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Perlecan HS produces TGF-β1 deficiency in mutant skin

The skin is the largest organ in the human body and one of it's most dynamic. Skin has a large surface area and protects the body from the external environment and is challenged by many poisonous substances and sources of infection on a daily basis thus it plays an important role in maintaining a barrier to invading organisms to keep the body in a healthy state. It is remarkable that skin is such a resilient tissue and it is one of a few human tissues which has the ability to undergo constant renewal throughout ones lifetime and has a high capacity for replacing damaged areas with new skin. To achieve this, the cells in skin (fibroblasts, keratinocytes) produce a number of small proteins called growth factors which help to maintain skin quality. When a wound occurs in skin these growth factors such as fibroblast growth factor-2 and transforming growth factor-β1 signal to brother and sister cells to produce new tissue.

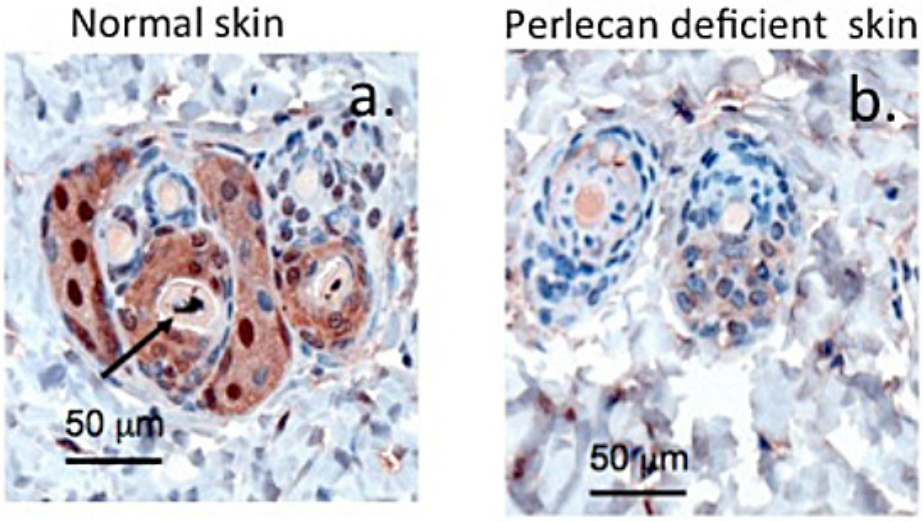

Fig. 1. Immunolocalisation of TGF-beta 1 in C57BL/6 wild type mouse skin (a) and in the Hspg2 exon 3 null HS deficient mouse.The arrow depicts a hair shaft.

In order for these growth factors to work properly they must be stored in skin tissue in a stable form attached to another class of protein known as proteoglycans. These proteins protect the growth factors and also act as structural proteins which provide resiliency to skin and also provide stability from mechanical damage. In individuals where there is a genetic defect the tissue proteoglycans may not be produced in sufficient levels to achieve this protective effect. Transforming growth factor-β1 and fibroblast growth factor-2 have important roles in stimulating the skin cells to undergo repair process thus in those individuals with deficient levels of a key proteoglycan called perlecan the skin becomes prone to damage and infective organisms can gain access to the body and can produce disease. Fibroblast growth factor-2 stimulates the production of new blood vessels which have roles in the healing process in skin, transforming growth factor-β1 also makes skin cells produce collagen which is the major structural component of skin and along with the new blood vessels help to repair wounds replacing these damaged areas with new skin. Figure 1 shows two examples of skin tissue from a normal mouse (C57BL/6 strain) and from a genetic variant where the proteoglycan perlecan is non-functional.

This results in this skin having an inability to store transforming growth factor-β1 and if damaged, this skin would be less capable of undergoing repair, open wounds are potential sites of infection leading to disease. This figure has been processed by a procedure known as histology and antibodies are used to identify areas where transforming growth factor-β1 is present, these areas have a red-brown colouration. By comparing the normal skin (a) and perlecan deficient skin (b) the differences in the localization of this growth factor is readily observed. Arrows in this figure depict a hair shaft within a hair follicle. The surrounding cells store transforming growth factor-β1. The other dark dots within the stained cells represent cell nuclei.

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Publication

The heparan sulphate deficient Hspg2 exon 3 null mouse displays reduced deposition of TGF-β1 in skin compared to C57BL/6 wild type mice.
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