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The WNT/Beta- catenin pathway in melanoma

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1. ABSTRACT

The Wnt/beta-catenin pathway is involved in various cellular activities — including determination, proliferation, migration and differentiation — in embryonic development and adult homeostasis. The deregulation or constitutive activation of the Wnt/beta-catenin pathway may lead to cancer formation. This review focuses on the role of the Wnt/beta–catenin canonical signaling pathway in the melanocyte lineage, and more specifically, in melanoma. Several components of the Wnt/beta-catenin pathway, such as APC, ICAT, LEF1 and beta-catenin are modified in melanoma tumors and cell lines, leading to activation of this signaling. A hallmark of the activation of this pathway is the presence of beta-catenin in the nucleus. Indeed, beta-catenin is found in about 30% of human melanoma nuclei, indicating a potentially specific role for this signaling pathway in this aggressive type of cancer. beta-catenin can induce ubiquitous genes such as *myc* or *cyclinD1*, cell lineage-restricted genes such as *Brn2* and melanocyte-specific genes such as *Mitf-M* and *Dct*. The *Mitf-M* and *Brn-2* genes encode transcription factors. Mitf plays a critical role in melanocyte survival, proliferation and differentiation. Brn-2 is involved in melanoma proliferation. Determining how the Wnt/beta-catenin signaling pathway, alone or with other pathways, orchestrates the induction of target genes involved in a diverse range of activities represents a major challenge in research into melanoma formation and tumor progression.

2. INTRODUCTION

Malignant melanoma is a highly aggressive skin cancer, the incidence of which is dramatically increasing in Western countries. Identification of the molecular mechanism underlying melanoma formation is of particular importance because this cancer has a high metastatic potential and is often resistant to treatment. Both epigenetic and genetic changes have been implicated in melanoma. Mutations have been described in genes encoding proteins involved in the MAP-kinase and Wnt/beta-catenin signaling pathways and in genes encoding cell cycle regulators, such as Ink4a, Arf and CDK4 (1-5) . Constitutive activation of the Wnt/beta-catenin signaling pathway is frequently observed in melanoma. However, only infrequent mutations have been found in genes encoding various components of this pathway that are commonly mutated in other cancers, such as those encoding Apc and beta-catenin (6-8). Wnt/beta-catenin signaling is probably activated by changes in the expression of genes encoding proteins directly involved in the signaling pathway or associated with the regulation of this pathway. A number of components of the Wnt/beta-catenin pathway have been identified, but their functions and regulation in the melanocyte lineage are far from understood. Indeed, in most cases, studies of the biological functions of these components have been carried out in epithelial cells, mostly in colon, breast cancers and hepatocarcinomas (9). Melanocytes are not epithelial cells, and the various components of the Wnt/beta-catenin pathway may function differently in this type of cell. Dissection of the Wnt/beta-catenin pathway in melanoma should provide insight into the melanocyte-specific molecular and cellular mechanisms involved in the initiation and/or progression of melanoma, and the role of this pathway in the malignant transformation of melanocytes.

3. THE WNT/BETA- CATENIN PATHWAY

The Wnt signaling pathway affects a number of cellular functions in embryonic development and adult homeostasis. Wnt proteins activate at least three different intracellular signaling pathways: the Wnt/beta-catenin, the Wnt/Ca^{2+} and the Wnt/planar polarity pathways (10). The type of Wnt protein secreted determines which of these three signaling cascades is activated. The Wnt/beta-catenin pathway is also known as the canonical pathway. The Wnt proteins activating this pathway trigger a cascade of events within the cell, resulting in stabilization of the free cytoplasmic pool of beta-catenin, and the translocation of this protein to the nucleus, where it regulates gene transcription (9, 11). We focus here on the Wnt/beta-catenin signaling pathway and the events involved in regulating beta-catenin levels and the subcellular distribution of this protein.

