GENETICS OF STRUCTURAL SKIN DISORDERS

Genetics of Structural Hair Disorders

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INTRODUCTION

The first successful application of positional cloning to a disorder of the skin involved the identification of steroid sulfatase as the gene mutated in X-linked ichthyosis (Ballabio *et al.*, 1987; Yen *et al.*, 1987). This groundbreaking discovery led to the cataloging of more than 500 unique protein-coding genes, underlying 560 different skin and hair abnormalities (Feramisco *et al.*, 2009; Betz *et al.*, 2012). Among skin appendages, the hair follicle (HF) has a remarkably complex architecture, comprised of concentric layers of epithelial cells, which surround and support the highly keratinized, rigid hair shaft. The shaft itself consists of a multicellular cortex and the hair cuticle encased by the three layers of inner root sheath (IRS). The IRS is surrounded by the companion layer and the outer root sheath, which is continuous with the basal layer of the epidermis. With every successive hair cycle, the proliferating matrix cells in the anagen hair bulb differentiate and keratinize, giving rise to the layers of the IRS, as well as the cuticle, cortex, and medulla of the hair (Langbein and Schweizer, 2005). Keratins, desmosomes, and lipids are abundantly expressed in the HF and are essential for maintenance of structural integrity and regulation of apoptosis, stress response, and protein synthesis (Takahashi *et al.*, 2003; Gu and Coulombe, 2007; Kim and Coulombe, 2007). In this review, we will focus on hereditary hair disorders and discuss the studies that linked these disorders to genes encoding structural components of the HF.

KERATINS AND ASSOCIATED HAIR DISEASES

Keratins are the major structural component of the HF and are generally divided into type I (acidic) and type II (neutral-basic) proteins. In addition to this classification, relating to chromosomal location, gene structure and ability to form heterodimers with the other type, keratins fall into two categories: keratins of the epidermis and the ''hard'' keratins of the hair. Hair keratins possess a highly cysteine-rich head and tail domains, allowing them to form tight cross links with keratin-associated proteins. This enables the formation of the tough structure of the hair and nails. Of the 54 functional keratin genes identified by the Human Genome Project, 11 type I keratins, designated as K31–K40, and 6 type II keratins, designated as K81–K86, are expressed specifically in HF and nails (Langbein *et al.*, 1999; Schweizer *et al.*, 2006). Keratin mutations cause fragility in epithelial cells and mutations in several hair keratins have been linked to human diseases (McLean and Moore, 2011).

The first and most common among the hair keratin diseases is monilethrix, a nonsyndromic hair disorder characterized by fragile, brittle scalp hair, and nail deformities. Morphologically, affected individuals display periodic changes in hair shaft diameter, resulting in a characteristic abnormality called beaded hair. The autosomal dominant form of the disease is caused by missense mutations in the conserved helix termination motifs of the type II hair keratins *KRT81*, *KRT83*, and *KRT86*. These proteins are highly expressed in the hair cortex, and the identification of these mutations provided the first direct evidence for the involvement of hair keratins in hair disease (Winter *et al.*, 1997; van Steensel *et al.*, 2005). K85 is a type II hair keratin linked to autosomal recessive pure hair and nail ectodermal dyplasia, a disorder manifested as a complete alopecia and nail dystrophy. The K85 protein is abundantly expressed in the matrix, precortex, and cuticle of the hair shaft and appears critical for the proper formation of keratin and desmosomes complexes in the hair and nails. The severity of this phenotype suggests that K85 is more essential to HF structure than proteins involved in monilethrix (Naeem *et al.*, 2006; Shimomura *et al.*, 2010b). In addition to mutations in hair keratin genes, autosomal recessive mutations in a regulator of hair keratin gene expression, the *FOXN1/WHN* gene, result in alopecia and nail dystrophy (Frank *et al.*, 1999). This syndrome, which also includes T-cell immunodeficiency, represents the human counterpart to the *nude* mouse phenotype (Nehls *et al.*, 1994).

