BBA - Reviews on Cancer 1877 (2022) 188795

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Homeostases of epidermis and hair follicle, and development of basal cell carcinoma

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ARTICLE INFO

Keywords:
Skin
Basal cell carcinoma
Sonic hedgehog
Hedgehog
Wnt
Notch
Skin homeostasis
Hair follicle
Hair follicle homeostasis
Skin differentiation
Hair follicle differentiation
Edar
Eda
Dermal condensate
Dermal papilla
Epidermal placode
Hair placode

ABSTRACT

Hedgehog signaling (Hh) plays a critical role in embryogenesis. On the other hand, its overactivity may cause basal cell carcinoma (BCC), the most common human cancer. Further, epidermal and hair follicle homeostases may have a key role in the development of BCC. This article describes the importance of different signaling pathways in the different stages of the two processes. The description of the homeostases brought up the importance of the Notch signaling along with the sonic hedgehog (Shh) and the Wnt pathways. Loss of the Notch signaling adversely affects the late stages of hair follicle formation and allows the bulge cells in the hair follicles to take the fate of the keratinocytes in the interfollicular epidermis. Further, the loss of Notch activity upregulates the Shh and Wnt activities, adversely affecting the homeostases. Notably, the Notch signaling is suppressed in BCC, and the peripheral BCC cells, which have low Notch activity, show drug resistance in comparison to the interior suprabasal BCC cells, which have high Notch activity.

1. Introduction

Hedgehog (Hh) signaling is required in the embryogenesis [1,2] including in the normal development of axial structures [3], neural tube [4], and hair follicles [5,6,7] but is reduced or absent in adult organisms [8]. On the other hand, the overactive Hh signaling may cause basal cell carcinoma (BCC), medulloblastoma, intestinal, pancreatic, and other cancers [6,9,10–12]. Sporadic BCC is the most common human cancer [8]. In addition to the sporadic BCC, Gorlin syndrome, a hereditary disease that primes individuals to develop skin tumors and birth defects, is caused by the inactivating mutations in the gene *patched* (PTCH) [13], preventing its ability to inhibit *smoothened* (SMO), activating the hedgehog pathway.

BCC develops due to a lack of immune surveillance [14]. Its development creates an immunosuppressive microenvironment, indicated by an increase in the myeloid-derived suppressor cells (MDSCs) and a decrease in the T-cells, with the help of the TGF-β signaling [15]. The chemokine CCL2 through its receptor CCR2, which is highly expressed in MDSCs, attracts them to the tumor site in response to the TGFβ signaling [15], causing immune suppression. On the other hand, the treatment of BCC with the Hh pathway inhibitors, vismodegib, and sonidegib, caused the influx of $CD4^+$, HLA-DR-class II^+, and $CD8^+$ cells within the tumor cell nests, activating the adaptive immune response and causing the disruption of the immune privilege at the tumor site [14]. Further, programmed death 1 receptor (PD-1), the immune checkpoint protein, which is expressed at low levels in the resting T cells and prevents the T-cell proliferation and cytokine production, is induced in the activated T-cells expressing TCR, thus, preventing a runaway immune response [16]. On the other hand, the immune suppression caused by the hyperactivity of PD-1 is involved in the tumor escape [16]. Furthermore, PD-1 expression on the activated T-cells is induced by TGF-β [16]. A phase 2 clinical trial found that cemiplimab, a monoclonal anti-PD-1 antibody, induced significant anti-tumor response in patients with metastatic BCC after progression or intolerance on the hedgehog

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https://doi.org/10.1016/j.bbcan.2022.188795
Received 29 December 2021; Received in revised form 10 March 2022; Accepted 3 September 2022
Available online 9 September 2022

inhibitor therapy [17], Further, cemiplimab has been approved for the treatment of the locally advanced BCC by the USFDA [18]. On the other hand, another immune modifier, imiquimod, approved to treat superficial BCC, induces interferon and other cytokines by activating the innate immune response through the toll-like receptor-7 [19], causing autophagy and apoptosis of the BCC cells [20].

Although the Shh pathway genes are the prime drivers, other pathways may have supplementary roles in the BCC development. Genetic profiling found mutations in the Hh pathway genes (e.g., PTCH1, SMO, SUFU) and TP53 in 85% of BCCs [21]. On the other hand, 85% of BCCs also had mutations in other cancer-related genes (e.g. MYCN, PPP6C, and PTPN14) [21]. Since DNA damage is not efficiently repaired in the keratinocytes deficient in protein phosphatase 6 (PPP6C), the loss of PPP6C increases the susceptibility of the skin to cancer development [22]. Similarly, a loss-of-function mutation in the non-receptor protein tyrosine phosphatase PTPN14, which negatively regulates the oncogenic function of YAP [23], predisposes individuals to the increased risk of BCC development [24]. Indeed, in BCC, the myc and the Hippo-YAP pathway target genes were upregulated [21] and mutations in MYCN, PPP6C, and PTPN14 were related to the increased risk of recurrence of BCC [21]. Thus, the supplementary mutations in other tumor activators/suppressors and the dysregulation of signaling pathways may confer BCC the diverse plasticity.

To find the causal basis of the development of BCC, understanding the homeostases of skin and hair follicles is warranted since the loss of homeostasis may be the prime reason for carcinogenesis. This article constructs the hair and epidermal homeostases, which elicits the importance of the Notch pathway in addition to the Shh and the Wnt pathways in the basal cell carcinoma. Notch is required for the late stages of the hair follicle development while Wnt and Shh are required for the hair follicle initiation and the dermal papilla formation, respectively. Thus, the loss of Notch, which allows the hair follicle stem cells to acquire the fate of the keratinocytes in the interfollicular epidermis (IFE) and upregulates the Wnt and the Shh pathways, may profoundly affect the hair follicle homeostasis midway, priming the skin to the development of BCC.

2. Hedgehog signaling and basal cell carcinoma

Retrovirally transduced human skin to overexpress Shh was grafted on to immuno-deficient mice [25]. This transgenic skin demonstrated histological features, e.g., growth of the epithelial buds into the dermis and separation of the epidermis from the dermis, of BCC development [25]. Further, the Shh skin expressed keratins expressed by the basal cells in the epidermis and decreased the expression of adhesion proteins BP180/BPAG2 and laminin 5, the features of human BCC [25], implicating the Shh pathway in the BCC development. Furthermore, the Shh cells expressed the Hh target gene, BMP—2B, in addition to Bcl-2, which is expressed by the keratinocytes in BCC [25].

Gli and Shh genes are normally expressed in the hair follicles [26]. However, the ectopic expression of Gli1 in embryonic frog epidermis caused tumors [26]. Further, Gli1, but not Shh and Gli3, is expressed by the human sporadic BCCs [26] and Gli1 expression in the basal cells of the epidermis caused BCC formation [26]. In contrast, the loss of *patched* (PTCH) or the overexpression of Shh is not sufficient to cause BCC as BCC does not occur consistently under these conditions [26]. Similar to the overexpression of Gli1, the overexpression of Gli2 caused BCC, which arose from the hair follicles, in mice. Further, the continued expression of Gli2 is required for the BCC growth [27] and Gli2 inactivation caused regression of tumors, leaving behind the slow-cycling long-lived residual tumor cells, which gave rise to BCC upon Gli2 reactivation [27]. Thus, the overexpression of Gli1 or Gli2 causes basal cell carcinoma while the loss of PTCH or overexpression of Shh is not sufficient to cause BCC.

In contrast to the BCC development due to the overexpression of Gli1 or Gli2, the BCC development due to the expression of constitutively active *smoothened* (SMO) is not consistent, a conclusion similar to the one drawn regarding the BCC development due to the loss of the gene *patched*. In one study, expression of a constitutively active *smoothened* mutant, using a truncated keratin 5 promoter in the skin, caused only a modest upregulation of the Hh target genes and benign basaloid follicular hamartomas instead of BCC [28]. In comparison, the BCC development required the higher upregulation of the Hh target genes including G1 cyclins D1 and D2 [28]. Thus, the magnitude of the Hh signaling strength may be important in the different types of skin tumor formation [28]. However, in another study, adult epidermis carrying a constitutively active *smoothened* mutant (SmoM2) developed BCC [29].

