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Genetic Profile of Basal Cell Skin Cancer. Modern Concepts about Pathogenesis and Histopathology of the Disease

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Abstract: Basal cell skin cancer (BCSC) has the highest prevalence in the group of non-melanoma skin tumors in the structure of cancer incidence. Histological subtypes of BCC have prognostically different dynamics of their morphology. The commonality of the tumor structure is that for each histological type, islands of tumor cells and the surrounding stroma are determined. Tumor cells resemble basal keratinocytes or hair follicle cells in appearance. The tumor is thought to originate from an undifferentiated pluripotent epithelial germ cell.

Keywords: basal cell skin cancer, genetic profile, oncology, skin cancer, oncogenesis.

These cells arise from interfollicular basal cells or from germinal progenitor cells of hair follicles or sebaceous glands and immunohistochemically and ultrastructurally have many features in common with follicular cells. BCC tumor cells are stroma dependent and are also capable of differentiation into any skin appendage, therefore, perhaps their pathogenetic mechanism is an incorrect rehearsal of embryological differentiation. For example, experimental studies have proven that during the process of dermis transplantation while preserving the recipient's epidermis, the temporal regulation of the development of skin appendages changes under the influence of the donor dermis. The effect of UV on unprotected skin of phototypes 1–3 correlates with the localization of tumors. Thus, most often the tumor can be found on the skin of the face and neck (up to 80% of cases) [2]. The likelihood of developing BCC increases in patients with a history (in childhood and adolescence) of severe sunburn, as well as episodes of excessive sun exposure (long stay in tropical and equatorial latitudes, solariums) in the first two decades of life. PUVA therapy is also one of the predisposing factors for the development of BCC [**Error! Reference source not found.**]. Skin damage caused by radiation, burns, tattoos and other forms of physical trauma, systemic immunosuppression , chronic arsenic poisoning, HIV infection, and leukemia/lymphoma have also been described as predisposing factors for the development of BCC [3].

The occurrence of BCC is caused by mutations that activate the hedgehog (HH) pathway, which is most active during human embryonic development. Genetic studies among patients with Gorlin-Goltz syndrome, who are diagnosed with multiple BCCs already at an early age, revealed the presence of germline mutations PTCH1 (9q22.32), PTCH2 (1p34.1) and SUFU (10q24.32), each of which causes defects HH signaling pathway [6]. Mutations in the PTCH1 or PTCH2 gene are detected in two thirds of BCC cases, while mutations in the SUFU gene are detected much less frequently (up to 5%). Approximately 10% of BCC cases have mutations in the SMO gene (9q32.1), which also cause the hedgehog signaling pathway to malfunction . Mutations of the SMO gene may be associated with a hereditary predisposition to the development of BCC, but they are not related to Gorlin-Goltz syndrome. All mutations are inactivating, which confirms that each of them is indeed a tumor suppressor gene. PTCH1 is a transmembrane protein, like its homologue PTCH2. These proteins serve as receptors for the ligand sonic hedgehog (SHH). PTCH forms a receptor complex with SMO. Upon SHH ligand binding, the inhibitory function of PTCH1 on SMO is released, leading to subsequent activation of the transcription factor GLI1. In the HH signaling pathway, the role of PTCH is to inhibit SMO, which in turn inhibits SUFU, a restraining transcription factor GLI1. In general, at least 85% of basal cell carcinomas have one of the described mutations in the SHH signaling pathway, and in almost all cases of sporadic BCC examined, overexpression of the GLI1 expression factor was

detected, which also confirms the importance of the HH signaling pathway in the pathogenesis of BCC development [9].

The HH signaling pathway is part of the so-called Wnt signaling cascade [8]. Activation of this cascade leads to the translocation of the beta- catenin protein into the nucleus, which acts as a transcription factor. Thus, in more than 50% of cases of BCC, overexpression of beta- catenin with nuclear localization is detected. Recent studies have revealed that due to activation of the Wnt /beta-catenin system, the SHH ligand attaches to the PTCH1 receptor. Thus, SHH and -catenin molecules βhave a very significant role in the process of induction of BCC tumorigenesis [11].

The Wnt signaling pathway plays a critical role in cell proliferation both during embryonic development and in adults. Aberrant activation of this signaling pathway (canonical Wnt / β-catenin pathway) can lead to the development of several types of cancer, one of which is BCC. Signaling through Wnt / β-catenin is known to promote stem cell maintenance and, in the case of tumors, tumor cell lineage division . Today, it is believed that BCC resistance to chemotherapy and tumor relapse are mediated precisely by the Wnt / β-catenin signaling pathway. Thus, the pathway has many targets and genes: hTERT (responsible for cell immortality, promotes tumor invasion and metastasis), BIRC5/ Survivin (inhibits caspases 3 and 7, which prevents cell apoptosis), Musashi-1 and Sox2 (markers of stem cells, form proliferative activity and drug resistance), MDR-1, CD44, MMP7, IL-10, as well as genes involved in cell cycle progression, migration, invasion and extracellular matrix remodeling [5].