Of the epidermal keratins, type I keratins, K25-28, and type II keratins, K71-74, are abundantly and differentially expressed in the three layers of the IRS (Langbein *et al.*, 2006; Schweizer *et al.*, 2006). Mutations in *K71*, identified in mice and dogs, are linked to the wavy coat phenotype called *Caracul* (Kikkawa *et al.*, 2003). Mutations in *K74*, which is highly expressed in Huxley's layer of the IRS, are associated with autosomal dominant woolly hair (ADWH), a condition characterized by slow hair growth and tightly curled hair (Shimomura *et al.*, 2010c).

In addition, a recent study identified a missense mutation in *K71* as the cause for ADWH in a Japanese family (Fujjmoto *et al.*, 2012). Taken together, these findings suggest a role for keratins in hair disorders and determinants of normal hair texture variation across species (Shimomura and Christiano, 2010).

DESMOSOMES AND ASSOCIATED HAIR DISEASE

Desmosomes are cell–cell adhesion complexes essential for morphogenesis, differentiation, and maintenance of tissues subjected to high mechanical stress, such as the skin and the heart. In both follicular and interfollicular epidermis, desmosomes anchor keratin intermediate filaments to the cell membranes and bind adjacent keratinocytes to each other, providing structural integrity and distribution of physical impact throughout tissue (McGrath, 2005; Bazzi and Christiano, 2007). The major structural components of desmosomes are the desmosomal cadherin family composed of desmogleins (DSGs) and desmocollins (DSCs), and the cytoplasmic plaque proteins plakoglobin (PKG), plakophilins and desmoplakin (DSP) (McGrath, 2005).

The importance of desmosome proteins to HF development and maintenance was first demonstrated by animal studies. Mutations in *Dsg3* were shown to be responsible for the naturally occurring *balding* mouse, and targeted ablation of this gene resulted in hair loss due to a defect in cell adhesion within the keratinocytes surrounding the club hair (Koch *et al.*, 1998). *Dsg2*-knockout mice die around the time of implantation, revealing the importance of this gene in general embryonic development (Eshkind *et al.*, 2002). More recently, a fourth member of the DSG family, *DSG4*, was shown to be the predominant DSG expressed in the HF (Bazzi *et al.*, 2006). DSG4 is a key mediator of keratinocyte cell adhesion in the HF, where it is expressed in the transition zone between proliferation and differentiation (Kljuic *et al.*, 2003). Mutations in DSG4 cause localized autosomal recessive hypotrichosis (LAH). LAH patients present with hypotrichosis limited to the scalp, chest, arms, and legs (Kljuic *et al.*, 2003). Some patients with *DSG4* mutations display fragile hair shafts with beaded morphology, suggesting that DSG4 is the causative gene for the autosomal recessive form of monilethrix (Schaffer *et al.*, 2006; Shimomura *et al.*, 2006). Recently, a homozygous, nonsense mutation in *DSC3* was reported to cause hypotrichosis and recurrent skin vesicles, a disorder that manifests as sparse scalp hair with fragile hair shafts and persistent fluid-filled skin vesicles (Ayub *et al.*, 2009). Corneodesmosin (*CDSN*), together with *DSG1* and *DSC1*, form the modified desmosomes of the epidermis (corneodesmosomes). *CDSN* is expressed in the IRS, beginning at a later stage of keratinization and continuing until the IRS is degraded (Mils *et al.*, 1992), suggesting that CDSN has a role in terminal differentiation of the IRS. Indeed, heterozygous nonsense mutations in the *CDSN* gene cause hereditary hypotrichosis simplex restricted to the scalp. Histological examination of patients' HF showed disruption of the IRS and aggregates of abnormal CDSN around the HF and the papillary dermis, implying that the mutant CDSN protein is acting in a dominant-negative manner (Levy-Nissenbaum *et al.*, 2003). Naxos and Carvajal syndromes are autosomal recessive disorders causing woolly hair (WH), palmoplantar keratoderma, and cardiomyopathy. These cardiocutaneous syndromes result from protein truncating mutations in the desmosomal components *PKG* and *DSP*, respectively (McKoy *et al.*, 2000; Norgett *et al.*, 2000; Bolling and Jonkman, 2009). Homozygous mutations in the *PKG* gene (both nonsense and splice site mutations) were also found to underlie skin fragility accompanied by WH, without heart abnormalities. Interestingly, one of these mutations resulted in very sparse WH, whereas patients harbouring the other mutation had abundant WH (Cabral *et al.*, 2010). Over 40 human mutations in the *DSP* gene have been shown to cause either skin or heart disease or a combination of skin, hair, and heart abnormalities, demonstrating the importance of this gene for the development and integrity of these tissues. *DSP* mutations can be associated with WH and hair loss (Bolling and Jonkman, 2009).