Interestingly, the transcriptional profiling of the SmoM2 expressing cells during the cancer initiation process revealed that these cells were reprogrammed to the embryonic hair follicle progenitor cell fate [29]. β-catenin signaling was activated during this process and was responsible for the reprogramming [29]. In agreement, the human BCC expresses genes of both the Wnt signaling and the embryonic hair follicle progenitor cell fate [29]. Thus, the combination of the Wnt and Shh pathways, causing reprogramming of the cells to the embryonic hair follicle progenitor cell fate, may govern the BCC formation. Further, the overexpression of Shh in the epidermis or the constitutive activation of *smoothened* in the dermis reinstalled the dermal papilla in the wound, causing hair follicle neogenesis [30]. Furthermore, although Wnt activation causes scarring, activation of the Shh signaling in the Wnt active cells leads to the hair follicle regeneration in wound healing [30]. In addition, Wnt5a is a Shh target gene in the hair follicle morphogenesis [31] and although Shh signaling is not essential for initiating hair follicle development [7], it is necessary for the morphogenesis of the hair follicles [7].

Notably, the constitutive active Hh pathway caused superficial BCC that resembles the embryonic hair germs, which are regulated by the Wnt signaling [32]. Further, the human BCC buds expressed the markers of early hair follicle lineage and the higher levels of β-catenin [32]. Thus, the BCC development and the hair follicle bud formation may be related, and the Shh and the Wnt pathways together play roles in the two processes. Furthermore, although the Shh and the Wnt pathways play an important role in the patterning during embryonic development, their overactivity may misspecify the epithelial cells to the stem cell-like fate and this misspecification may be important in the development of many cancers [33].

3. Molecular targets and drugs to inhibit the Hh pathway for the treatment of BCC

Notch, playing critical role in the epidermal differentiation [34–36], is frequently mutated in BCCs [37,38]. The low Notch activity in BCC causes tumor persistence while activating the Notch signaling causes tumor regression [39]. Further, the peripheral basal cells of BCC having high Hh activity and low Notch activity are resistant to vismodegib, a drug that blocks the Shh pathway and has been approved to treat BCC, while the interior suprabasal cells with high Notch activity undergo apoptosis under the drug treatment [39]. Furthermore, the downregulation of Hh target genes caused by the vismodegib treatment was unaffected by the inhibition of the Notch signaling, however, the apoptosis induced by the vismodegib treatment was severely reduced when Notch was inhibited [39]. Thus, the high Notch activity helps cause the vismodegib induced apoptosis of the BCC cells. In addition, the Hh activity is inversely correlated with the activity of the Notch pathway, suggesting that the overactivity of the Hh pathway may circumvent the vismodegib treatment through the suppression of the Notch pathway [39]. Thus, the crosstalk between the two pathways may determine the outcome of the drug treatment that inhibits the Hh pathway. Interestingly, a peptide of the Notch ligand Jagged1 caused apoptosis of the BCC cells due to the expression of the Fas ligand by these cells [40], involving the innate immune response. Further toward combining the vismodegib treatment with the Notch activation, the

Notch activating antibodies, or modulation of the activator (a complex of Presenilin, Nicastrin, PEN-2, and APH-1) of γ-secretase, which cleaves the active Notch intracellular domain (NICD), or modulation of the Notch repressor complex (a complex of RBP-Jk, CtIP, CtBP, and SHARP), which represses the Notch target genes, need to be explored (Fig. 1).

Vismodegib caused tumor regression by preventing the hair follicle-like fate of the tumor cells and causing their differentiation [41]. However, the tumor relapsed following the discontinuation of the vismodegib treatment [41]. The relapse was caused by the slow-cycling tumor cells expressing LGR5, an enhancer of the Wnt signaling, and characterized by the active Wnt signaling [41]. In a mouse model, combining the LGR5 ablation or the Wnt signaling inhibition with the vismodegib treatment led to the eradication of BCC [41]. Further, BCC patients treated with vismodegib were at an increased risk of developing cutaneous squamous cell carcinoma and other non-BCC malignancies [42], suggesting that the disruption of the epidermal and hair follicle homeostasis may be at the core of these malignancies.

While vismodegib has been approved to treat both locally advanced (laBCC) and metastatic (mBCC) BCCs [43], another drug, sonidegib, which inhibits SMO as the vismodegib does, has been approved to treat only the laBCC patients since it did not meet certain efficacy criteria for the treatment of mBCC patients [44]. Other molecular targets and the known inhibitors of the Hh and the Wnt pathways have been shown in Figs. 2 and 3.

4. Hair follicle homeostasis

4.1. Hair follicle development

In hair follicle formation, the first step is the thickening of the epidermis which leads to the formation of the epidermal placode (Pc) at stage 1 of the hair follicle development (Fig. 4A) [45]. The formation of the placode causes mesenchymal cells to aggregate, forming dermal condensate (DC), a precursor to dermal papilla (DP) [45]. A pair of placode and dermal condensate constitute the formation of the hair germ, which forms at stage 2 (Fig. 4A) [45]. With the down growth of the placode, the hair germ develops into a hair peg at stage 3 (Fig. 4A) [45]. A dermal condensate niche forms and is surrounded by the follicular epidermis, forming the dermal papilla (DP) at stage 4 [45]. Hair follicle starts to form at stage 5 and its formation completes at stage 8 (Fig. 4A) [45]. After formation, the hair follicle undergoes the cycles of growth (anagen), regression (catagen), and termination (telogen) throughout the life of the organism (Fig. 4B) [45]. Interaction between the follicular epidermis and dermal papilla drives the hair cycle [45].

In the section below, we construct the follicular homeostasis and describe the roles of different pathways in this process (Fig. 5).

4.2. Epidermal Wnt signaling is necessary and sufficient to initiate the hair folliculogenesis

Hair folliculogenesis starts with a pre-placode. Pre-placode is molecularly identified to express DKK4 and Edar (*downless*) [46]. Pre-placode cells secrete the Wnt signal, which activates the dermal Wnt activity [46]. Subsequently, an unidentified dermal signal causes the fate specification in the pre-placode [46]. Progenitor placode cells, thus formed, then migrate to a physically identifiable placode (Pc) [46]. Progenitor cells then signal to the dermis to initiate the formation of the dermal condensate (DC) [46]. A reciprocal exchange between the Pc and the DC causes the down-growth of the polarized hair germ [46] (Fig. 5). The DC finally gets engulfed by the placode progenitors, forming the dermal papilla (DP) of the hair shaft-producing bulb [46].

Intraepidermal Wnt signaling is necessary and sufficient to initiate hair follicle formation [47]. Further, the ectopic expression of Dickkopf 1 (DKK1), a potent inhibitor of the Wnt signaling, blocked the hair placode formation, suggesting that the Wnt signaling is essential for initiating the folliculogenesis [48]. Consistent with the role of β-catenin, knockout mice lacking LGR4, an enhancer of the Wnt signaling, had less hair placode formation with reduced expression of LEF1, an effector of

