It is clearly necessary for land based mammals to have a skin. The epithelial permeability barrier (EPB) prevents dehydration, the ingress of microorganisms and toxins, and permits some forms of selective absorption. The skin also has an important role in temperature regulation. But there are some surprises in how we get it.

By 4 weeks gestational age in Man, the ectoderm has given rise to a basal layer of keratinocytes covered by a layer of periderm cells. By 9–10 weeks, progressive stratification becomes evident and the main components of the skin then begin to develop. The epidermis forms a proliferative compartment, from which cells become irreversibly committed to terminal development. There is a differentiating zone and a senescent outer layer, and the balance between the cellular activities that form the components of these zones is mostly maintained by communications by gap junctions in keratinocytes in the differentiating layer. These communications are specialized; different gap junction proteins (connexins) are expressed in the different zones. There is limited expression in the basal layer, more in the spinous layer, less in the granular layer and none in the stratum corneum. Some of the later changes in skin development are integrin-dependent; these cell surface glycoproteins, consisting of one alpha and one beta subunit, have their specificity of binding to receptors determined by heterodimer composition, which changes as the skin matures. In the epidermis these glycoproteins are confined to the basal layer, and the loss of integrin-dependent adhesiveness to fibronectin, laminin and collagen, as keratinocytes differentiate, may also determine their superficial migration.

In premature infants, dehydration and loss of temperature regulation are major clinical problems, due in part to the late stage in intra-uterine development at which the EPB becomes effective. This is certainly a late change: even by 16 days gestation in the rat, the intercellular junctions are in an immature form, the collagen content of the skin is around 1/20th of normal adult values, and its cross linkages are less well developed.

The barrier functions of the skin depend on the assembly of a number of proteins and lipids into what are sometimes called cornified envelopes (CE). The keratin component of the cytoskeleton becomes bundled in keratohyalin granules; involucrin, small proline-rich proteins and other membrane components are added. Tight junction formation is also essential for the integrity of the barrier functions of the epidermis, and the recent identification of the role of a family of membrane proteins called claudins (generally more than one at a time in the standard CE) indicates a rather more specific form of regulation than had been supposed.

Hardman et al. have also shown that the barrier function of the skin is acquired late in development. They found that the barrier forms in a patterned manner by spreading out from specific sites, moving around the embryo as a front, the development of which depends on the development of a stratum corneum. The typical extracellular dispersion of lipid-containing lamellar bodies on the surface of the keratinized cells develops, and the packed keratin filaments form a dense matrix. The authors comment that the pattern of initiation sites appears to be species-specific.

In a later paper, the same group found that in human fetuses there was evidence of regional initiation of a barrier function comparatively earlier than in the rat, at 20–24 weeks gestational age. Interestingly, this is at what most of us would consider to be the current lower limit of viability; efforts to understand this process might improve the management of the very small baby.

Does this link with the other oddity of fetal skin—scarless healing? The successful repair of life-threatening congenital defects in utero has lead to increasing interest in differences in wound healing in the fetus. The repair of any wound with a ‘scarless’ wound would permit the normal growth of many primordia which would otherwise be progressively distorted by the failure of normal interactions (for
example, of the maxillary processes of the face, in cleft lip and palate) and offer an enormous potential benefit.

Fetal skin heals by the simple reformation of normal structures; there is no scarring until late in gestation. The skin is very plastic in early stages of development, but the stratification described above, together with extensive fibrogenesis in the dermis, alters this. However, the process of healing is not radically different from that in mature skin; from the data of Ihara and Motobayashi\(^2\) based on experiments in 16-day rat skin (the time when barrier functions are being acquired), the rapid inward spreading of epithelial cells that occurs in wound closure in later life is well established. This process can be inhibited by cytochalasin B but not by hydroxyurea, suggesting a microfilament-mediated phenomenon rather than an effect of cell proliferation, so we cannot assume this is a proliferative response. Mesenchymal activity was essential for proper wound healing in these experiments, however, so perhaps it is organogenesis that confounds plasticity, as at other sites in embryogenesis.

Other findings support this conclusion. In studies on the healing of lip wounds, Whitby and Ferguson\(^3\) found the principal difference between fetal, neonatal and adult wound healing was the time of appearance of tenascin in the wound. Tenascin is a glycoprotein present in mesenchyme during development (and found in large amounts in the stroma of breast carcinomas). It inhibits the cell-adhesion effect of fibronectin by interaction with cell surface receptors of the integrin family, and during development its appearance correlates with the onset of cell migration (notably in the CNS). The rapid epithelialization seen in fetal wounds appears is facilitated by this, and is a major factor in the absence of scarring.

Whitby and Ferguson found that collagens form normally in fetal wounds but remodel very effectively; the absence of scarring could not be attributed to lack of collagens I, II, III, IV, V or VI. Importantly, there was no morphological evidence of inflammation in their study. Lorenz et al.,\(^4\) using a model of human fetal skin grafted to athymic mice, confirmed these findings but also showed, by the nature of their model, that fetal serum (the developmental experimentalists’ chicken soup) and amniotic fluid were not important in this phenomenon. It is probably the absence of inflammation that matters. Many insults to the fetus fail to result in an inflammatory response (although one can be mounted from 16–18 weeks on). Apoptosis is better than necrosis in terms of subsequent remodelling.

It seems that the appearance of an effective EPB and plasticity in healing are linked only in the sense that they are aspects of the developmental state: as one is acquired (or just before), the other is lost.

References


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