Hypertrophic scars

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Skin wound healing is an interactive process characterized by sequential events that begin directly after injury. It can be divided into four overlapping phases; hemostasis, inflammation, proliferation and remodeling. Hemostasis starts directly after injury when bleeding occurs as a result of the disruption of blood vessels. In order to stop bleeding, blood vessels constrict within seconds, platelets become activated, aggregate and release soluble wound healing mediators (e.g. TGF-β1, PDGF and VEGF). [1-3] Together this results in the fibrin clot. [1,2] Besides forming a temporary cover for the wound, the clot also serves as a network for cells migrating into the wound bed and a reservoir of growth factors and cytokines which are required during the later stages of the wound healing process.

An inflammation response is also initiated immediately after injury to counteract infection and to drive wound closure. The cytokine and chemokine cascade which is initiated by the damaged cells within the wound bed results in the infiltration of leukocytes (e.g. neutrophils, monocytes, macrophages) to kill bacteria and clear damaged matrix proteins. [1,4] Macrophages have dynamic and plastic phenotypes (existing as a continuum between the M1 and M2 extremes) that change with the local environment. [5] During inflammation, macrophages have a more M1 phenotype and remove senescent cells and debris in the wound bed (innate immune system), present antigens of pathogens to T-lymphocytes (adapted immune system) and produce large amounts of cytokines and growth factors to further amplify the inflammatory response. M2 macrophages are more associated with tissue repair and fibrosis.

The proliferation phase of wound healing is associated with wound closure. In this phase M2 macrophages predominate where they suppress inflammatory responses by secreting factors like IL-10 and TGF-β1 and promote angiogenesis, tissue remodeling and repair. [5] Fibroblasts proliferate and migrate into the fibrin clot where they secrete extracellular matrix (granulation tissue, consisting of collagens fibronectin, glycosaminoglycans and proteoglycans). [6] TGF-β results in a subgroup of fibroblasts differentiating into α-smooth muscle actin expressing myofibroblasts. [7] These myofibroblasts induce wound contraction (contributing to wound closure) and also deposit extracellular matrix. At the same time, endothelial cells sprout from pre-existing vessels into the wound matrix. This sprouting is stimulated by e.g. VEGF, FGF2 and TGF-β1, which are mainly produced by keratinocytes, macrophages, platelets and fibroblasts, to form new vessels. [6] The formation of granulation tissue within the open wound enables keratinocytes, from the wound margins and hair follicles, to proliferate and migrate across the new tissue resulting in re-epithelialization of the wound. This is mainly stimulated by factors (e.g. EGF, KGF TGF-α) secreted by macrophages, platelets and fibroblasts. [1]

Finally tissue remodeling occurs, cell proliferation decreases and the levels of collagen production and degradation equalize. [6] Myofibroblasts and macrophages undergo apoptosis or leave the wound region. [8] Collagen III, which is prevalent in granulation tissue, is replaced by the stronger collagen I and the extracellular matrix is further strengthened by cross-linking and re-aligning disorganized collagen fibers. [1,9] This tissue is called a normotrophic scar which is hardly visible since it is smooth, pale and flattened.

Abnormal wound healing can lead to the development of a hypertrophic scar (HTS). HTS remain a challenging problem in burn wounds as well as surgical wounds. Hypertrophic scars are thickened and stiff scars, defined as raised above skin level, but confined to the boundaries of the original wound. [10-12] In addition to a modified inflammatory response and increased neoangiogenesis, there is a disturbed balance of extracellular matrix (ECM) deposition and degradation in HTS formation. [13,14] In some individuals HTS seems to be a physiological process in wound healing, since it has a temporary character and regresses within several months. [15,16] But in other patients HTS is not transient and the scar remains thickened and rigid, which can cause significant morbidity because of the unaesthetic appearance, symptoms such as pain and itch and mechanical problems such as impaired limb mobility when the scar is situated over a joint. [17] Literature reports incidences of HTS varying from 40 to 94 percent post-surgery and 30 to 91 percent post-burn. [10,17] To date, there is no optimal therapy available for HTS and many aspects of the mechanism of hypertrophic scar formation still need to be elucidated. A reduced amount of inflammatory cytokines in wounds which resulted in HTS has been described. [13-15] The fact that wounds which end up hypertrophic contain less

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inflammatory mediators implies a reduced immune response in individuals who develop HTS. Parallel to the need for understanding the mechanisms underlying HS formation, a reliable and easily manageable clinical tool to identify individuals predisposed to HTS formation is lacking. Such a prognostic tool would enable an early start of treatment thus reducing patient comorbidity and loss of quality of life. For elective (aesthetic) surgery, an opt out decision may be made when the benefit of the procedure does not outweigh the chance of developing HS.

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Samenvatting

Hypertrofe littekenvorming is een groot probleem bij de genezing van brandwonden en chirurgische wonden. Hypertrofe littekens zijn verdikt en stijf (liggen op de huid), maar blijven wel altijd binnen de grenzen van de originele wond. Bij hypertrofe littekenvorming is er sprake van een veranderde immuunrespons, verhoogde neoangiogenese en een verstoorde balans in de aanmaak en afbraak van extracellulaire matrix. Bij sommige patiënten lijkt hypertrofe littekenvorming een fysiologisch proces en verdwijnt het hypertrofe litteken na een aantal maanden vanzelf. Echter, er zijn ook patiënten waarbij het hypertrofe litteken niet verdwijnt en het littekenweefsel stijf en verdikt blijft. Dit leidt tot aanzienlijke morbiditeit door het esthetische aspect, pijn, jeuk en bewegingsproblemen wanneer het hypertrofe littekenweefsel zich rond een gewricht bevindt. Er is tot op heden nog geen optimale behandeling voor hypertrofe littekens, en de onderliggende mechanismen die een rol spelen in het ontstaan van hypertrofe littekens zijn nog grotendeels onbekend. Daarnaast bestaat er nog geen makkelijke en betrouwbare manier om het ontstaan van hypertrofe littekens te kunnen voorspellen.

Trefwoorden

wondgenezing – hypertrofisch litteken – prognosehulpmiddel

Summary

Hypertrophic skin scars (HTS) remain a challenging problem in burn wounds as well as surgical wounds. Hypertrophic scars are thickened and stiff scars, defined as raised above skin level, but, in general, confined to the boundaries of the original wound. In addition to a modified inflammatory response and increased neoangiogenesis, there is a disturbed balance of extracellular matrix (ECM) deposition and degradation in HTS formation. In some individuals HTS seem to be a physiological process in wound healing, since they have a temporary character and regresses within several months. But in other patients HTS is not transient and the scar remains thickened and rigid, which can cause significant morbidity because of the unaesthetic appearance, symptoms such as pain and itch and mechanical problems such as impaired limb mobility when the scar is situated over a joint. To date, there is no optimal therapy available for HTS and many aspects of the mechanism of hypertrophic scar formation still need to be elucidated. Also, a reliable and easily manageable clinical tool to predict HTS formation in patients prior to surgery is lacking.

Keywords

wound healing – hypertrophic scar – prognostic tool

Conflicts of interest
Nothing to declare

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