Genetics of Basal Cell Carcinoma

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Basal cell carcinoma (BCC) is a significant public health concern, with more than 3 million cases occurring each year in the United States, and with an increasing incidence. The molecular basis of BCC is complex, involving an interplay of inherited genetic susceptibility, including single nucleotide polymorphisms and genetic syndromes, and sporadic somatic mutations, often induced by carcinogenic exposure to UV radiation.

Keywords: basal cell carcinoma ; skin neoplasms ; dermatology ; review ; molecular genetics ; germline mutation ; somatic mutation ; molecular targeted therapy

1. Overview

Basal cell carcinoma is the most common human cancer worldwide. The molecular basis of BCC involves an interplay of inherited genetic susceptibility and somatic mutations, commonly induced by exposure to UV radiation. In this review, we outline the currently known germline and somatic mutations implicated in the pathogenesis of BCC with particular attention paid toward affected molecular pathways. We also discuss polymorphisms and associated phenotypic traits in addition to active areas of BCC research. We finally provide a brief overview of existing non-surgical treatments and emerging targeted therapeutics for BCC such as Hedgehog pathway inhibitors, immune modulators, and histone deacetylase inhibitors.

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2. Basal Cell Carcinoma

Of all human cancers, basal cell carcinoma (BCC) is the most common worldwide, and in many countries, its incidence continues to increase, representing a significant public health burden [1]. Each year in the United States, more than 3 million cases occur, and one in five individuals in the U.S. are estimated to develop at least one BCC during their lifetime [2]. In addition to the potential morbidity of BCC, the cancer has a significant economic impact, with annual U.S. healthcare expenditure for these tumors reaching almost $4 billion [3][4][5]. The molecular pathogenesis of BCC is complex, and involves an interplay of inherited genetic susceptibility [6] and sporadic somatic mutations [7]. The former predisposes an individual towards the development of BCC, and can include single nucleotide polymorphisms (SNPs), inherited disorders, and genetic traits [6], but the latter is generally required to induce carcinogenesis. While the types of variants that induce susceptibility to BCC are varied, the sporadic mutations often function to activate the Hedgehog (HH) signaling pathway, a growth and development pathway integral to the pathogenesis of BCC. This review will discuss in more depth the currently known germline and somatic mutations implicated in the pathogenesis of BCC, as well as the underlying molecular pathways affected. We will also give an overview of established and emerging targeted, non-surgical, therapeutics which could revolutionize the treatment of this common and important skin cancer.

3. Genetic Syndromes Associated with BCC Development

Some individuals face a much greater heritable risk of BCC than the general population, through inheritance of high penetrant germline mutations associated with one of 19 rare syndromes that have been linked to increased propensity of

BCC. Research in the 1990s into the molecular basis of a rare genetic disorder known as Gorlin syndrome (also known as Nevoid Basal Cell Carcinoma syndrome) led to new understanding of the key oncogenic pathway underlying the etiology of BCC. Gorlin syndrome affects as many as 1 in 31,000 individuals in the U.K. [8], and is inherited through an autosomal dominant pattern with a high degree of penetrance but with variable phenotype [9]. Major clinical features of the syndrome include multiple, early-onset BCCs, jaw odontogenic keratocysts, palmar and plantar pits, and lamellar calcification of the falx cerebri [10]. BCCs present at a median age of 25, typically on sun exposed sites, and can range from few to thousands in number [11][12]. Interestingly, African American patients with Gorlin syndrome demonstrate less frequent development of BCC, reflecting the role of genetic factors such as pigmentation and epigenetic factors such as UV susceptibility in modulating carcinoma formation [12]. Similarly, SNPs in genes related to skin pigment, such as the melanocortin-1-receptor (*MC1R*) gene, have been associated with earlier and more severe onset of BCC [11].

The most frequent mutations attributed to causing Gorlin syndrome are germline loss of function mutations affecting *PTCH1* on chromosome 9q22.3 [13][14]. These inactivating mutations lead to premature termination of the PTCH protein, which is 7-transmembrane inhibitory receptor in the HH signaling pathway [15]. Interestingly, like the ocular cancer retinoblastoma, which similarly can be caused by inherited mutations in a recessive oncogene, a “two-hit hypothesis” has been proposed. This theory of carcinogenesis states that healthy cells require two separate mutagenic hits to produce carcinoma. Patients with inherited cancer syndromes, such as retinoblastoma and Gorlin, already have a preexisting germline mutation in one of their two copies of a tumor suppressor gene (i.e., *PTCH1*). This mutation alone is insufficient for cancer to occur. A second somatic mutation, as a result of UV radiation exposure for example, may subsequently induce malignancy through loss of the second copy of the tumor suppressor gene [16]. Other less commonly mutated genes implicated in Gorlin syndrome include *PTCH2* and *SUFU* [13].