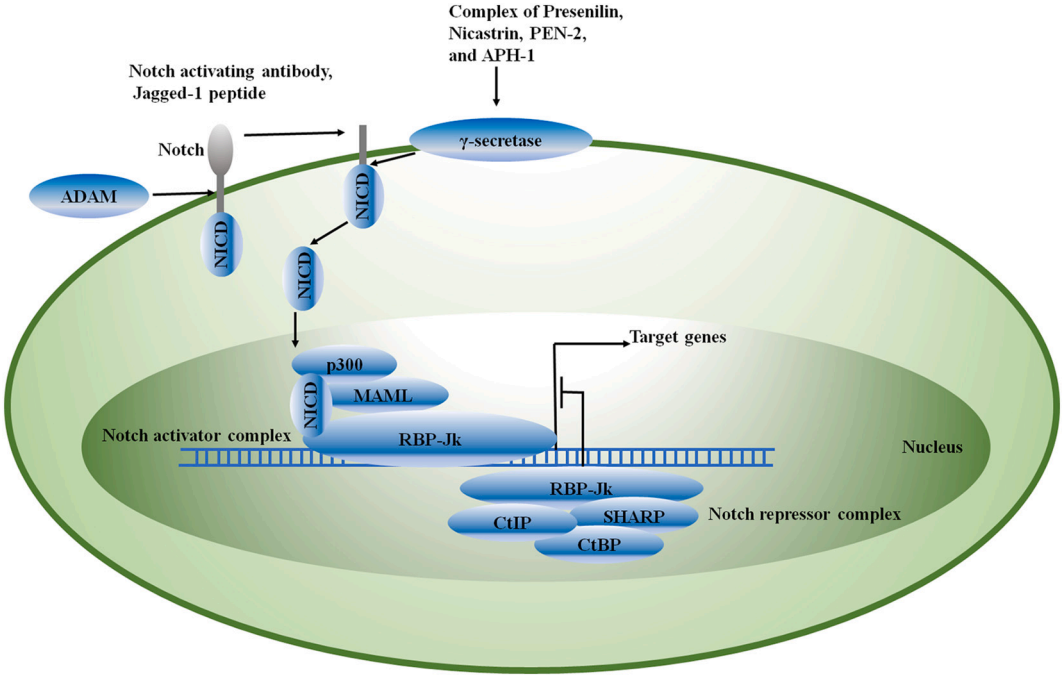

Fig. 1. Notch pathway. RBP-Jk functions either as a transcriptional activator or repressor depending on whether it recruits coactivators (MAML and p300) or co-repressors (SHARP, CtIP, CtBP) [97]. The intracellular domain of the Notch receptor (NICD) translocates to the nucleus upon activation of the Notch signaling and recruits the activator complex causing the transcription of Notch target genes while the repressor complex silences the Notch target genes in the absence of NICD [97]. Cleavage of the Notch receptor happens in two steps by ADAM and γ-secretase releasing NICD in response to the ligand binding to the Notch receptor [98]. A complex of Presenilin (PS), Nicastrin, PEN-2, and APH-1 is required for γ-secretase's activity [99]. Positive modulation of Notch signaling can be caused by the Notch activating antibodies or peptides derived from the ligand Jagged-1 or via the activators of γ-secretase.

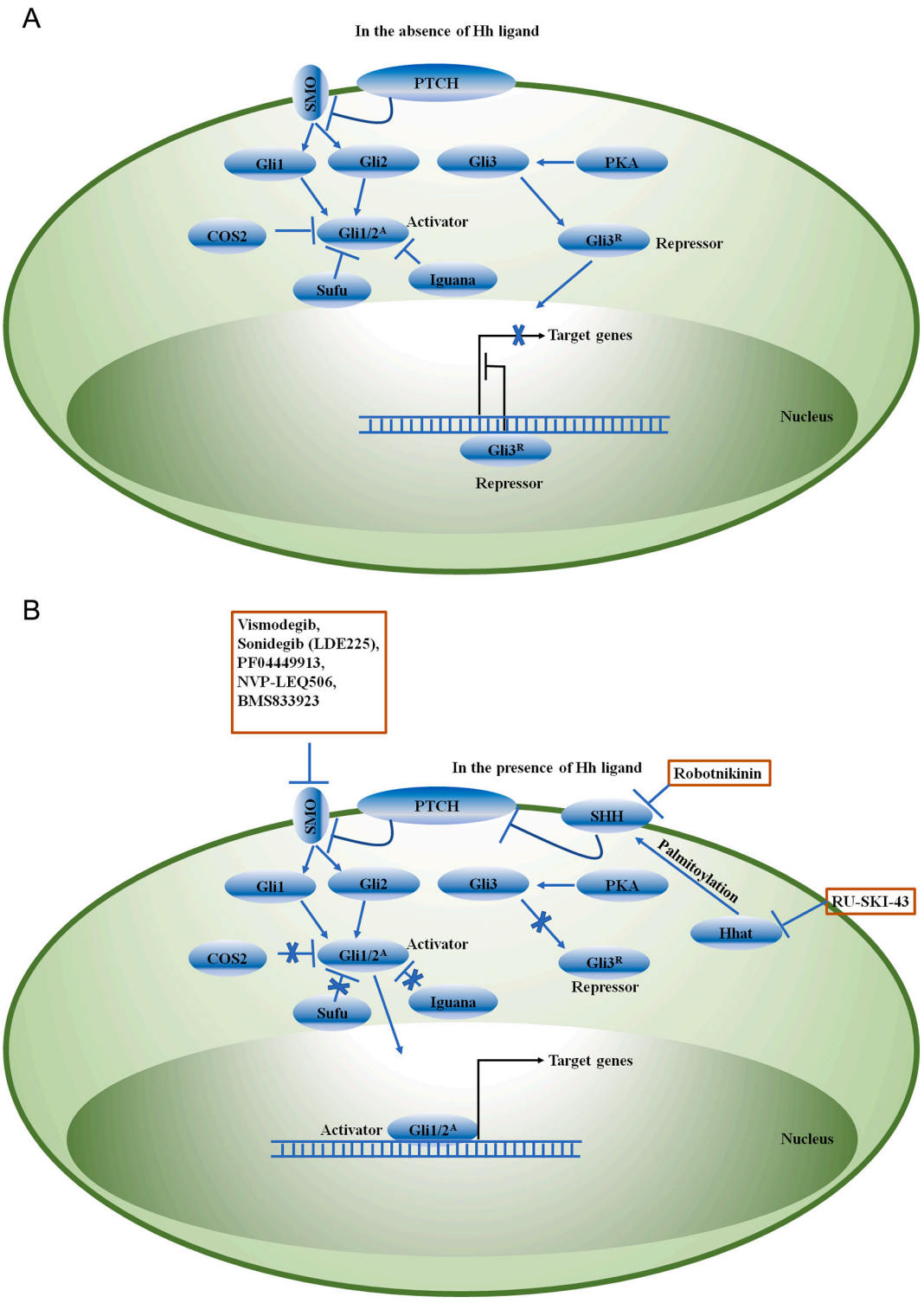

Fig. 2. Hedgehog pathway and its inhibitors. (A) In absence of Hh ligands, SMO is inhibited by PTCH. Further, Gli3 is processed into its repressor form and translocates to the nucleus while Gli1/2 are inhibited by COS2, Sufu, and Iguana, repressing the Hh target genes [100] (B) In the presence of the Hh ligands, SMO inhibition by PTCH is relieved and SMO activates Gli1/2. Further, processing of Gli3 into its repressor form is inhibited while inhibition of Gli1/2 by COS2, Sufu, and Iguana is relieved, activating the Hh target genes [100]. In addition, palmitoylation of the ligand sonic hedgehog, caused by the Hedgehog acyltransferase (Hhat), is critical for the Hh signaling [101]. Small molecule chemical inhibitors in this pathway have been shown [98,102–108].

the Wnt pathway. In addition, the LGR4 ablation also reduced the expression of Edar and Shh and increased the phosphorylation of Smad 1/5/8, the effectors of the BMP signaling, which inhibits the hair follicle formation [49], suggesting that the Wnt pathway promotes the hair follicle formation through the Edar and the Shh pathways and inhibition of the BMP pathway. Consistent with the above conclusion, Noggin neutralizes the inhibitory activity of BMP-4, upregulating the transcription factor LEF1, stimulating the hair follicle induction [50].

