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Hypertrophic scarring: the rabbit ear model for studying dermal fibrosis

Skin is the largest organ in body with multiple vital functions. Apart from its significant role in maintaining the body temperature and prevention of water loss, the appearance of skin has a significant effect on one's psychological well-being. As a result, restoration of skin integrity and structure following injuries is a crucial issue. The healing process in human skin is complex and any disruption of the normal wound healing may lead to a non-healing wound at one end or the hypertrophic scar (HSc) at the other end of the healing spectrum. HSc is a red, elevated, firm, and irritable (or asymptomatic) scar, which begins to develop weeks following injuries such as deep trauma, severe burn, or surgical incision. Although, HSc continues to enlarge for 3–6 months, it remains confined to the site of injury for more than a year, and then gradually regresses afterwards to become flatter and softer at later time points. Histologically, HSc is characterized by an excessive deposition of extracellular matrix components, especially type I collagen.

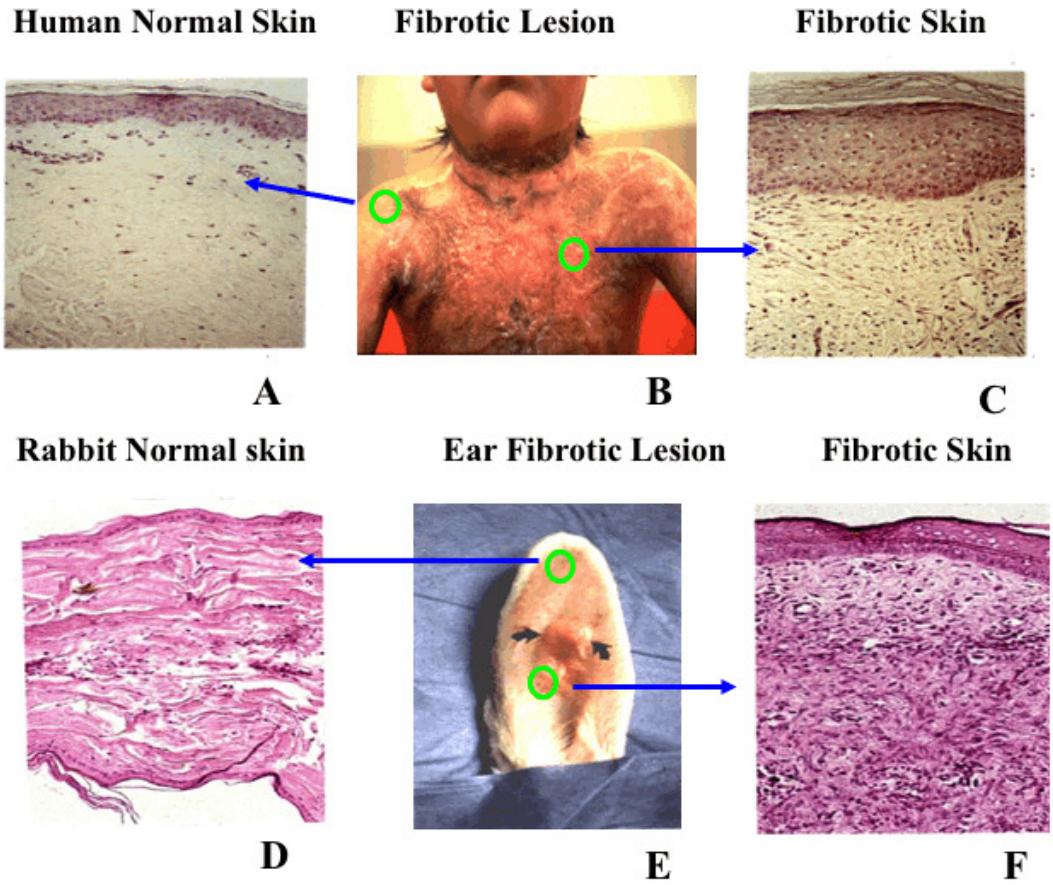

Fig. 1. Histology of normal and fibrotic human skin in comparison to normal and fibrotic skin in the rabbit ear model.

Development of the HSc on exposed areas (face, neck, or hands), or over the joints, especially when it is extensive (after burn injury), significantly reduces patient's quality of life by limiting the normal movement

and unsightly appearance. Despite all the advances in surgical techniques and wound care, the prevention or treatment of HSc remains a challenge. The dynamic nature of skin scarring and the ethical limitations for human studies encourages the development of animal models to assess the efficacy and safety of new therapies.

Over the past decades different animal models have been developed to investigate the pathophysiology of HSc and test the new therapeutic modalities. Rodents are the most popular animals used in laboratory for generating conditions resembling human diseases, because of their ease of care and costs associated with their maintenance. However, the rodents have loose skin and an extra layer of thin muscle under their skin, the panniculus carnosus, which causes wound contraction and faster healing that prevents HSc formation.

The rabbit ear model was first established by Morris et al., following observations that some surgical wounds in the rabbit ear remain raised for a few months after healing. In this model a full-thickness excisional wound to the cartilage surface was created over the ventral side of rabbit ear. Depending on the size of the original wound, this technique was used to develop an acute or chronic scarring model. Clinically, the large wounds (1.5 × 4.5–7.0 cm) healed with visibly raised and palpable scars which remained elevated up to 90 days or more post wounding. The healed small wounds (6 mm in diameter) also remained elevated until they were harvested at 22 days post wounding.

The rabbit ear model of hypertrophic scarring has several advantages over other models of fibroproliferative disorders. (1) The rabbit ear has no panniculus carnosus; as a result, significant wound contraction is excluded, and healing occurs similar to healing in human skin (granulation tissue formation and re-epithelialization). (2) The histology of the HSc in the rabbit ear shows increased deposition of collagen fibers, and the number of inflammatory cells, along with the density of blood vessels is similar to the HSc in humans. The presence of irregularly arranged collagen fibers with circular or spiral (“whorled”) pattern is also common between the rabbit ear model and human HSc (Fig. 1).

The relatively simple procedures needed to generate a hypertrophic scar in the rabbit ear model and its reproducibility, make it a useful model to explain factors involved in pathogenesis of dermal scarring or to investigate the anti-fibrogenic effect of prospective treatment options.

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