In the process of studying the histogenesis of BCC, it was revealed that the tumor-initiating cell repeats the fate of the epithelial cell , the precursor of the hair follicle in the embryonic period of development (the first 4 months of embryonic development) [4]

The mechanisms regulating the early stage of BCC formation include the expression of Smo. The molecule accelerates and modifies gene expression. The fate of the keratinocyte progenitor cell changes, and the cell acquires a morphology and genetic profile that bears striking similarities to follicular progenitor cells. Expression of Smo rapidly activates the Wnt/β-catenin signaling pathway , which regulates hair follicle reprogramming and supports positive feedback signaling of the hedgehog pathway. This is how the development of BKK is initiated. This scheme makes it possible to track and isolate the cell that is the precursor of BCC, which makes it possible to analyze the cellular and molecular structure of BCC with reference to a specific time.

An additional mechanism for the development of BCC is a mutation in the tumor suppressor gene - TP 53. Mutations in TP 53 are observed in a variety of other tumors, such as SCRC or, less commonly, melanoma. In BCC, TP 53 mutations are found in approximately 2/3 of patients.

Table 1. Comparison of hair follicle embryogenesis with tumorigenesis of basal cell skin cancer

Embryogenesis of the hair follicle	Histogenesis of BCC
Induction. Wnt initiates communication between mesenchymal cells and the overlying epidermis. The latter begins to thicken and forms a placode	Initiation. Tumor initiating cells undergo rapid reprogramming into embryonic precursor cells of the hair follicle, where activation of Wnt / β-catenin and SmoM2 play a major role
Organogenesis. The placode signals the underlying dermal cells to proliferate and form " dermal condensate". After its formation, feedback signaling to the epithelium occurs with the help of SHH about the start of proliferation and downward growth. Moreover, Wnt/-catenin and ectodysplasin βA form a receptor apparatus for the perception of the SHH signaling molecule in epithelial cells	Wnt / β-catenin - mediated intercellular signaling between the epidermis and the underlying dermis. Next, the cellular growth scenario changes from epithelial to follicular. Basal keratinocytes proliferate and penetrate deep into the dermis
Cytodifferentiation . Follicular epithelial cells	Further tumor progression and invasion

envelop the dermal condensate, after which the formation of the hair apparatus is completed	

Since UV radiation is recognized as the main provoking factor of BCC, the statement about the occurrence of sporadic mutations in the PTCH 1 / 2 and TP 53 genes when exposed to it is true. Characteristic mutations in the TERT gene promoter contribute to carcinogenesis by accelerating cell proliferation and slowing down the processes of cell aging, and are also UV mediated. It is believed that the susceptibility of patients to the development of BCC is determined by a reduced ability to repair DNA after UV-induced damage. Recently, mutations in the RAS and MYC signaling pathways have been identified in a number of patients with BCC, as well as several other oncogenes and tumor suppressors observed in various other neoplasms. Thus, it is true that basal cell carcinoma exhibits a genetic profile distinct from the surrounding basal keratinocytes . Also of interest is the difference in genetic profiles between different histological types of BCC; for example, the morphea-like variant is more aggressive and exhibits a completely different genetic profile than less malignant forms of BCC, such as superficial or nodular [10].

Numerous worldwide studies studying the genetic profile of BCC have identified the main mutations from the group of tumor suppressor genes and proto-oncogenes, which are key components of the Hedgehog signaling pathway (PTCH 1, SMO, TP 53), as well as members of the RAS family - proto-oncogenes that determine tumorigenesis in the case of basal cell skin cancer . Thus, UV-mediated aberrant activation of the HH pathway or loss of heterozygosity of the PTCH 1 gene has long been considered the only trigger mutations for BCC. Today, the ability to study the genetic profile of patients has improved, and in this regard, detailed analysis of large cohorts of patients with BCC has made it possible to identify other mutations and signaling pathways that determine tumorigenesis. Recent studies have identified that mutations in PTPN 14, LATS 1 (effectors of the Hippo - YAP signaling pathway) and MYCN are also associated with BCC. The most recent studies have also identified frequent non-coding regulatory promoter mutations in the TERT and DPH 3 - OXNAD 1 gene sequences [12].

Thus, it is clear that a much larger network of genetic mutations is involved in BCC carcinogenesis. Subsequently, knowing the mutation profile of patients, we will be able to judge the type of differentiation of a particular tumor and obtain more information about its histogenesis. However, the practical application of this information is that we obtain targets for identifying specific diagnostic markers and creating targeted therapy for BCC. This will speed up the diagnostic process, make it more accurate, and also increase the efficiency of patient treatment.

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