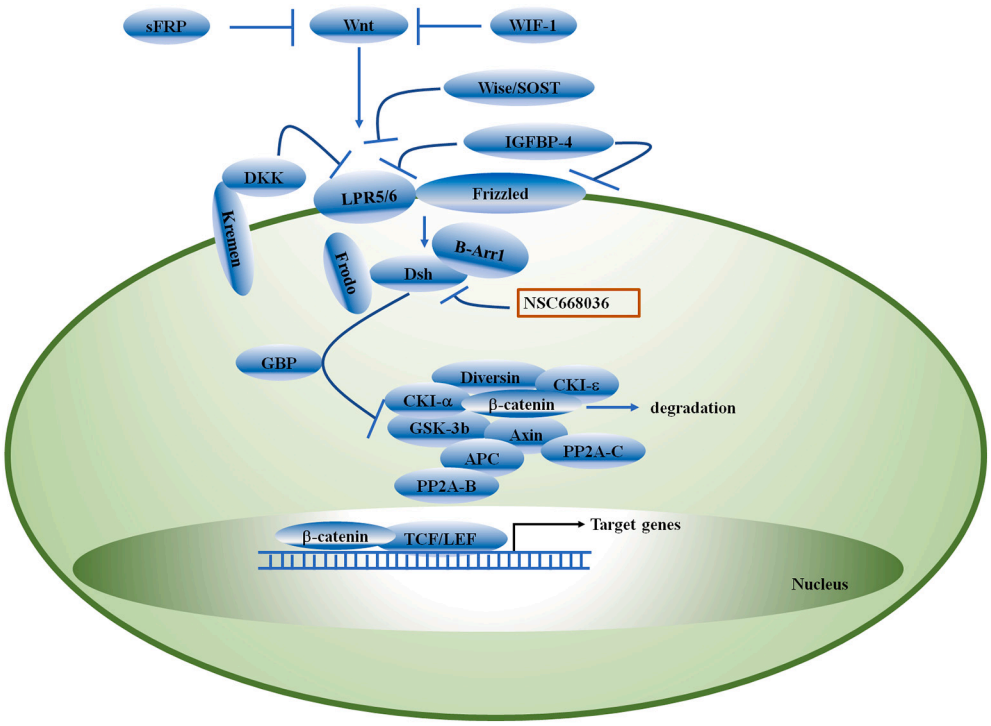

Fig. 3. Wnt pathway and its inhibitors. In the absence of Wnt ligand, β-catenin is phosphorylated by CKIα and CKIε, leading to its further phosphorylation by GSK3β triggering β-catenin's ubiquitination and degradation [109]. Phosphorylation of β-catenin occurs in a multiprotein complex organized by the scaffold protein axin [109]. In the presence of the Wnt ligand, dishevelled (Dsh) displaces GSK3β from the scaffold protein axin, preventing the degradation of β-catenin [109]. Then, β-catenin translocates to the nucleus, causing the activation of Wnt target genes. Cell secreted negative regulators that inhibit the Wnt ligand and its receptors LPR5/6 and Frizzled [110,98], and a small-molecule chemical inhibitor that inhibits dishevelled [111,98] have been shown.

4.3. A positive feedback loop between the Wnt and the Eda pathway is important for the hair placode formation

Stages after the follicle initiation require the reciprocal interaction between the placode and the dermal condensate [47]. Among the reciprocal signaling, Wnt signaling is the most upstream, followed by the Eda signaling, which is required for the Wnt signaling and placode stabilization [46] (Fig. 5). On the other hand, Eda expression is stimulated by the Wnt signaling through LEF1 [51]. Eda (*Tabby*) and Edar (*downless*), the ligand and the receptor of the TNF pathway, respectively, which is active in the epithelial compartment, affect the formation and/or the function of the hair placode [51] (Fig. 5). Further, Wnt and Edar signaling form a positive feedback loop, which is important in the hair placode formation [52] (Fig. 5).

4.4. FGF20, a Wnt target gene, is required for the dermal condensate niche specification through the waves of upregulation of transcription factors

FGF20, a Wnt target gene, is required for the dermal condensate (DC) niche specification and the dermal papilla (DP) formation involving the cell aggregation [46]. The transition of the dermal fibroblasts from the unclustered DC precursors to DC niche fate happens through the waves of the upregulation of transcription factors and signaling molecules in the dermis [46]. Further, the unclustered DC progenitors form due to the pre-existing placode progenitors [46]. Furthermore, the ablation of the Wnt signaling in the dermal condensate blocks the follicle formation after the initial induction, and this effect of the Wnt signaling is mediated by the FGF pathway [53]. Thus, while the epidermal Wnt signaling is important for the hair follicle initiation, the dermal Wnt signaling is required for the dermal condensate niche specification and the DP formation through the FGF pathway.

4.5. Ectopic sustained activation of Wnt impairs the hair follicle development

The ectopic activation of β-catenin converts the embryonic epidermis to the epidermal placode fate [54]. Further, due to the sustained activation of β-catenin in the epidermis, mesenchymal Wnt signaling was elevated, and the BMP signaling throughout the skin was elevated [55], consistent with the conclusion that the Wnt pathway is linked with the BMP pathway and that the epidermal Wnt signaling is linked with the dermal Wnt signaling (Fig. 6). Furthermore, the sustained epidermal β-catenin caused the precocious and excessive formation of the hair follicles even in the absence of the Edar signaling [55] while the down-growth of the follicle and the hair shaft production was impaired [55], suggesting that the sustained Wnt signaling causes the impairment of hair follicle development at a downstream level, which controls the down-growth and the subsequent stages of hair follicle development (Fig. 5), by affecting the hair follicle homeostasis.

4.6. Edar through NF-kB regulates LHX2 and TGFβ2, causing the placode down-growth and the loss of E-cadherin in the follicular epidermis

The loss of NF-kB signaling does not affect the primary placode formation but affects the formation of the proper placode with the down-growth [56] and the loss of E-cadherin in the follicular epidermis. NF-kB affects the Wnt and the Shh signaling (Fig. 5) but this does not fully represent the phenotype observed in the NFκB loss [56]. Instead, LHX2 and TGFβ2, the targets of NFκB, accounted for the phenotype observed under the loss of NFκB signaling [56]. LHX2, a transcription factor, is downstream of the hair follicle stem cell fate but upstream of the activated-hair stem cell fate, which is destined to terminally differentiate [57]. Further, LHX2 maintains both the growth and the undifferentiated state of the hair follicle progenitor cells [57]. In the Edar or NFκB deficient epidermis, the hair placode starts to develop but the hair follicle development aborts [58], suggesting that the maintenance of the stem cell characteristics of the progenitor cells through LHX2 and TGFβ2 is critical for the formation of a proper placode. Further, in this signaling, NFκB lies downstream of Edar and conveys the signal to Shh, causing the subsequent down-growth of the placode [58] (Fig. 5).