LIPIDS AND ASSOCIATED HAIR DISEASES

Lipids are abundant both in the IRS of the HF and on the surface of the hair shaft cuticle, where they are covalently bound to hair proteins. Integral hair lipids form cell membranes that provide structural support and protect the hair shaft from environmental insults. Recent studies have demonstrated that lysophosphatidic acid (LPA), an active lipid with many biological functions, has a significant role in HF morphogenesis and cycling (Takahashi *et al.*, 2003). The first report linking lipid biology to hair disorders showed that mutations in lipase H (*LIPH*) cause autosomal recessive hypotrichosis (Kazantseva *et al.*, 2006). Subsequent reports have described other mutations in *LIPH* causing not only hypotrichosis, but also autosomal recessive WH (ARWH) (Ali *et al.*, 2007; Nahum *et al.*, 2009; Shimomura *et al.*, 2009). These patients feature slow or arrested hair growth, resulting in shorter length of the hair shaft. *LIPH* encodes a phospholipase responsible for the formation of LPA from phosphatidic acid. LPA signals by binding to the orphan G-protein-coupled receptor P2RY5, encoded by the *LPAR6* gene (Yanagida *et al.*, 2009). Both *LIPH* and *LPAR6* are abundantly expressed in the IRS of the H and are likely involved in maintenance of hair shaft integrity. Accordingly, mutations in *LPAR6* were also found to be associated with recessive hypotrichosis and WH. Affected individuals with LIPH or *LPAR6* mutations displayed WH primarily during early childhood but then exhibit wide variability in hypotrichosis phenotype with aging (Petukhova *et al.*, 2008; Shimomura *et al.*, 2008). The range of phenotypes displayed by these patients suggests that they may be influence by other genetic or environmental factors, but taken together, these studies point at a role for LPA-mediated signaling in hair structure and growth.

HAIRLESS AND APCDD1

Although not strictly resulting in structural defects, mutations in two genes, *hairless* and *APCDD1*, underlie several important hair disorders. Atrichia with papular lesions (APL) is an autosomal recessive disorder characterized by early onset and complete hair loss, followed by the appearance of dermal cysts over the skin surface (Ahmad *et al.*, 1998; Panteleyev *et al.*, 1999). Marie Unna hypotrichosis (MUH) is an autosomal dominant disease, presented as sparse scalp hair at birth, followed by complete alopecia or hypotrichosis in adulthood (Lefevre *et al.*, 2000; Sreekumar *et al.*, 2000). Both syndromes are caused by mutations in the *hairless* (*HR*) gene. HR is a zinc finger transcription factor, postulated to function as a histone demethylase (Shimomura and Christiano, 2010). HR regulates the transition into catagen phase, including processes such as hair club formation, maintenance of dermal papilla–epithelial integrity, and IRS degradation. APL in humans, as well as in several animal models, is caused by homozygous loss-of-function mutations in *HR*. Strikingly, *HR* mutations result in abnormal degeneration of epithelial cells in the catagen HF, leaving behind the dermal papilla in the dermis (Ahmad *et al.*, 1998; Panteleyev *et al.*, 1999). MUH-causing mutations were mapped to the 5′ UTR of the HR and the results are consistent with a gain of function and regulation at the translational level (Wen *et al.*, 2009).

