Mini Review

Relationship of mutation in adhesion molecules and cytokeratins with hair follicle diseases

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Received: 29 May 2019 / Accepted: 20 July 2019

Abstract

Adhesion molecules and cytokeratins are essential for the development of hair follicles and their maintenance. These molecules seem to be responsible for the follicular germ downgrowth and signaling with mesenchymal cells for the correct development of hair follicles. In adulthood, changes in their functions are related to numerous pathologies that lead to hair shaft disorders and cicatricial and non-cicatricial alopecia. This work reviews the main adhesion molecules: cadherins, integrins and cytokeratins and their relationship with hair follicle pathologies.

Keywords: cytokeratin, hair diseases, hair follicle, monilethrix, vascular cell adhesion molecule

Introduction

Adhesion molecules are responsible for orchestrating vital biological phenomena such as embryogenesis, proliferation, differentiation and cell death [1]. They are also responsible for defining the structure and architecture of the skin, controlling cellular polarization and modulating signals that regulate the level of cellular maturation [2,3].

Alopecias are a group of diseases that can lead to loss of body hair or scalp, which may be total or partial and reversible or irreversible depending on the structure of the hair follicle affected [4].

Given the importance of adhesion molecules and cytokeratins (CK) in hair follicle development and the scarcity of information on this subject, we review the importance of adhesion molecules and CK in human hair follicle diseases [5,6].

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DOI: 10.5455/im.54631
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Integrins

Integrins are transmembrane heterodimers composed of two subunits, alpha and beta, which are non-covalently bound and are dependent on bivalent cations (Figure 1A). Interaction between the cell and extracellular matrix affects cell migration, proliferation and differentiation (7-9). Integrin subunits are composed of extra-cytoplasmic domains, a transmembrane portion and a short cytoplasmic tail. In total, 24 integrin heterodimers have been identified and these recognize components of the extracellular matrix as well as components of the external environment and the surface of other cells, through their extra-cytoplasmic region. The intracytoplasmic portion establishes direct contact with the cytoskeleton to provide a channel of communication [10].

Figure 1. Schematic figures of integrins (A), cadherins (B) and cytokeratins (C).

Deficiencies in the expression of adhesion molecules and CK are related to some hair diseases. A relationship between hypotrichosis and primary hair shaft disorders with mutations in some of these molecules is reported. Some authors have speculated the participation of these molecules in other diseases with unknown etiology [11-14]. Alopecias are hair disturbances that can become permanent by the destruction of follicular stem cells; when this happens, they are termed as cicatricial alopecias.

Lichen planus is a common cause of cicatricial alopecia. Some authors have shown that there is a different pattern in the distribution of adhesion molecules in this disease. The expression of Beta 1 and Beta 4 integrins is not the same as that in normal patients. Beta 4 integrin is exclusively distributed in the basal layer in normal patients, whereas in areas with active disease, the pattern of Beta 4 integrin distribution is discontinuous and basolateral and Beta 1 distribution is pericellular. It’s an important role in the anchorage of hair follicles and might be the reason why anagen hair can be easily removed from the scalp of lichen planus patients with active disease [15]. Other authors have reported that Beta 1 integrin deletion promotes hair loss after birth and other epidermal changes in animals although no such syndrome is known in humans [16,17].

Cadherins

Cadherins are calcium-dependent transmembrane molecules containing a cytoplasmic tail that serves as a link to the cytoskeleton through specific bonds with catenin molecules (Figure 1B). Their complex with catenin functions to mediate binding between actin filaments of the cytoskeleton and provides adhesive character to the cadherin extracellular domain [18,19]. This association is essential for cellular morphogenesis, cell shape changes and establishment of cell polarity [20].