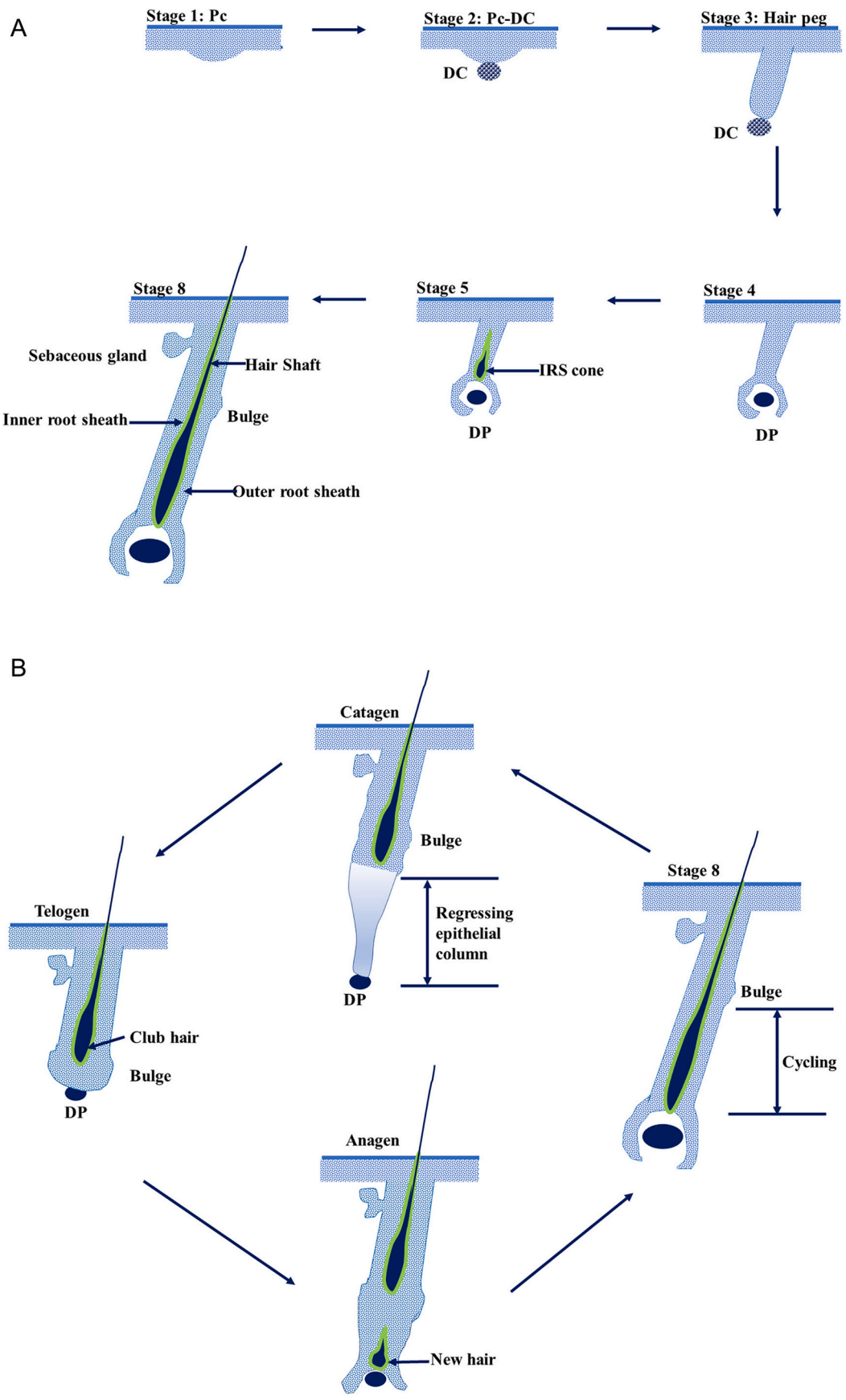

Fig. 4. Hair follicle development and cycling. (A) Stages of hair follicle development have been shown [45,112]. (B) Phases of hair follicle cycling have been shown [112]. IRS: inner root sheath.

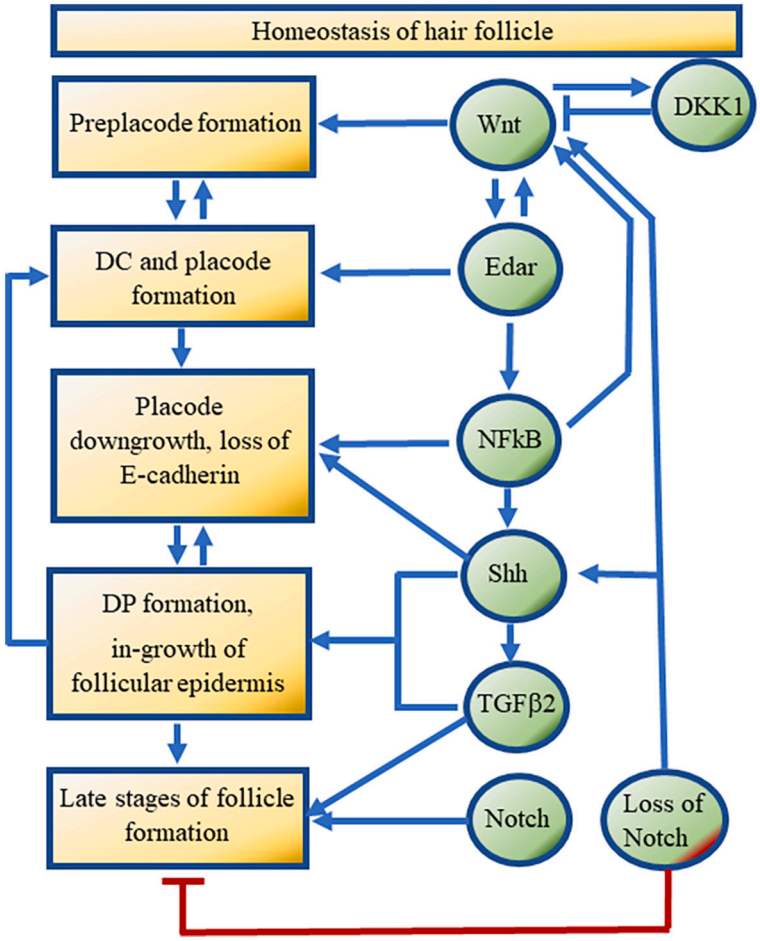

Fig. 5. Homeostasis of a hair follicle. Stages from hair follicle initiation to maturation and the roles of different signaling pathways in each stage have been shown. An arrow represents a positive regulation while a line (a minus sign) represents a negative regulation.

4.7. Shh signaling affects the dermal papilla formation and the downgrowth of the follicular epidermis

The hair germs were found both in the wild type and the Shh−/− embryos but the Shh−/− germs failed to progress through the subsequent stages of the hair follicle development [59]. Similarly, ablation of Shh does not affect the germ formation and the expression of Wnt10b, BMP2, and BMP4 proteins, which are required for the initiation of hair follicle formation [7]. Further, a reduction in Gli1 and *patched* (PTCH) expressions was found in the mutant dermal condensates that fail to develop into dermal papillae, suggesting that Shh is important for the dermal papilla (DP) formation [59] (Fig. 5). In agreement, Shh has been found to affect the dermal papilla formation and ingrowth of the epidermis affecting the morphogenesis of the hair follicles [7]. On the other hand, the late-stage follicle differentiation markers were found in the Shh−/− skin [59]. Thus, Shh lies in the middle of the initiation and the maturation of the hair follicles downstream of NFκB (Fig. 5). Further, Wnt10b is a direct target of NFκB, which is involved in hair germ formation [52] (Fig. 5) unlike Shh, while the follicular epithelium and the bulge cells, which regenerate the hair follicle, are derived from the cells expressing Shh [60], suggesting that Shh is important for the hair follicle regeneration in addition to its critical role in the dermal papilla formation, affecting the hair follicle homeostasis.

4.8. TGFβ2 is required for the skin appendage formation and lies downstream of the Shh signaling

Epithelial placode causes dermal condensations, which are responsible for skin appendage morphogenesis [61]. TGFβ2 can substitute for the epithelial placodes in the skin appendage morphogenesis [61]. Further, TGFβ2 lies downstream of the Shh pathway in this process [61] (Fig. 5). Furthermore, TGFβ2 is required and sufficient for murine hair follicle formation [62] after its initiation by the Wnt pathway. Thus, in the hair follicle homeostasis, Wnt lies the most upstream while TGFβ2 lies the most downstream before the Notch pathway (Fig. 5).

4.9. Notch1 is involved in the late stages of hair follicle development and its reduction causes the sustained activation of Gli1 and enhances β-catenin activity

The embryonic, tissue-specific, ablation of Notch1 did not affect the hair placode formation but it affected the follicle invagination into the dermis [63]. Further, the postnatal loss of Notch1 caused the loss of hair follicles and cyst formation [63]. Furthermore, the loss of Notch1 also affected the hair cycling [63]. In addition, along with BMP-2, BMP-4, the TGFβ related growth factors, and the TGFβ signaling, Notch is important for the differentiation of the hair follicle matrix cells into the hair shaft cells [64]. Thus, Notch1 affects the late stages of follicle formation and hair homeostasis [63] (Fig. 5).

Interestingly, Notch1 ablation in skin and primary keratinocytes caused the sustained upregulation of Gli2 and BCC-like tumors [65], suggesting that the loss of Notch activates the Shh pathway. Further, the Notch1 ablation enhances the β-catenin signaling [65]. Conversely, the dominant active form of the Notch receptor blocks the β-catenin activity [65]. Thus, the Notch1 ablation activates both the Shh and the Wnt pathways, affecting the hair follicle homeostasis and the formation of