The Sonic HH signaling pathway is an embryologically conserved pathway that is vital for determining tissue patterning and cell fate during embryo development [17]. Within the skin, the HH pathway is responsible for stem cell maintenance and developmental control of the hair follicles and sebaceous glands [7]. HH signaling is activated when the HH ligand binds to a transmembrane receptor complex formed by the proteins PTCH and Smoothened (SMO). When not bound by the HH ligand, PTCH acts as a regulatory molecule, inhibiting translocation of SMO thereby reducing HH signaling. When HH ligand binds to PTCH, the HH-PTCH complex is degraded by lysosomes which de-represses SMO, upregulating the pathway’s downstream signaling cascade via several proteins including suppressor of fused (SUFU). The ultimate result of this cascade is the release of members of the GLI protein family, which are ordinarily sequestered in the cytoplasm [7][17]. GLI acts as a transcription factor, which upon release can translocate to the cell nucleus and trigger transcription of genes involved in cell renewal, fate, and survival, as well as angiogenesis [7]. The normal functioning of the HH pathway is outlined in **Figure 1**. In Gorlin syndrome, germline inactivation of one copy of the *PTCH1* gene followed by somatic loss of the second allele result in loss of SMO suppression and hence constitutive overexpression of the HH signal. The downstream effect is overproduction of the GLI1 transcription factor, which acts to drive BCC tumorigenesis [16][18][19].

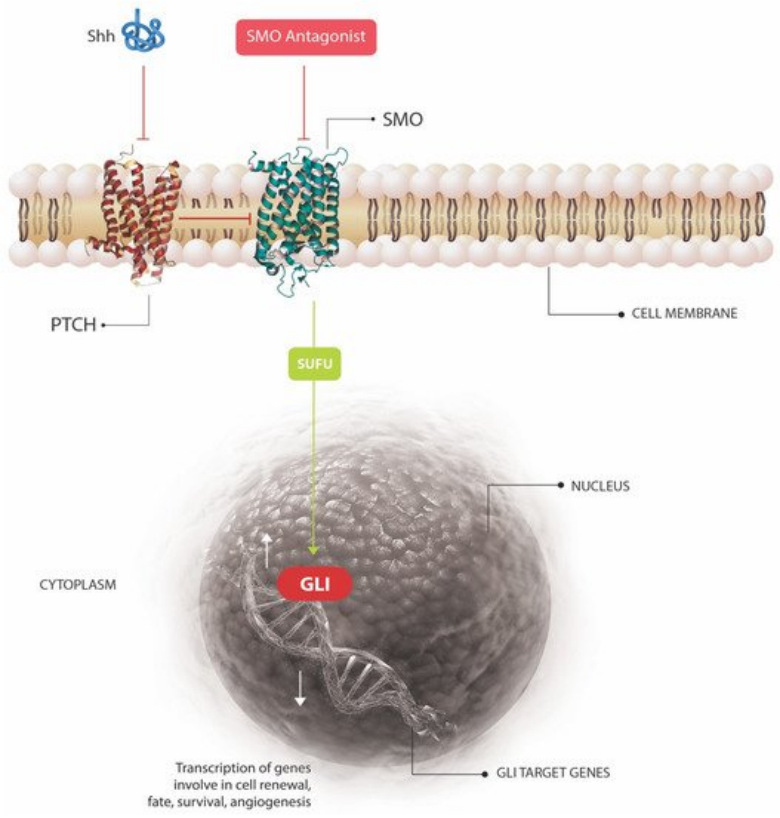

Figure 1. Overview of the Sonic Hedgehog signaling pathway. The HH ligand binds to a transmembrane receptor complex formed by the proteins PTCH and Smoothened (SMO). When not bound by the HH ligand, PTCH acts as a regulatory molecule, inhibiting translocation of SMO cilia thereby reducing HH signaling. When HH ligand binds to PTCH, the HH-PTCH complex is degraded by lysosomes which de-represses SMO, upregulating the pathway's downstream signaling cascade via several proteins including suppressor of fused (SUFU). This ultimately results in release of members of the GLI protein family, such as GLI1, which are ordinarily sequestered in the cytoplasm [7][17]. GLI1 acts as a transcription factor, which upon release can translocate to the cell nucleus and trigger transcription of genes involved in cell renewal, fate, and survival, as well as angiogenesis [7].

Bazex-Dupre-Christol syndrome is another genetic syndrome associated with the HH pathway and the development of multiple BCCs, alongside congenital hypotrichosis, follicular atrophoderma and milia [20]. It is inherited through an X-linked dominant pattern, with mutations in the *ACTRT1* gene most commonly implicated. These mutations lead to premature truncation of the ARP-T1 protein, which normally functions as an inhibitor of the GLI1 transcription factor through function at the *GLI1* gene promotor site. The mutation in *ACTRT1* consequently results in enhanced *GLI1*-induced oncogenic transcription [21].

In addition to germline defects in the HH signaling pathway, BCC susceptibility may occur due to inherited deficiencies in DNA repair. Xeroderma Pigmentosum (XP) is autosomal recessive disorder caused by inherited mutations in any one of eight possible genes required for nucleotide excision repair (NER). NER is the process by which NER endonucleases repair segments of DNA containing pyrimidine dimers, the major signature of UV-induced DNA damage characterized by covalent bonding of adjacent thymine nucleotides. Without repair, the shape of the DNA strand becomes disrupted. Consequently, XP patients have a significant UV-induced mutational burden, with strict lifelong avoidance of UV necessary for the prevention of skin cancer, including BCC, squamous cell carcinoma (SCC) and melanoma [22][23].

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