3.1. Signaling at the membrane

The Wnt family contains at least 19 secreted, cysteine-rich glycoproteins in humans (12). Wnt proteins are difficult to purify in an active form and only a few antibodies are available for their detection. However, RNA detection methods have shown that the expression of Wnt genes is tightly regulated during development. Three main Wnt proteins (Wnt-1, 3a and 8) are involved in the Wnt/beta-catenin pathway. Wnt proteins bind to target cells via two families of receptors: Frizzed (Fzd) and LDL-receptor-related proteins (13, 14). Ten Fzd and two Lrp (5 and 6) proteins are involved in the Wnt/beta-catenin pathway in humans. The canonical Wnt pathway is activated only in response to the formation of a complex containing Wnt, Fzd and Lrp. The formation of this complex induces a cascade of intracellular events, leading ultimately to the stabilization and accumulation of beta-catenin. The affinities and intensities of the associated signals of the various Wnt proteins for the different Fzd-Lrp proteins remain unknown. These elements must be determined if we have to understand the modulation of the Wnt signal in each cell. Moreover, the activation of this signaling cascade is strictly regulated in space and time, with many different regulatory mechanisms to activate or to silence the Wnt/beta-catenin pathway. Wnt induction is blocked by five classes of proteins (Dkk, Wise, Sfrp, Wif and Cerberus) competing for the Wnt-ligand or for the Lrp-Frz-receptor (15-20). The binding of Dkks and Wise to Lrp5/6 renders Lrp-Frz receptors inaccessible to Wnt molecules, preventing induction of the Wnt/beta-catenin pathway. Sfrp, Wif and Cerberus interact with Wnt directly, preventing the binding of Wnt to Frz, also inhibiting the Wnt/beta-catenin pathway.

3.2. Signaling in the cytoplasm

Beta-catenin stabilization is the signature of Wnt/ beta-catenin signaling. In the absence of Wnt, beta-catenin levels are regulated by a multiprotein complex including adenomatous polyposis coli (APC), axin, and glycogen synthase kinase (Gsk3beta). beta-catenin is serine-threonine phosphorylated by Gsk3beta. This phosphorylation leads to the ubiquitination of the protein and its degradation by the proteasome (21). In the presence of Wnt, the Lrp5/6 receptor is serine-phosphorylated by an unidentified kinase. This phosphorylation induces the formation of docking sites for axin at the cell membrane, which inhibits any interaction of axin with Gsk3beta (22, 23). In addition, the interaction of Wnt with Fzd leads to the recruitment of Dishevelled (Dsh) at the membrane and its phosphorylation. This results in the formation of a new Dsh-axin complex at the membrane. So, the cytoplasmic supercomplex containing Dsh, axin and Gsk3beta is disrupted, Gsk3beta is consequently phosphorylated and therefore inactivated. In consequence, beta-catenin starts to accumulate in the cell because it cannot be phosphorylated by Gsk3beta. It is generally thought that this cytoplasmic accumulation leads to the translocation of beta-catenin to the nucleus.

APC may be seen as a negative regulator of Wnt signaling. It presents beta-catenin to the degradation complex, and also captures nuclear beta-catenin and escorts it to the degradation complex in the cytoplasm (24). Wnt signaling is constitutively activated in many tumors; the overexpression of Apc and axin has a tumor-suppressing effect, leading to reversion of the malignant phenotype.

Signaling by the Wnt complex, from the membrane to the cytoplasm, can be mimicked by directly increasing beta-catenin level. This can be achieved by mutating the Gsk3beta phosphorylation sites in beta-catenin, preventing the phosphorylation and degradation of the resulting protein (21). This approach has been used *in vitro* and *in vivo* in many different cell systems, facilitating characterization of the consequences of Wnt induction in each system and identification of the specific target genes.

In epithelial cells, most of the beta-catenin is associated with the cell-cell adhesion molecule, E-cadherin, at the adherens junction. In the adhesion complex, beta-catenin links E-cadherin, via α-catenin, to the actin cytoskeleton. Any free beta-catenin, not bound to cadherins, is ubiquitinated and degraded by the proteasome complex. From this point of view, cadherins play a very important role in regulating the cytoplasmic pool of beta-catenin available for signaling, thereby modulating the response to Wnt induction (25). Some growth factors also affect the cytoplasmic pool of beta-catenin. Cell induction by insulin-like growth factor (IGF) induces the rapid release of beta-catenin into the cytoplasm from the membrane, increasing the pool of cytosolic beta-catenin available for Wnt signaling (26). In other words, IGF interacts with the IGF1R/E-cadherin/catenin complex, inducing the IGF pathway and intracellular E-cadherin signaling, leading to the tyrosine-phosphorylation of beta-catenin and its release into the cytoplasm.