At least 80 molecules belonging to the cadherin superfamily have been found, among these, the main molecules include the classical cadherins, desmogleins and desmocollins. These molecules are involved in intercellular adhesion in a homotypic manner [21]. Desmogleins and desmocollins are desmosomic glycoproteins that play a role in the cellular adhesion of the epidermis. Changes in desmoglein 4 and desmocollin 3 are related to primary hair shaft genetic diseases [22,23]. Plakoglobin is a member of the catenin family and a cytoplasmic component of desmosomes and mutations in this gene are related to cardiac and hair abnormalities [24]. Some studies have reported the role of P-cadherin in the formation of human hair, eyes and limbs. Loss of function and mutation in the CDH3 gene that encodes P-cadherin results in two autosomal recessive allelic diseases: hypotrichosis with juvenile macular dystrophy and hypotrichosis and acroactyly with juvenile macular dystrophy. In both syndromes, patients have sparse hair and progressive loss of vision, in the second, defects in limb development also occur, such as malformations on the hands and feet [14].

Missense mutations in cadherins are related to some other hair diseases. Isolated hypotrichosis is a genetic hair shaft disease characterized by hypoplasia or aplasia in the hair, scalp, eyebrows, body hair and eyelashes associated with hair growth disturbances.
The phenotype ranges from short, thin hair to complete alopecia [11]. To date, 15 types of congenital hypotrichosis have been described and the major genes involved in these pathologies are CK and adhesion molecule genes. For example, desmocollin 3, a cadherin family member, is related to a special kind of hypotrichosis, one form of which is associated with transient cutaneous vesicles [23]. Another cadherin, desmoglein 4 was described as a cause of autosomal recessive hypotrichosis and woolly hair in Pakistani families [25-27]. Woolly hair is a genetic condition of variable inheritance wherein hair is short, thin, curled and dried along with changes in the shape and growth of hair (Figure 2A-B). Naxos syndrome shows the presence of woolly hair associated with palmoplantar hyperkeratosis and cardiac defects such as arrhythmogenic dysplasia with the involvement of the right ventricle. This occurs due to a mutation in the PKP1 gene that encodes plakoglobin, another member of the cadherin family [12]. This disease has variants, all of which involve cadherin family members. In Carvajal syndrome, the left ventricle is also affected by the associated desmoplakin mutation [24] whereas another form is associated with a mutation in desmocollin 2 [28].

Monilethrix is a primary genetic disease characterized by the poor formation of the hair shaft, which shows the shape of rosary beads (Figure 3A-B). There is a regular alternation between normal areas and areas with constrictions where fragility occurs. Its transmission may be autosomal dominant or recessive, with variable penetrance. Another cadherin associated with these pathologies is desmoglein 4 in its autosomal recessive form [22].
remains uncertain these molecules in patients and healthy individuals have failed to show differences in expression and the etiopathogenesis of the formation, leading to breakage with minimal effort (Fig.

Pili annulati is a rare, autosomal dominant genetic disease characterized by air formation in the medulla of the hair shaft, alopecia areata where this loss of attachment does not occur.

Adhesion molecules also seem to play a role in non-cicatricial alopecias, particularly for lichen planus, as fibrosing frontal alopecia and lupus erythematosus [34,35].

Cytokeratins

CKs are major proteins that structure epithelial cells. They are divided into two families: type 1, acid keratins and type 2, basic or neutral keratins (Figure 1C). Genes encoding these types of keratin are located on chromosomes 17q21.2 and 12q13.13, respectively [29]. The three-dimensional structure of keratinocytes is maintained by the presence of CK that make up their cytoskeleton. They have a central stable helical alpha domain that is interrupted by non-helical segments and amino and carboxyl terminal domains. CKs are present in all types of epithelium and can be used as markers of cell differentiation [29].

According to their expression, the CK may be epithelial including those specific to the hair follicle. In total, 54 CK genes [30,31] are divided into type I KRT25-KRT28 and type II KRT71-KRT74; these keratins are expressed in the hair follicle, particularly in the medulla of the hair shaft, at the inner root sheath [32,33].

A large number of mutations associated with CK genes interfere with hair structure and density in humans and animals [25,32]. Recently, CK25 was found to be related to cases of hypotrichosis with woolly hair in families in Russia [33] and mutations in keratins KRT81, KRT83 and KRT86 are related to autosomal dominant forms of monilethrix [22].