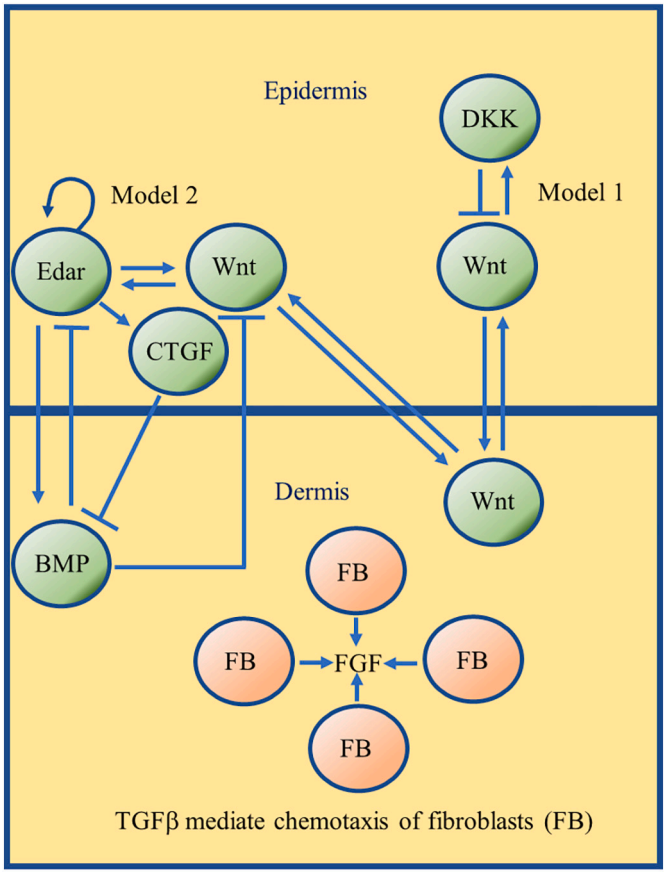

Fig. 6. Models of dermal condensate- epidermal placode formation. Dermal condensate forms due to TGFβ mediated chemotaxis of the fibroblasts toward the FGF sources. On the other hand, epidermal placode may form due to the Turing instability involving Wnt and DKK (Model 1). Epidermal placode may also form due to the interplay between Edar-Wnt, their inhibitor BMP, and the BMP inhibitor, connective tissue growth factor (CTGF) (Model 2). Further, epidermal and dermal Wnt signaling are linked through a positive feedback loop. An arrow represents a positive regulation while a line (a minus sign) represents a negative regulation.

BCC.

5. Models of dermal condensate- epidermal placode formation

A model of dermal condensate-epidermal placode formation can be given [66]. In this model, the TGFβ signaling causes the aggregation of the fibroblast cells through chemotaxis/directed cell migration toward the site of FGF production [66] (Fig. 6). Indeed, TGFβ2 is expressed by the human dermal papilla cells and the inhibition of TGFβ2 signaling caused the impaired hair follicle development and maturation [67]. Moreover, TGFβ has been shown to cause the chemotaxis of the human fibroblasts [68].

On the other hand, there are two models of epidermal placode formation. In the first model, epidermal placode forms due to the Turing instability caused by the negative feedback loop between Wnt and DKK in the epidermis [69] (Model 1 in Fig. 6). In the second model, the Edar and the Wnt signaling are linked in a positive feedback loop (Fig. 6) in the epidermis. Further, Edar causes the expression of BMP4/7, the inhibitors of the epidermal Edar and Wnt signaling, [70] (Fig. 6). In addition, Edar causes the expression of the connective tissue growth factor (CTGF), an inhibitor of the BMP signaling [70] (Fig. 6). Thus, Edar causes the expression of its negative regulator BMP4/7 as well as the negative regulator of the BMP4/7 i.e., CTGF, restricting the inhibitory action of BMP on Wnt/Edar only at a distance from the Edar expression, creating a pattern [70] (Fig. 6).

In addition, the epidermal Wnt ligands are required for the uniform dermal Wnt activity that precedes the hair follicle development [71]. Further, the dermal Wnt activity is required for the patterned upregulation of the epidermal Wnt signaling [71] (Fig. 6). This positive feedback loop between the epidermal and the dermal Wnt signaling, linking the dermal and the epidermal patterns, is important for the formation of the epidermal placodes and the dermal condensates [71] (Fig. 6). Further, an epidermal prepattern precedes the dermal condensate formation [66]. Thus, the Wnt signaling positively affects the pair of patterns, while BMP functions as an inhibitor, and FGFs are both required and inhibitory to the formation of the pair of patterns [66]. For example, FGF7/KGF inhibits the hair follicle development [72] and, instead, promotes the epidermal differentiation and development [72]. In contrast, the ablation of Fgfr2-IIIb, the KGF receptor, causes impaired hair formation and patterning [73]. Thus, FGF7/KGF affects the hair follicle formation both negatively and is required for follicle formation. Further, the ablation of Fgfr2-IIIb signaling does not affect LEF1, the transcription factor in the Wnt signaling, and Shh, and Bmp4 expressions [73], suggesting that the role of FGF7 is independent of the three pathways.

6. Role of the notch pathway in the skin homeostasis

In differentiating keratinocytes, Notch1 regulates $p21^{WAF1/Cip1}$ both directly through RBP-Jκ and indirectly by increasing the activity of calcineurin/NFAT, which involves the downregulation of calcipressin, an inhibitor of calcineurin, through HES1 [74] (Fig. 7). Further, the downregulation of calcineurin B1 results in cyclic alopecia phenotype due to the alteration in the expression of Notch target genes [74], suggesting that the Notch pathway is important for hair follicle cycling and differentiation. Indeed, Notch is involved in the differentiation of the epidermis [34] [35] [36], hair follicle, and sebaceous gland and acts as a tumor suppressor [34]. In this context, the Notch deficiency causes hair follicles to convert to epidermal cysts [75] and Notch1 deficiency in the interfollicular epidermis (IFE) causes hyperplasia and tumor formation. In the epidermis, keratinocytes undergo growth arrest and terminal differentiation, which are regulated by the Notch pathway through p21 [34] (Fig. 7). On the other hand, asymmetric cell division is important for skin stratification [35]. Compromising the asymmetric division compromises the skin stratification and the barrier function [35] through the Notch pathway.

Further, the Notch signaling acts to prevent the bulge cells (HFSCs) acquire the interfollicular epidermis cell (IFEC) fate [75] (Fig. 7). In the absence of the Notch pathway, the bulge cells convert and migrate to become the cells of the IFE [75]. Furthermore, Notch1 deficiency in the keratinocytes of the hair follicle caused the higher expression of TGFβ ligands, which caused the elevated secretion of the diffusible insulin-like growth factor antagonist IGFBP by the dermal papilla (DP), decreasing the IGF to IGFBP ratio [76] (Fig. 7). IGF to IGFBP ratio affects the proliferation of the hair follicle matrix keratinocytes (HFMCs) [76] (Fig. 7). Thus, the Notch1 pathway is involved in the DP-hair matrix interaction, affecting the proliferation of the hair follicle matrix cells (HFMCs) [76], and prevents the hair follicle stem cells (HFSCs) take the IFE cell (IFEC) fate thereby affecting the skin homeostasis.

In addition, the ablation of the Notch pathway causes the activation of the Wnt and the Shh pathways in the skin [65], affecting the hair follicle homeostasis (Fig. 5). Thus, the epidermal and the hair follicle homeostases are linked through the Notch pathway (Fig. 7) and the dysfunction of the Notch pathway may be at the core of the BCC development.

In IFE, cyclin D1 overexpression causes the abnormal differentiation of the epidermal keratinocytes [77] (Fig. 7). In this context, the homeodomain interacting protein kinase 2 (HIPK2) regulates the stem cell and the differentiated cell compartments of the IFE by forming a repressor complex with β-catenin, LEF1, and CtBP (Fig. 7) [78]. This

