabbit where the content of glycosaminoglycan, namely, hyaluronic acid was shown to be markedly greater than in the adult wound and 10-fold greater than in the unwounded fetal rabbit.[16] Such prolonged presence of hyaluronic acid in fetal wounds may provide the matrix signal orchestrating healing by regeneration rather than by scarring. Moreover, amniotic fluid has been shown to contain high concentration of hyaluronic acid, therefore, fetal skin is bathed in amniotic fluid that contains hyaluronic acid and HA-stimulating activity.[9,17] This may also be an additional mechanism by which HA is deposited in the matrix of fetal skin wounds. This HA rich fetal wound matrix environment may enable cell motility and proliferation unique to fetal wound healing.

COLLAGEN

The relative collagen synthesis of fetal fibro-

blasts is known to be much higher than that of adult fibroblasts. Fetal fibroblasts also synthesize more type III and IV collagen compared to adult counterparts. Duncan et al. have demonstrated that prolyl hydroxylase activity, an important rate-limiting step in collagen synthesis, is significantly higher in the fetal fibroblasts up until 20 weeks gestation.[12]

However, the mechanism of scarless wound healing in the fetus seems to be related more to the orderly deposition of collagen fibrils in a HA-rich matrix environment than to differences in the collagen synthetic ability.[18] ECM and growth factor differences may also affect fibrillogenesis in the fetus. The initial framework of fibrin and fibronectin laid down in the wound may also have important influence on collagen fibril orientation. Furthermore, the fetal wound fibroblasts can migrate freely and rapidly in the loose lattice containing high levels of proteoglycans and glycosaminoglycans. Observation of a rapid increase in collagen fibril diameter in midgestation when both HA and chondroitin sulfate of the matrix declined seem to support such assumption.[19]

ADHESION MOLECULES, GROWTH FACTORS

Various adhesion glycoproteins mediate interaction of cellular components and the ECM. Some examples are fibronectin, thrombospondin and tenascin. These bind to specific integrins or cellular receptors to modulate cell migration, proliferation and attachment. To date, relatively earlier deposition of fibronectin and tenascin in the fetal wounds have been proved and thought to be a possible mechansim of rapid reepithelization in the fetus.[20]

Peptide growth factors, such as TGF-β and EGF, PDGF have been implicated as having important regulatory roles in fetal wound healing. The effect of TGF-β is organs specific in its effect, and also modulated by varying concentrations of its various isoforms. TGF-β stimulates the synthesis of ECM components such as fibronectin, proteoglycan and collagen, but the exact role of TGF-β in the local fetal wound environment remains unclear. Recent studies suggest that the differential expression of TGF-isoforms rather than the mere presence of TGF-β may determine the biologic activity and scarring in tissue repair in the fetus and adult tissue.[21]

Epidermal growth factor (EGF) stimulates cells to become dedifferentiated and to rapidly continue the cell cycle. EGF is also chemotactic for epithelial cells and increases the secretion of collagenase by fibroblasts, which is an important step in tissue remodeling. In the fetal wound TGF-α may act as EGF through cellular receptor binding causing similar alterations in cellular physiology.[22] It has been shown in an excisional fetal rabbit wound experiment that a single local dose of EGF accelerates reepithelization.[23]

Platelet-derived growth factor modulates tissue induction and remodeling during wound healing and osteogenesis. PDGF has many potential roles in wound healing through its chemotactic effects on fibroblasts, monocytes, and neutrophils. PDGF also has mitogenic effect on cells of mesenchymal origin. When implanted into fetal skin, PDGF markedly increased acute inflammation, fibroblast recruitment, collagen and hyaluronic acid deposition.[24] Persistence of PDGF in the fetal wound reflects binding of the highly cationic factor to components of the ECM such as glycosaminoglycans, a mechanism responsible for prolonging the local activity of the factor at the site of the wound.

The definite role of cytokines in fetal wound healing is obscured by the complexity of the cytokine millieu. In summary, it is most probable that it is the balance of various cytokines rather than one factor being soley responsible for the scarless repair observed in the fetal skin tissue.

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