Skin Organogenesis and Dysmorphogenetic Factors in Skin Diseases (Review)

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The study of the epidermis and derma histogenesis, including its epigenetic regulation, is an actively developing field of histology and embryology. The results of the study can elucidate the mechanisms of pathogenesis of some skin diseases of unknown etiology. Wnt signaling is a key regulator of the main morphogenetic processes — cell proliferation and differentiation. Downstream of Wnt signaling is carried out by canonical and non-canonical pathways. Impairments of Wnt signaling in prenatal and postnatal development lead to degenerative and tumor diseases of the skin and hair.

Clinical manifestations of the prenatal disorders of skin development epigenetic regulation in the period may appear long after the birth. Identification of factors that disturb the regulation of morphogenetic processes is an important task for investigators. It was found out that activation of the mother’s immune system in the early pregnancy resulted in the development of transient alopecia in the offspring of mice. There was the correlation established between the disorders of epidermal and dermal histogenesis and alopecia as well as the development of regional dysmorphogenetic changes in the skin, which indicate the need to study the rates and features of skin development in various parts of the body.

Key words: skin; hair follicle; Wnt signaling; β-catenin; morphogenesis; skin diseases; skin tumors; alopecia.

Introduction

Among the diseases of skin and its appendages there are mostly nosologic disorders of unknown etiology and understudied pathogenesis [1–7]. The achievements of modern embryology, histology, and molecular biology make a considerable input into the understanding of epidermis and derma histogenesis mechanisms and allow targeted investigation of the role of epigenetic regulation mechanisms of morphogenetic process as their impairment is underlying some skin diseases [8, 9]. Regulation of intracellular signal pathways which manage various morphogenesis processes, such as proliferation, differentiation, migration and apical-basal polarization of epidermis cells, is determined by secreted Wnt proteins, primarily by β-catenin, which is an activator of canonic Wnt signaling [10–15].

The role of Wnt signaling in prenatal skin development

It is known that after gastrulation the surface of an embryo is represented by one layer of ectoderm which then forms a neural tube and skin ectoderm [16]. When there is no signal of fibroblast growth factor the ectoderm cells start expressing bone morphogenetic proteins and are determined to form epidermis. And on the contrary, the nervous system development occurs when ectoderm can accept and modify the signals activating fibroblast growth factor and then inhibiting bone morphogenetic proteins [17–21]. Activity of bone morphogenetic proteins plays a crucial role in the formation of a border area between skin ectoderm and neuroectoderm [22]. The key regulator of divergence is Wnt signaling which blocks an ability of ectoderm to react to fibroblast growth factor.

Wnt signaling can be transduced by canonic and non-canonic pathways [23–30]. Non-canonic transduction of Wnt signaling happens via G proteins, such as Rho/Rac, which control cell polarity by remodeling an active cytoskeleton or by changing intracellular concentration of calcium ions [24, 31]. In the canonic Wnt pathway the key transcription co-activator and transmitter of an extracellular signal activating target genes is β-catenin. β-catenin transcription activator is stabilized when Wnt

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is stimulated, then it penetrates the nucleus and binds with TCF/LEF1 factor (T cell factor/lymphoid enhancer factor 1) activating Wnt-sensitive target genes [11–13].

There are several different Wnt proteins and receptors in the vertebrates, and their expression in time and space is regulated during the development [10, 32]. It is highly probable that one Wnt protein activates a combination of several signal cascades which can act independently or together. Addition of a greater number of complexity levels, co-factors, secreted antagonists and co-receptors of Wnt signal transmission modulates both canonic and non-canonic actions. It is known that non-canonic Wnt pathways can inhibit signal connection that depends on β-catenin. However, the mechanism underlying this inhibition is still unknown. Possible explanations include competition of Wnt ligands for binding with their receptors [33], suppression of β-catenin with E3-ubiquitin of Siah2 ligase [34] or inhibition of transcription activity of Wnt/β-catenin signaling via TAK1-NLK (TGF-β-activated kinase 1 and nemo-like kinase)-mediated phosphorylation of T cell factors [35].

At early stages of skin development dynamic cross signals between embryonic epidermis and derma occur. The connection between the tissues mediates the formation of a basal membrane, epidermis stratification and induction of hair follicles (HF) [36]. The cells are differentiated into keratinocytes and form a basal layer of the embryonic epidermis. Keratinocytes in the newly formed embryonic basal layer substitute for 8/18 type keratin expression for 5/14 types of keratin [37]. At the initial stage of epidermal stratification the basal cells form a transient layer called periderm which protects these cells from the constant effect of amniotic fluid [38].