3.3. Signaling in the nucleus

In the absence of Wnt signaling, the lymphocyte enhancer factor (LEF) acts as a transcriptional repressor, recruiting Groucho/transducin-like enhancer (TLE) proteins, which in turn recruit histone deacetylase or histones to the target gene promoters. Changes in chromatin structure are required to relieve the transcriptional repression mediated by these protein complexes (27, 28). In the presence of Wnt, beta-catenin is translocated to the nucleus, where it interacts with multiple proteins: the histone acetylase CBP/p300, a component of the SWI/SNF chromatin-remodeling complex, Brg-1, general transcriptional activators such as TATA-binding protein, the Legless/Pygopus complex, and the LEF/TCF proteins (29, 30). Thus, beta-catenin interacts with Wnt pathway-specific proteins and general factors involved in transcriptional activation. Nuclear beta-catenin levels are controlled by both APC, which can export this protein to the cytoplasm for degradation, and by LEF1, which retains it in the nucleus. The mechanisms controlling the balance between beta-catenin export to the cytoplasm and retention in the nucleus are unclear.

More than 70 Wnt/beta-catenin target genes have been identified. Some target genes encode proteins involved in the Wnt/beta-catenin pathway, such as axin-2 and LEF1, suggesting that there may be a feedback loop controlling the activity of the pathway. beta-catenin target genes encode proteins located in all cell compartments, with a wide diversity of activities. A consensus LEF/TCF binding site "A/T A/T CAAAG" has been identified in the promoters of target genes.

A negative regulator of the Wnt/beta-catenin pathway, ICAT, has been identified by two-hybrid screening in yeast. ICAT prevents beta-catenin from interacting with LEF and p300. Little is known about the physiological role of ICAT, but Satoh *et al.* (31) showed that this protein induced forebrain cells by inhibiting Wnt signaling. ICAT may play a more extensive role in the cell, interfering with the cadherin/beta-catenin complex in the cytoplasm, as suggested by (32).

4. NORMAL AND PATHOLOGICAL MELANOCYTE DEVELOPMENT

Wnt signals have been implicated in both the development of melanocytes from the neural crest and in the malignant transformation of melanocytes. Dissection of the Wnt/beta-catenin pathways operating during development and malignant transformation thus provides complementary information. Indeed, the molecular and cellular mechanisms involved in the proliferation and migration of melanoblasts during development and of melanoma cells during tumor progression are often closely related.

4.1. From neural crest to melanocyte

Melanocytes are derived from neural crest cells — considered by many authors to be the fourth embryonic layer — which give rise to various cell types. In the trunk region, neural crest cell precursors are located at the border of the neural and non-neural ectoderm, in a region constituting the apex of the neural fold. In the trunk, corresponding to somites 8 to 28, neural crest cells emerge from the neural fold and proliferate extensively along two main migration pathways: the dorso-ventral and dorso-lateral pathways. Cells migrating along the dorso-ventral pathway — between the neural tube and the somites — give rise to neurons, Schwann cells (spinal sensory, sympathetic and parasympathetic ganglia), and chromaffin cells in the adrenal medulla. Most of the cells migrating along the dorso-lateral pathway — between the somites and the ectoderm —give rise to melanocytes. In the dorso-lateral pathway, melanoblasts first migrate through the forming dermis. They then cross a basement membrane and penetrate the epidermis, remaining in contact with the basement membrane on the epidermal side (33). Most melanoblasts migrate to the growing hair follicle in mice. These follicular melanoblasts are concentrated in the niche of the hair follicle and differentiate into mature melanocytes, in which melanin will be produced. Thus, in mouse skin, most of the melanocytes are present in the hairs. In contrast, most human melanocytes are found in the epidermis, where they establish close contacts with the neighboring keratinocytes, together forming the epidermal melanin unit. Each melanocyte transfers its melanosome, containing melanin, to about 40 basal keratinocytes. The melanocyte/keratinocyte ratio is constant, suggesting that the proliferation of these cells is tightly controlled. The loss of E-cadherin-mediated interactions between melanocytes and keratinocytes is an important step in the malignant transformation of melanocytes (34).

4.2. From melanocyte to melanoma

The transformation of normal melanocytes into melanoma cells is a multistep process, as in other cancers. A group of melanocytes may proliferate to form a nevus, also known as a mole. Nevus formation does not necessarily result in malignant transformation. Normal melanocytes are dispersed throughout the epidermis, where they interact heterotypically with the surrounding keratinocytes. The formation of nevi by melanocytes tends to favor homotypic cell-cell interactions, with the cells tending to aggregate. Nevus cell proliferation remains self-limiting in most cases. If proliferation gets out of control, then the assembled cells form a primary melanoma. However, the malignant transformation of melanocytes to melanoma may occur directly, without prior nevus formation. Various pathological classifications have been established, and we favor that of Herlyn (35). The horizontal or radial growth phase (RGP) is the first step towards the invasive phenotype. It is followed by a vertical growth phase (VGP), in which tumor cells penetrate into the hypodermis. Metastatic melanoma cells may eventually pass through the endothelium and settle in another part of the body. Invasion and metastasis are highly dependent on changes in adhesion.