Some authors report that loss of expression of some CK might be a marker of cicatricial alopecia, particularly for lichen planus pilaris [34]. Other authors have proposed that CK may play a role in lichen planus, however, the loss of CK15 expression that may occur in lichen planus is not specific to this pathology and can also occur in other cicatricial alopecias of the same pathological lichenoid spectrum such as fibrosing frontal alopecia and lupus erythematosus [34,35].

Lanoue and colleagues have developed a diagnostic model for the identification of lichen planus pilaris using CK903 as an adjuvant tool to diagnose this pathology [36].

Adhesion molecules also seem to play a role in non-cicatricial alopecias such as androgenetic hair loss. Loss of attachment between the bulge stem cell population and the arrector pili muscle may explain why miniaturization is irreversible in androgenetic alopecia but not alopecia areata where this loss of attachment does not occur. In fact, the specific molecule involved in this event is not clearly identified. Pili annulati is a rare, autosomal dominant genetic disease characterized by air formation in the medulla of the hair shaft, which generates hair with characteristic brightness, characterized by light and dark bands. Areas of fragility can occur in light bands, coinciding with air formation, leading to breakage with minimal effort (Figure 4A-B) [37]. Due to its characteristics, it is suggested that there is a change in the CK or adhesion molecules that justify the poor hair shaft formation, but immunohistochemical studies comparing the expression of these molecules in patients and healthy individuals have failed to show differences in expression and the etiopathogenesis of this disease remains uncertain [13,38,39].

**Table 1. Important hair diseases related to adhesion molecules and cytokeratins**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetic inheritance</th>
<th>Gene</th>
<th>Gene product</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotrichosis</td>
<td>- Simplex scalp</td>
<td>AD</td>
<td>CDSN</td>
<td>Alopecia</td>
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<tr>
<td></td>
<td>- Macular dystrophy</td>
<td>AR</td>
<td>CDH3</td>
<td>+ Blindness</td>
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<td></td>
<td>- Transient vessels</td>
<td>AR</td>
<td>DSC3</td>
<td>+ Skin vesicles</td>
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<tr>
<td></td>
<td>- Localized autosomal recessive hypotrichosis</td>
<td>AR</td>
<td>DSG4</td>
<td></td>
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<tr>
<td>Monilethrix</td>
<td>AD</td>
<td>KRT81</td>
<td>Keratin 81</td>
<td>Short, dry hair</td>
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<tr>
<td></td>
<td>AD</td>
<td>KRT83</td>
<td>Keratin 83</td>
<td>Breakage</td>
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<tr>
<td></td>
<td>AD</td>
<td>KRT86</td>
<td>Keratin 86</td>
<td>Alopecia</td>
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<tr>
<td></td>
<td>AR</td>
<td>DSG4</td>
<td>Desmoglein 4</td>
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<tr>
<td>Woolly hair</td>
<td>- Hypotrichosis</td>
<td>AR</td>
<td>KRT71, JUP/DSC2</td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td>- Naxos disease</td>
<td>AR</td>
<td>DSP</td>
<td>+ arrhythmia</td>
</tr>
<tr>
<td></td>
<td>- Carvajal syndrome</td>
<td>AR&gt;AD</td>
<td>DSP</td>
<td>+ arrhythmia</td>
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<tr>
<td></td>
<td>- Skin fragility</td>
<td>AR</td>
<td>Desmoglein 2</td>
<td>+ skin blisters, erosion</td>
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<td>Plakoglobin /desmoglein 2</td>
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Conclusion

Considering the importance of adhesion molecules and CK to the skin and hair follicles and the scarcity of information on this subject, additional studies are needed to better clarify the role of these molecules in the hair follicle. Improved knowledge of these molecules may help discover therapeutic targets for many pathologies or histological markers to diagnose these entities. We emphasize the importance of multidisciplinary evaluation in the presented pathologies as genetic hair disorders can be associated with more complex mutations such as those with cardiac or ophthalmologic involvement.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

There was no funding received for this article.

References