The next layer of the epidermis formed between the basal layer and the periderm is called an intermediate layer, and its development is connected with asymmetric division of epidermal basal cells [39]. At the molecular level the process of epidermal stratification is organized by several transcription regulators and signal pathways [40–42]. When stratification program is completed, the epidermis consists of an internal layer of basal cells with a proliferative potential and suprabasal layers of differentiated cells.

**The role of Wnt signaling in the formation and development of a hair follicle**

HF morphogenesis includes the following three main stages: formation of hair placode, organogenesis and cytodifferentiation [43, 44]. The consequent events during morphogenesis are regulated by signals transmitted between the derma and epidermis [45, 46]. Wnt pathway is considered the main regulator among all these signals.

Before the formation of placode skin fibroblasts get Wnt signals from the epidermis causing aggregation of epidermal basal cells which results in placode formation [47–50]. Notably, HF induction patterns depend on the competition between slowly diffusing Wnt ligands and faster diffused Wnt inhibitors [51].

After initial induction a developing placode produces Wnt ligands for the induction of underlying fibroblasts forming dermal condensate [52]. At the same time a placode is continuously growing, penetrating the derma layer in the form of invaginations and then it is bound with dermal condensate forming the first structure of HF organogenesis — the first hair lineage. Epidermal cells proceed penetrating into the derma and form a multi-layer prolonged column named hair strand. Meanwhile dermal condensate becomes a spherical dermal papilla. The hair strand is thickened at the lower end to form a hair bulb. When the primary follicle grows into the hair strand, various epidermal layers are visualized and a hair shaft appears. As HF growth reached the subcutaneous layer, the program of cytodifferentiation starts. At this stage the dermal papilla becomes thinner and closes completely, a sebaceous follicle starts being formed in the upper part of HF. Then a fully formed hair shaft appears above the hair surface and HF reaches its maximum length [43]. Different stages of HF follicles are easy to identify according to their morphological and biochemical specific properties [53].

Inside each mature HF there are seven concentric rings of terminally differentiated cells which are derived from the cell matrix. Each ring had a specific ultrastructure. Transmission of Wnt/β-catenin signaling is first regulated evenly in the upper layer of the derma and then focally both in the hair placode and in the underlying dermal condensate [54–57]. When signalization of Wnt/β-catenin switches off, the formation of HF is blocked [58–60]. Excessive expression of a stable form of β-catenin or LEF1 induces the formation of a HF de novo [61, 62].

**Wnt signaling in hair follicles in the postnatal period**

In the postnatal skin mature HF are exposed to repeated growth cycles [63]. Like in HF morphogenesis initiation of a new growth phase and as a consequence proliferation, differentiation and regress of a follicle are connected with wide interaction between dermal and epidermal cells [64]. Many studies [65–72] suppose that the same signal pathways which are active during HF embryogenesis are repeatedly used in cyclic processes occurring in a postnatal HF. In particular, it was shown that Wnt/β-catenin signaling plays an important role at the several stages of hair development beginning from the earliest stages of transition from resting to growth and differentiation of a HF.

In the postnatal period the epidermis is continuously regenerating due to proliferation of the basal cells of interfollicular epidermis (IE). This IE cell pool gives birth to the cells which will be differentiated into suprabasal cells migrating into the overlying layers. During this process a number of epidermal cells remains
constant as the number of newly generated cells exactly compensates for the number of cells which are differentiated or die [73].

To explain how stem cells of the basal layer replenish IE cells, the following two models were suggested: hierarchical and stochastic [74]. A hierarchical model states that a slow cycle of stem cells occurring in each epidermal proliferative IE unit generate short-living transient amplifying cells which later on give birth to differentiated cells. A stochastic model means that the ancestors of IE basal layer have an equal potential for generation of daughter cells which remain as predecessors or are differentiated into suprabasal cells [75].

In the developing epidermis a high level of Wnt/β-catenin signal transmission is necessary for HF induction. Weakening of these signals from the epidermis worsens HF formation but does not affect IR integrity [76]. Notably, the loss of β-catenin in IE even causes its hyperproliferation [77]. Nevertheless the studies of cell line tracing show the presence of signal activity of Wnt/β-catenin in basal cells of glabrous skin. When these cells run out of β-catenin, proliferative capacity of the epidermis is sharply decreased [78, 79]. Different results of epidermis proliferation can be partially explained by fundamental differences between the epidermis of hairy skin and glabrous skin as it is believed that epidermal hyperproliferation of hairy skin can be partially resulted from an inflammatory response to HF decay [80].