Hereditary hypotrichosis simplex, an autosomal dominant disorder, is characterized by degenerative HF miniaturization, leading to the conversion of thick terminal hair to fine vellus hair (Toribio and Quinones, 1974). *APCDD1*, a gene abundantly expressed in both epidermal and dermal compartments of the human HF, is mutated in this disease (Shimomura *et al.*, 2010a). APCDD1 has been implicated in linkage intervals in families with androgenic alopecia (Hillmer *et al.*, 2008) and alopecia areata (Martinez-Mir *et al.*, 2007). Our laboratory demonstrated that *APCDD1* is an inhibitor of the Wnt signaling pathway, raising the possibility that *APCDD1* may regulate Wnt-dependent processes in other cell types as well (Shimomura *et al.*, 2010a).

POSITION EFFECTS AND HYPERTRICHOSIS

A ''position effect'' is defined as an alteration in gene expression caused by a change in the position of a gene relative to its native chromosomal surroundings (Kleinjan and van Heyningen, 1998). Mechanisms may include chromosomal rearrangements, insertions, deletions, inversions, copy number variation (CNV) among others, thus these diseases tend to be very rare in the population. Paradoxically, a position effect may generate a distinct phenotype from the one(s) caused by loss-of-function mutations in the coding region of the same gene. For example, mutations in *TRPS1*, a zinc finger transcription factor with GATA and Ikaros-like domains, account for both hypo- and hypertrichosis disorders. Patients with Ambras syndrome display excessive ectopic hair growth and abnormal craniofacial features. Chromosomal rearrangements in these patients mapped to an interval on chromosome 8q, which includes *TRPS1* (Tadin *et al.*, 2001; Wuyts *et al.*, 2002; Fantauzzo *et al.*, 2008). *Koala* mice carry an inversion just upstream of the *Trps1* gene and display excess hair on the muzzle and ears (Fantauzzo *et al.*, 2008). In contrast, germline mutations in *TRPS1* result in autosomal dominant inheritance of trichorhinophalangeal syndromes types I and III. These syndromes are characterized by sparse scalp hair, and craniofacial and skeletal abnormalities (Momeni *et al.*, 2000; Lüdecke *et al.*, 2001). Deletion of the GATA-type zinc finger domain of *Trps1* in mice mirrors the phenotype of human TRPS patients (Malik *et al.*, 2002). Analysis of these mutant mice revealed a role for *Trps1* as a repressor of the expression of extracellular matrix proteins (Fantauzzo and Christiano, 2012). In addition to Ambras syndrome, two additional forms of hypertrichosis have been reported that result from position effects. Autosomal dominant hypertrichosis was linked to a microdeletion on 17q24, near the *SOX9* gene (Sun *et al.*, 2009), suggesting that CNVs close to this gene, which encodes an essential regulator of HF stem cells (Nowak *et al.*, 2008), may exert a position effect on the expression of SOX9 (Sun *et al.*, 2009). Generalized, X-linked hypertrichosis was mapped to chromosome Xq24-q27.1, however, no causative genes have been identified (Figuera *et al.*, 1995). A recent study revealed an interchromosomal insertion at Xq27.1 in a Chinese family with X-linked congenital hypertrichosis, and suggested that a position effect on *SOX3*, located upstream of the insertion site, may be responsible for the phenotype (Zhu *et al.*, 2011), however, the specific genetic mechanism defect for X-linked hypertrichosis remains unknown.

SUMMARY

The identification of causative genes carries the promise of new and innovative therapeutic strategies for both inherited and acquired hair disorders. Moreover, the delineation of the relationships between similar phenotypes, resulting from mutations affecting seemingly distinct regulatory pathways, paves the way to improved diagnosis and treatment. Finally, understanding the biological processes governing HF development and maintenance may have implications for more general disease processes in the skin, such as inflammation and cancer.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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