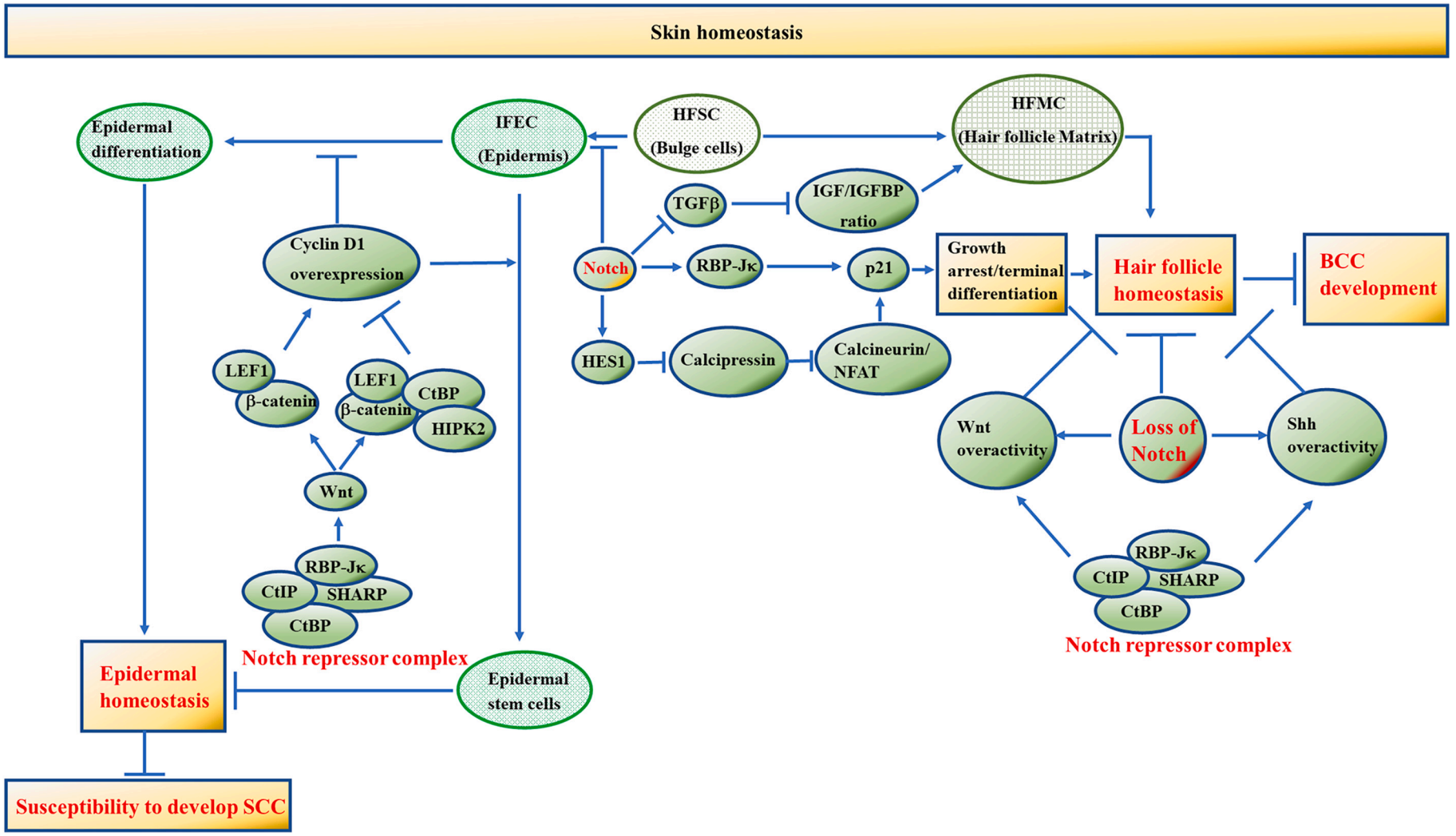

Fig. 7. Role of the Notch pathway in skin homeostasis. The central role of the Notch pathway in IFE and hair follicle homeostases has been shown. An arrow represents a positive regulation while a line (a minus sign) represents a negative regulation.

complex suppresses the LEF1/β-catenin-mediated transcription of the cyclin D1, establishing a balance between the two compartments (Fig. 7) [78]. Conversely, the loss of HIPK2 caused the rapid G1-S transition and expansion of the epidermal stem cells through the overexpression of cyclin D1 (Figs. 7, 78]. The expansion of epidermal stem cells coupled with the abnormal epidermal differentiation caused by the cyclin D1 overexpression upsets the epidermal homeostasis increasing the susceptibility to develop squamous cell carcinoma (SCC) (Fig. 7). Notably, a gene expression profile of human SCC found dysfunction of the epidermal homeostasis [79]. The markers that promote epidermal stem cell proliferation and inhibit their differentiation were upregulated while those that keep the stem cells in the quiescent phase were downregulated [79], suggesting that the stem cells may be at the core of the epidermal homeostasis and carcinogenesis.

6.1. The crosstalk among the notch, the Wnt, and the hedgehog pathways

In the absence of the Wnt activation, the TCF family of the HMG box transcription factors repress the Wnt target genes [80]. Upon the Wnt activation, the interaction of TCF with the stabilized β-catenin converts the TCF into a transcriptional activator [80]. In the repressor function of TCF, the C-terminal binding protein-1 (CtBP1) binds with TCF4 and functions as a corepressor of the Wnt target genes [80] (Fig. 8A). Similarly in the hedgehog pathway, zinc-finger homeobox protein TSHZ2 forms a ternary complex with CtBP2 and Gli1, suppressing the transcriptional activity of Gli1 [81] (Fig. 8A). Notably, the presence or the absence of this ternary complex may be a key factor in tumorigenesis [81]. Further, the antagonism between CtBP and the Hh pathway is evolutionarily conserved since the expression of the mutant CtBP1

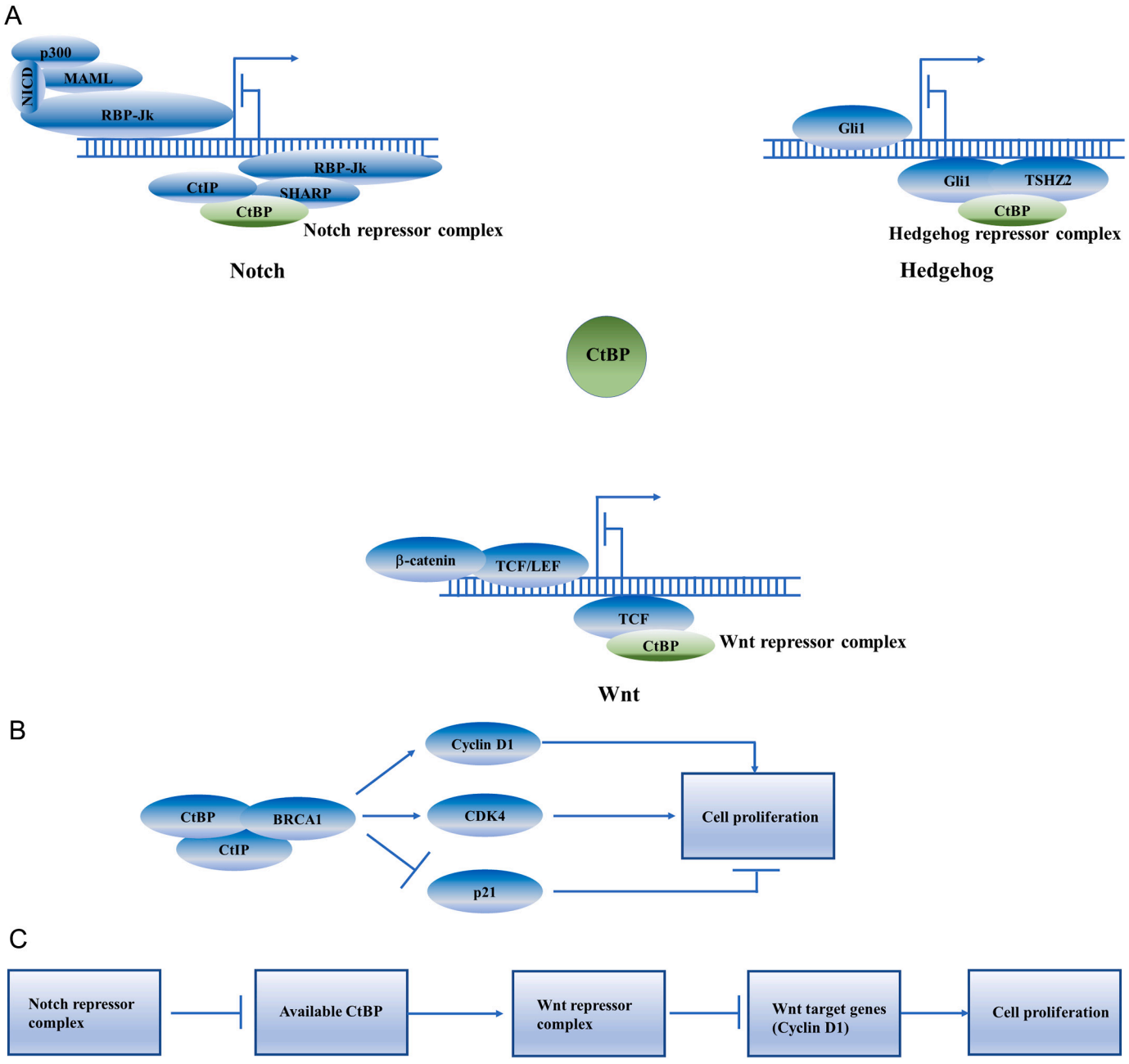

Fig. 8. The role of CtBP in the Notch, the Wnt, and the hedgehog pathways. (A) CtBP is a part of repressor complexes that repress the three pathways. Thus, the common pool of CtBP molecules balances the activities of the three pathways. Further, the excessive repression of one pathway may activate the other two pathways. (B) CtIP/CtBP/BRCA1 complex causes cell proliferation through cyclin D1 (C) Formation of the Notch repressor complex may deplete the pool of CtBP, reducing the amount of the Wnt repressor complex, causing the cell proliferation through the transcription of the Wnt target genes e.g., cyclin D1.

caused upregulation of the hedgehog-related genes in *C. elegans* [82]. On the other hand, CtBP also forms a repressor complex that represses the Notch target genes (Fig. 1). Thus, CtBP forms repressor complexes with the activators of the Wnt (i.e., TCF), the Hh (i.e., Gli1), and the Notch (i.e., RBP-Jk) pathways that coexist along with the corresponding activators (Fig. 8A), maintaining a balance among the activities of the three pathways. Further, the repressive state of the Notch pathway may deplete the limiting repressor CtBP, increasing the activity of the Wnt and the hedgehog pathways. Therefore, in the hair follicle homeostasis, a balance maintained by CtBP among the activities of the Wnt, the Hh, and the Notch pathways may be important.