The role of impairment of Wnt/β-catenin signaling in pathogenesis of skin diseases

Taking into consideration the important role of Wnt/β-catenin signal transmission it is easy to understand the impairment of the activity of signal pathways can lead to congenital abnormalities and diseases [81–84]. Excessive activation of transmission of these signals causes different tumors in transgenic mice. In HF constitutive expression of stabilized β-catenin leads to the formation of pilomatrixcomas which are densely packed benign tumors with the center from the cells of hair strand surrounded by matrix cells or trichofolliculomas which regress when the pathway activation stops [82]. Many human pilomatrixcomas also contain mutations stabilizing β-catenin [85]. On the contrary when Wnt/β-catenin signaling in transgenic mice is suppressed, tumors of sebaceous follicles are developing more frequently [59, 86]. It also happens in human tumors as one third of them contain mutations which block β-catenin binding [87].

The studies showed that unfavorable environmental condition during pregnancy can have a negative impact on the development and functioning of various organs of the offspring. These manifestations can have long-term consequences and even fixe as a hereditary quality [88–90]. Impaired expression of β-catenin in prenatal and postnatal development mediates dysmorphogenetic disorders and can be the cause of pathogenesis of a number of diseases (see the Figure). Thus, reduced function of β-catenin in the embryonic period of development can lead to the reduced proliferation of epithelial cells of a hair bulb [77], HF regeneration impairment [91] and reduced proliferation of keratinocytes of glabrous skin [52, 87]. And on the contrary, recovery of β-catenin function in the embryonic period in the postnatal period leads to an early transition into anagen [92, 93], hyperplasia and HF cyst formation [56].

Congenital HF defects are rather rare and are usually caused by mutations in genes coding keratins and other structural proteins [94]. To the acquired defects one refers alopecia which can have inflammatory and non-

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**Diagram:**

- **Lost β-catenin function**
  - Impairment of formation of hair follicle buds
  - Alopecia and formation of cystic-modified hair follicles in pre-pubertal period
  - Hyperproliferation of epitheliun in pubertal period
  - Reduced proliferation of derma fibroblasts

- **Recovery of β-catenin function**
  - Formation of hair follicles from interfollicular epidermis de novo
  - Development of trichofolliculomas and pilomatrixcomas
  - Early transition into anagen
  - Hyperplasia of hair follicles at the stage of anagen

**Dysmorphogenetic consequences of impairments of canonical Wnt/β-catenin signaling in the epidermis and hair follicles in mice**

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**Skin Organogenesis and Dysmorphogenetic Factors in Skin Diseases**

CTM 2018 vol. 10 No.4 197
inflammatory etiology [44, 95, 96]. Inflammatory alopecia can result from a bacterial infection, dermatophytosis, and bites of external parasites, autoimmune diseases, injuries or toxin effects (for instance, mercury, thallium or iodine). The reason for non-inflammatory diseases which lead to alopecia is the deficit of nutrients, endocrine disorders, childbirth, anemia and intake of cytostatic medications [97].

One of the important tasks is to determine specific factors that can change epigenetic regulation in the prenatal and postnatal periods of human ontogenesis. It was found out [98] that short-term activation of the maternal immune system at the early pregnancy leads to transient hereditary alopecia in the offspring and that impairment of the development of skin and its integumentary structures is caused by the effect of cytokines produced by the cells of the mother’s immune system. The studies showed that on day 17 of postnatal development the offspring got alopecia in the area of the back and abdomen and in several days it turned into complete loss of fur in these areas. Histological investigation of the skin in these areas showed cysto-widened HF containing broken hair shafts and reduced HF number, slowed formation of connective components of derma, lowered number of amorphous component of intercellular matrix. The fur in these animals was restored along with thickening of the derma and the amount of amorphous component of intercellular matrix in them and it confirms a pathogenic role of derma immaturity in hair growth disorder [99, 100]. The most probable mechanism of reduction of HF number in the offspring skin during activation of the mother’s immune system is impairment of Wnt signals providing HF formation. The lack of changes in the head skin shows regional differences in the regulation of the skin histogenesis. There are findings that if there common stages of formation of the epidermis and derma, thickening of the epidermis and increase in the number of its layers on the head skin happens faster than in body skin due to different rates of the main morphogenetic processes — proliferation and apoptosis [101–103]. Consequently, impairments of transcription regulation of morphogenetic processes in the embryo skin can be not general, but local.

Conclusion

Investigations of regulation of morphogenetic processes in the skin show an important role of epigenetic regulation both morphogenetic and dysmorphogenetic factors. Impairments of canonic Wnt signaling in the prenatal period can be underlying pathogenesis of different diseases of the skin and its appendages of tumor and non-tumor character. The findings of many works show that a specific feature of impairments of epigenetic regulation of skin organogenesis in the prenatal period can be long-term clinical manifestations in the postnatal period. These findings prove the need for further search of the regulation impairment causes and their consideration in patients’ medical history as possible etiological factors of a number of skin diseases.

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Skin Organogenesis and Dysmorphogenetic Factors in Skin Diseases

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