Melanocyte homeostasis is controlled by the regulated production of various factors in the skin. These factors include basic fibroblast growth factor (bFGF), endothelin (ET), melanocyte-stimulating hormone (MSH), stem cell factor (SCF), hepatocyte growth factor (HGF), and Wnt. During transformation to melanoma, the autocrine production of these factors may favor autonomous tumor growth.

5. WNT/BETACAT SIGNALING IN THE MELANOCYTE LINEAGE

Canonical Wnt signaling has been extensively studied in developmental models (such as neural crest cell formation) and in the formation of various cancers, including melanoma. Interestingly, in cases in which Wnt/beta-catenin signaling controls cell fate, it also controls stem cell activity and oncogenesis.

5.1. Wnt/beta-catenin signaling in melanoblasts

Wnt/beta-catenin signaling is important in many developmental processes including the formation of neural crest-derived melanocytes. The contribution of the Wnt/beta-catenin signaling to the generation of various neural-crest derivatives, early in neural-crest emigration and expansion, has been reviewed elsewhere (36-39). The Wnt factors involved in the melanocyte lineage are Wnt-1 and Wnt-3a. Both these factors have been implicated in earlier events in dorsal neural tube derivative specification. They have also been implicated in pigment cell fate: transgenic mice deficient for both Wnt-1 and Wnt-3a have no neural-crest melanocytes (40), and migrating murine neural-crest melanocytes requires Wnt-1 for both expansion and differentiation (41). beta-catenin has been directly implicated in melanoblast determination, in various species, by means of gain- and loss-of-function approaches. In zebrafish, the overproduction of beta-catenin in premigratory neural crest cells induces pigment cell formation (42), and in mice, the conditional loss of function of beta-catenin has been shown to lead to a loss of melanoblasts (43). These results demonstrate the importance of the Wnt/beta-catenin signaling pathway in cell fate and cell expansion. However, the significance of Wnt/beta-catenin signaling in late melanoblast development, such as late proliferation and invasion of the epidermis from the dermis has not yet been studied. This aspect of melanoblast development remains a mystery.

5.2. Wnt/beta-catenin signaling in melanocytes and melanoma

The importance of Wnt/beta-catenin signaling in melanocytes and melanoma has been studied at the molecular and cellular levels. At the molecular level, identification of the Wnt/beta-catenin target genes in melanocytes constituted a major step towards understanding the consequences of this signaling. At the cellular level, it remains difficult to identify a correlation between activation of the Wnt/beta-catenin cascade and a specific cellular event.

5.2.1. Signaling at the membrane

5.2.1.1. Wnt

The principal Wnt proteins involved in the canonical Wnt/beta-catenin pathway are Wnt-1, Wnt-3a and Wnt-8. Wnt-8 has never yet been implicated in any aspect of melanocyte lineage differentiation, but other Wnt molecules such as Wnt-2, 4, 5a, 7b, and 10b may be involved. These Wnt proteins have been found in melanocytes or melanoma cells or their immediate environment and the non-canonical Wnt/beta-catenin pathway has been shown to affect the Wnt/beta-catenin pathway itself. We therefore decided to include these proteins in this review.

Very little is known about the physiological source of Wnt proteins and the spatial and temporal patterns of production of these proteins in neonatal and adult skin. Wnt-4 and Wnt-10b are present in adult mouse epidermis (44), but their possible role in melanocyte homeostasis remains unclear.

The discovery of Wnt-1 was largely due to the oncogenic activity of this protein in mouse mammary epithelia (45). However, there are currently few known examples in which Wnt proteins as such have been implicated in human tumors, but very often other members (APC, axin, beta-catenin) of this pathway are involved. A pilot study of Wnt production in nevi and melanoma reported the presence of large amounts of Wnt-2, Wnt-5a, Wnt-7b and Wnt-10b in all nevi tested. However, the pattern of Wnt production did not correlate with Clark's classification or with the depth of invasion in melanoma (46). Further evidence that Wnt-5a and Wnt-2 play a role in melanoma has been provided by other studies. Wnt-5a was found to be upregulated in about 50% of melanoma cell lines (47). Wnt-5a increases cell motility and invasion in melanoma (48), consistent with its high levels of production in this highly aggressive tumor (49). Wnt-5a signals via non canonical pathways but also inhibits the

