Desmosome

Skin Needs Plakophilin-1

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In 1997, McGrath *et al*. (1997) described a condition called ectodermal dysplasia/skin fragility syndrome and showed that it was caused by mutations of the plakophilin-1 gene, the first mutations to be discovered in a human desmosomal gene. Effectively a plakophilin-1 knockout, the discovery gave novel insights into the function of this protein in desmosomal adhesion and keratin filament attachment to the desmosomal plaque.

At birth, the proband suffered from severe blistering of his face, soles and buttocks. Nevertheless he survived and, although small, grew at a normal rate. By 5 years of age, he showed complete absence of hair, widespread crusts and erosions on his skin, marked hyperkeratosis on the palms and soles, and abnormal nails. Wide intercellular spaces, indicative of loss of keratinocyte adhesion, were revealed by histological and ultrastructural examination of the epidermis. Moreover, keratin filaments were withdrawn from the keratinocyte peripheries and aggregated around the nuclei. Desmosomes were small, with widened intercellular spaces and greatly reduced intercellular plaques, suggesting that the syndrome might be due to a desmosomal abnormality. The nature of this was revealed by immunofluorescence with specific desmosomal antibodies. Desmosomal cadherins and plakoglobin were normally distributed, but desmoplakin was diffuse and, crucially, cytoplasmic staining for plakophilin-1 was absent.

Mutational analysis of the plakophilin-1 gene revealed distinct mutations in the paternally and maternally inherited alleles, both resulting in premature termination due to the insertion of stop codons and in severe truncation of the polypeptide.

A study of this human syndrome had revealed that plakophilin-1 is a key component of the desmosomal plaque, being somehow involved in the location of desmoplakin, and through this, the anchoring of intermediate filaments. Loss of plakophilin function also reduced desmosomal adhesion. Subsequently, plakophilin-1 was localized to the outer dense plaque, to bind to desmoglein, desmocollin, desmoplakin and keratin and to recruit desmosomal proteins to the cell periphery (Smith and Fuchs, 1998; North *et al*., 1999; Hatzfeld *et al*., 2000). Furthermore, Grossman *et al*. (2004), studying plakophilin-2 knockout in mice, confirmed plakophilin's role in the location of desmoplakin to the desmosomal plaque.

Plakophilin-1 is a member of the armadillo gene family and one of three plakophilin isoforms to have been identified. All three are present in the epidermis, and this may account for the nonlethality for the viability of the proband in this case; plakophilins-2 and -3 may compensate for the loss of plakophilin-1.

Besides being desmosomal components, plakophilins are widely distributed in the cytoplasm and nuclei of various cells. Their nuclear function is unclear, but a recent study suggests an involvement with RNA-binding proteins and involvement in translation and RNA metabolism (Hofmann *et al*., 2006).

Several other inherited diseases involving desmosomal components have since been discovered. These disorders include a variety of defects in the skin, hair and the heart, and vary in severity from mild to lethal (reviewed in McGrath, 2005). Collectively, such studies have provided a greater understanding of the cellular mechanisms underlying skin biology that may aid the future treatment of skin diseases and how desmosomal components contribute to tissue structure, regulation and function.

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