CURRENT KEY DEVELOPMENTS

Molecular genetics of the skin: the implications of understanding

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Building on the foundations of biochemical studies in the 1970 and 1980s, in the past two decades molecular genetics has progressed rapidly in elucidating single gene disorders and complex traits of skin. The challenge now is to apply this knowledge in prevention and treatment. In a brief review it is possible only to give examples.

Single gene disorders: blistering

Study of single gene disorders causing blistering has contributed to a detailed picture of epidermal growth and differentiation, as well as of its integrity. For example, ultrastructural and immunocytochemical studies found that the severe blistering disorder recessive dystrophic epidermolysis bullosa (RDEB) is caused by loss of the anchoring fibrils, composed of type VII collagen, which attach the basement membrane to the dermis.[1,2] Molecular genetics then defined the different mutations in the COL7A1 gene which cause dominant as well as and recessive forms of EB.[3] Subsequently defects in other components of the basement membrane and hemidesmosomes – such as laminin 332, $\alpha_6\beta_4$ integrin, collagen XVII and plectin – were shown to be responsible for other neonatal blistering disorders.[4] Similarly, the biological properties of keratin intermediate filaments were established biochemically and ultrastructurally,[5,6] but molecular genetics demonstrated that defects in specific keratins in epidermis, appendages and mucosa are responsible for a wide range of phenotypes – blistering and hyperkeratosis, pigmentary and hair defects – which reflect not only the tissue and differentiation-specific distribution of the keratins,[7] but also their non-structural properties. Blistering and hyperkeratotic phenotypes also result from defects in cell adhesion: directly in the case of desmosomal proteins or, with endoplasmic reticulum (ER) and Golgi calcium ATPase dysfunction in Darier and Hailey-Hailey disease, via abnormal membrane protein processing. Intriguingly, the widespread distribution of these ATPases contrasts with the cutaneous localisation of the disorders. For example SERCA2, defective in Darier disease, is the major cardiac ER calcium ATPase. Conversely, the association of some defects in plakoglobin and desmoplakin with arrhythmogenic cardiomyopathies reflect the broader importance of cell junctions.

These discoveries have implications for clinical care. RDEB produces lifelong skin and mucosal bullous disease, leading to contractures and strictures, disability and, by early adult life in a majority of cases, aggressive and often fatal squamous cell cancer. Better care for children with EB in the UK has been championed by the charity DEBRA (www.debra.org.uk), which has also been a major supporter of research. In prevention, prenatal diagnosis has spared many families a second affected child.[8] Diagnostic techniques have paralleled better understanding, progressing from prenatal skin biopsy, to chorionic villus sampling for DNA analysis, and preimplantation genetic diagnosis. In treatment, cell and molecular therapy is tantalising. Approaches under investigation include restoration of collagen VII expression via transfected fibroblasts, bone-marrow transplantation, and grafting with genetically modified autologous epidermis.[9–11] For other disorders caused by dominant dystrophic gene defects, knockdown of gene expression using small interfering RNAs (siRNA) offers a prospect of specific therapy.[12] In disorders due to premature termination codons, agents promoting read-through may permit restoration of gene expression.[13] Despite proof of principle for many of these approaches, practical delivery remains challenging.

Complex traits: inflammatory skin disease

Common inflammatory skin diseases for which there is a major genetic component include psoriasis, eczema, acne, alopecia areata and many others. For psoriasis and eczema, conventional mapping studies and genome-wide analysis have shown multiple susceptibility loci. The significance of all these loci is not yet understood, but the recent finding that polymorphisms in the interleukin 23 receptor and its ligand interleukin 12 influence susceptibility to psoriasis reflects evidence that biological therapy directed against these cytokines is effective.[14,15] In the case of atopic eczema, a predisposition locus at the epidermal differentiation complex is due at least in part to common null mutations in the gene encoding the epidermal barrier protein filaggrin.[16] Ten per cent of European subjects carry such mutations, which in the homozygous state cause ichthyosis vulgaris.[17] In the heterozygous state they produce a threefold increased risk of not only atopic eczema, but also of other atopic disease, and are a marker for persistence of eczema into adult life.[18] The relevance of epidermal defects to systemic atopic disease is even clearer in Netherton syndrome, in which absence of a serine protease inhibitor (LEKTI) in skin produces neonatal erythroderma and ichthyosis, but also severe cutaneous and respiratory atopy. These discoveries suggest new avenues for prevention and therapy of atopic disease.

Genetic predisposition to skin cancer

Study of the skin has also contributed to progress in cancer biology. Defects in the complex of proteins underlying different forms of xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome have provided opportunities to understand DNA repair.[19] The human *hedgehog* signalling pathway has been dissected in part as a result of recognition of *PATCH* defects in Gorlin (naevoid basal cell carcinoma) syndrome.[20] Other

pathways relevant to skin cancer are diverse[21]; ranging from skin colour (see below), cyclin-dependent kinase inhibitor 2A (CDKN2A/p16INK4a) in familial melanoma, detoxifying cytochromes in basal cell carcinoma, to gap junction communication in keratitis, ichthyosis, deafness (KID) syndrome. In many other disorders, molecular defects leading to internal neoplasia are accessibly manifest in skin.[22]

Skin colour

Among the most critical genetic adaptations during human history have been those in genes regulating skin and hair colour. In European populations, there is evidence of positive selection for skin colour variants (for example those in the melanocortin 1 receptor (MC1R) which underlie the red hair/fair skin phenotype) probably because fair skin increases ultraviolet (UV)-dependent vitamin D synthesis in northern latitudes.[23] Other skin colour genes include SLC24A5, TYR, and OCA2 and genome-wide analysis has identified more loci.[24,25] Increased UV exposure is, however, also associated with increased skin cancer susceptibility, including melanoma, so it is not surprising that pigmentary loci also influence cancer risk.[26–28] However, susceptibility may not be solely dependent on the pigmentary pathways.[26]

Summary

During recent decades, discoveries in genetic skin disease have produced insights into the biology of the skin, and in some cases permitted preventive prenatal diagnosis, but application of this knowledge in palliation or cure remains a tantalising prospect.

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The burden of skin disease: quality of life, economic aspects and social issues

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Doctors looking after patients with skin disease have probably always been aware that the condition can have a devastating effect on many patients' lives. However, the physician-centred view of medicine focused on diagnosis and therapy rather than