Wnt/beta-catenin pathways by activating Gsk3beta, thereby stimulating beta-catenin degradation (50). The role of Wnt-5a in melanoma if far from completely understood as high levels of this protein and its activity are linked to aggressiveness in melanoma, in contrast to the downregulation of beta-catenin and the tumor suppressor activity observed in other types of tumor (51). Wnt-2 is also overproduced in human melanoma cell lines and tumors (52). Antibodies against Wnt-2 suppress tumor growth *in vivo* by inducing programmed cell death, consistent with the possible future use of these antibodies as a therapeutic agent.

5.2.1.2. DKK

Fibroblasts in the skin produce different members of the DKK family, depending on their precise location: DKK1 in palmar and plantar skin and DKK3 in skin in other areas (53). DKK1 decreases melanocyte proliferation and melanin synthesis, probably by inhibiting the canonical Wnt signaling pathway. In contrast, DKK3 has no effect on melanocyte growth and function. As suggested by Yamaguchi *et al.*, this observation may partly explain the hypopigmentation of skin on the palms and soles and the lack of migration of melanocytes to these areas, containing high levels of DKK1 protein, during development. The role of DKK proteins in melanoma is totally unknown.

5.2.2. Signaling in the cytoplasm

5.2.2.1.Beta-catenin

A possible role of aberrant Wnt signaling in melanoma was first suggested by the identification of a mutated beta-catenin as a melanoma-specific antigen recognized by tumor-infiltrating lymphocytes (54). The discovery of mutations in beta-catenin or APC associated with the presence of abnormally large amounts of beta-catenin protein in seven of 26 melanoma cell lines studied later suggested that the canonical Wnt pathway plays a major role in this cancer (5). Several other studies have confirmed that beta-catenin is frequently found in the cytoplasm or nucleus in melanoma (6, 7, 55). However, the frequency of beta-catenin and APC mutations has been a matter of controversy for some years. It has become clear that the rate of beta-catenin mutation is lower than initially thought and higher *in vitro* than *in vivo.* A compilation of various analyses showed that nine of 107 melanoma cell lines (8.5%) displaying beta-catenin gene mutations (5, 7, 54, 56); our laboratory, [18 cell lines]), and seven of 210 melanomas "*in vivo*" (3.3%) displayed such mutations (6-8); our laboratory, [25 melanomas]). The higher rate of beta-catenin mutation in melanoma cell lines may be accounted for by two non-mutually exclusive hypotheses: (i) beta-catenin mutations may arise stochastically in culture, with cells with beta-catenin mutations having shorter doubling times. Under these conditions, the selection of melanoma cells with beta-catenin mutations is likely to occur. (ii) beta-catenin mutations may already be present in the tumor and the tumor cell immortalization may be more efficient in cells bearing beta-catenin mutations. The consequences of beta-catenin activation in melanocytes are not known. However, it has been shown that the ectopic production of beta-catenin in melanoma cells stimulates cell proliferation and clonogenic growth in these cells, which have no endogenous nuclear beta-catenin (57). An *in vivo* approach involving the production of activated beta-catenin in melanocytes should improve our understanding of the specific role of canonical Wnt signaling in melanomagenesis.

5.2.2.2. APC

APC mutations are not frequent in melanoma cells lines and tumors (2.5%) (8, 58). Hypermethylation of APC promoter 1A seems to be more frequent (15% of cell lines and biopsy samples) but does not necessarily increase Wnt signaling (58, 59). However, the downregulation of APC levels linked to hypermethylation of the promoter 1A in melanoma is associated with poor prognosis (59). The stable suppression of APC transcripts in melanoma cells increases cell proliferation and reduces invasive capacity on collagen type I (58). Thus, the loss of APC promotes cell proliferation but does not necessarily favor invasion of the epidermis and/or dermis by malignant cells.

5.2.2.3. GSK3beta

In melanoma and melanocyte cell cultures, GSK3beta phosphorylates Ser298 of Mitf (60). This serine phosphorylation enhances Mitf binding to the tyrosinase promoter, increasing the melanin content of the cell.