6.2. A key role of the notch signaling in maintaining the balance between the epidermal stem cells and their differentiation

In keratinocytes, the activation of the Notch pathway causes growth arrest of the cells [34,83]. Further, while Notch1 is expressed by all living layers of the epidermis, the expression of its ligand Delta1 is confined to the basal layer, especially in the regions where the stem cells reside, suggesting that the epidermal stem cells have a key role in initiating the differentiation of the transit-amplifying cells of the epidermis through the Notch signaling [36].

Conversely, the repression of Notch target genes by the Notch repressor complex (Fig. 1) may favour the proliferation of the cells. In this context, the DNA damage repair protein CtIP (i.e., CtBP interacting protein) interacts with the tumor suppressors RB1 and BRCA1 and regulates G2/M DNA damage checkpoint and homologous recombination, processing DNA double-strand breaks (DSBs) [84]. Further, CtIP through CtBP and BRCA1 represses p21 and increases cyclin D1 and CDK4 levels, promoting G1/S transition and proliferation of cells (Fig. 8B) [85] Thus, CtIP and CtBP have a pro-proliferation role in the cells. Interestingly, CtIP and CtBP are also important components of the Notch repressor complex involving RBP-Jk, and SHARP (Fig. 1). Thus, the formation of the Notch repressor complex and the simultaneous formation of CtIP/CtBP/BRCA1 complex may block the transcription of the Notch target genes (Fig. 1) and simultaneously induce proliferation of the cells through cyclin D1 (Fig. 8B). Similarly, since CtBP also represses the Wnt pathway (Fig. 8 A), the use of the limiting protein CtBP in the Notch repressor complex may deplete the Wnt repressor complex, causing the activation of the Wnt target genes, especially cyclin D1, inducing the cell proliferation (Fig. 8C). Thus, while the activation of the Notch pathway causes differentiation and inhibits proliferation of the cells, the repression of the Notch target genes by the Notch repressor complex favours the proliferation of the cells through cyclin D1 expression caused either by the formation of CtIP/CtBP/BRCA1 complex (Fig. 8B) or by the Wnt pathway (Fig. 8C).

Further, CtIP regulates the Notch1 expression [86]. Thus, CtIP may prepare the epidermal stem cells for their eventual differentiation through the Notch1 expression while causing their expansion through the cyclin D1 expression (Fig. 8B) so that the epidermal cells differentiate, should their environment present the Notch ligand. Thus, the balance between the Notch activator complex, causing cell differentiation, and the Notch repressor complex, causing cell proliferation (Fig. 8C), may be the key to maintaining the balance between the epidermal stem cell compartment and the differentiation of the epidermal cells.

7. ATM/ATR DNA damage checkpoint signaling affects the notch activity and the immune-checkpoint signaling

7.1. ATM/ATR signaling affects the notch signaling

Ataxia-telangiectasia mutated (ATM), a DNA damage checkpoint protein, regulates DNA damage response and genomic stability [87]. Further, ATM has been found to maintain the stemness and reduce the senescence of the adult neural stem cells through the Notch pathway [87]. Furthermore, CtIP activates ATR, triggering the ATR-dependent DNA damage checkpoint signaling [84]. On the other hand, ATR phosphorylates CtIP recruiting it for the repair of the double-strand breaks (DSBs) [88], limiting the role of CtIP in the Notch repressor complex (Fig. 1). Thus, ATM/ATR checkpoint signaling has been implicated in the Notch activity through CtIP.

7.2. The use of PARP and ATR inhibitors for the treatment of cancer

Olaparib, a potent PARP inhibitor targeting DNA damage response (DDR), has been approved to treat recurrent ovarian cancer and has shown promising outcomes in patients with metastatic prostate or breast or pancreatic cancers [89,90,91,92,93]. Furthermore, combining the PARP inhibition with ATR inhibition has shown promising results in patient-derived xenografts models of ovarian cancer resistant to the PARP inhibition, and platinum chemotherapy [94]. Since the DNA damage response through ATM/ATR may affect the Notch activity, the use of the PARP and ATR inhibitors, currently under study/evaluation for the treatment of ovarian, breast, prostate, and pancreatic cancers may need to be evaluated for the treatment of BCC.

7.3. ATM/ATR DNA damage checkpoint signaling is linked with the immune checkpoint signaling

The error-prone DNA damage response (DDR) such as the processing of the DNA double-strand breaks (DSBs) activates the DNA damage checkpoint signaling through the ATM/ATR pathway causing the cell survival. In addition, the error-prone DDR activates the innate immune response, processing any neoantigens produced by the DDR [95]. On the other hand, the ATM/ATR signaling concomitantly upregulates the immune-checkpoint signaling through the PD-1 receptor by upregulating its ligand PD-L1, causing immune suppression, balancing the immune response to the neoantigens [95]. Thus, the DNA damage checkpoint signaling and the immune checkpoint signaling are linked. Interestingly, the ATR inhibition downregulates PD-L1 and promotes the T-cell-mediated killing of the tumor cells [96]. Thus, the effectiveness of the immune checkpoint blocking antibody, cemiplimab, can be improved by combining it with ATR inhibition. Moreover, the ATR inhibition may restore the balance among the Notch, the Wnt, and the Shh pathway activities, maintained by CtBP/CtIP (Fig. 8A), by freeing CtIP from the DNA damage response.

8. Conclusion

Constitutive activation of Gli1 and Gli2 in the skin causes BCC. In contrast, constitutive activation of *smoothened* or loss of *patched* does not cause BCC consistently. Further, the strength of Shh signaling and high upregulation of Shh target genes are important in BCC development. Furthermore, BCC cells express genes of the embryonic hair follicle progenitor cell fate and the Wnt pathway. In addition, histologically, BCC development resembles the hair follicle bud formation.

Wnt signaling is required for the initiation of the hair follicle development while Shh signaling is required for the dermal papilla formation and Notch signaling is required for the late stages of folliculogenesis. In addition, the Shh pathway is also required for the generation of the bulge cells, which are essential for hair regeneration. Further, CtBP/CtIP may be central to maintaining the balance among the activities of the Wnt, the Shh, and the Notch pathways, playing an important role in the hair follicle homeostasis. Furthermore, the DNA damage response especially the ATM/ATR checkpoint signaling has been implicated in the Notch activity and the immune-checkpoint signaling through PD-1. Thus, the DNA damage response, the ATM/ATR signaling, the activities of the Notch, the Wnt, and the Shh pathways, and the immune checkpoint signaling through PD-1 are linked.

Loss of Notch activity allows the bulge cells to acquire the fate of the keratinocytes in the interfollicular epidermis. Further, low Notch

activity may reduce the proliferation of the hair follicle matrix cells. In addition, low Notch activity may increase the activities of the Shh and the Wnt pathways. Thus, Notch signaling affects both the hair follicle and the epidermal homeostases. Since Notch signaling is required for the late stages of folliculogenesis, upregulation of the Shh and the Wnt activities due to the low Notch activity along with the adverse effect of the low Notch activity on the late stages of the hair follicle development may profoundly affect the hair follicle homeostasis, priming the skin to BCC development.

Declaration of Competing Interest

The authors declare no competing interest.

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