GSK3beta is serine-phosphorylated (Ser9) and inactivated via the insulin and Wnt pathways (61). Akt has been shown to phosphorylate GSK3beta in insulin induction but the kinases phosphorylating GSK3beta during Wnt induction are unknown. Akt is induced by various tyrosine kinase receptors, such as PDGFR and IGF1R. After induction by insulin or PDGF, the phosphotyrosines on IGF1R or PDGFR participate in the activation of cytoplasmic signaling pathways. The tyrosine-phosphorylated IGF1R (or PDGFR) recruits and phosphorylates various cytoplasmic proteins, such as phosphatidylinositol 3-kinase (PI3K). The recruitment and tyrosine phosphorylation of PI3K by IGF-1R activates this enzyme. PI3K activation leads to the activation of PDK1 (phosphatidylinositol-dependent kinase 1). At this time, Akt is appropriately localized at the membrane, facilitating its phosphorylation on threonine 308 by PDK1 and on serine 473 by PDK2. The identity of PDK2 is unclear and it has been suggested that PDK2 is actually Akt. In conclusion, once AKT is phosphorylated on T308 and S473, it becomes fully active and can phosphorylate GSK3beta. In melanocytes and melanoma cells, induction of the Wnt and insulin pathways should repress GSK3beta and tyrosinase activities and induce cell proliferation.

It has been shown that cAMP inhibits the activation of GSK3beta by PI3K and Akt, via a protein kinase A-independent mechanism (62). Strict regulation of GSK3beta, depending on the environment, controls the activity of one of the master regulators of normal and pathological melanocyte development, Mitf.

In conclusion, the constitutive activation of Wnt/beta-catenin signaling pathways is observed in one third of melanomas, but the molecular mechanisms underlying this activation are still not fully understood. All

components of the Wnt/beta-catenin cascade may be involved alone, or in collaboration with other proteins altered during oncogenesis.

5.2.3. Signaling in the nucleus

5.2.3.1. LEF

LEF1, a member of the LEF/TCF family, plays a specific role in the melanocyte lineage. Firstly, LEF1 (and not TCF1) interacts with the melanocyte master transcription factor MITF-M, and secondly, LEF1 is overproduced in melanomas, in which other members of this family are produced in only small amounts (63). Interactions between LEF1 and MITF-M seem to be important for activation of the *Dct* promoter because LEF1 and MITF-M, alone, each have only weak effects on transcriptional activation (64, 65). This interaction also regulates the *Mitf-M* promoter via a regulatory element that does not involve direct binding to MITF-M. LEF activity can therefore be regulated by MITF-M, which in this case functions as a nuclear mediator of Wnt/beta-catenin pathways. The consequences of LEF1 overproduction for transformation have not yet been investigated.

5.2.3.2. ICAT

One study has focused on ICAT production in melanoma, and showed the levels of this molecule to be low in most of the tumors analyzed (8). Other studies on ICAT production and function are required to increase our understanding of the role of ICAT in melanoma progression and metastasis.

5.2.3.3. Proven targets of beta-catenin in melanocytes and melanoma

A large number of genes have been shown to be targets of beta-catenin/LEF (about 70). In the melanocyte lineage, *Mitf-M, Brn2,* and *Dct* are among the genes formally identified as beta-catenin targets.

5.2.3.3.1. Mitf-M

The link between Wnt/beta-catenin signaling and the transcription program underlying melanocyte formation and function was revealed when it was found that the promoter driving production of the microphthalmia-associated transcription factor, Mitf, was a target of Wnt/beta-catenin signaling in both zebrafish and mouse (42, 66). The *Mitf* gene has five promoters, generating five different isoforms, one of which is specific to the melanocyte lineage (Mitf-M). The human and mouse Mitf-M promoters contain beta-catenin/LEF binding sites in a region containing multiple target sites for other transcription factors, such as Sox10, the cyclic-AMP responsive factor CREB and the paired homeodomain transcription factor (Pax3). Thus, the Wnt/beta-catenin pathway controls *Mitf-M* gene expression in concert with multiple transcription factors belonging to other signaling cascades.

Mitf is a basic helix-loop-helix leucine zipper transcription factor that regulates genes essential for pigmentation and survival; mutations in *Mitf-M* result in melanocyte deficiency in humans and mice (67, 68). It was recently demonstrated that Mitf-M induces cell cycle arrest in G1 that is dependent on the p21 cyclin-dependent kinase inhibitor (69). This may explain how Mitf-M induces exit from the cell cycle and activates the melanocyte-specific transcription program. Mice without beta-catenin in their neural crest cells generate a fewer Mitf-positive cells, demonstrating that beta-catenin plays a specific role in determining the fate of melanocytes (43, 70). beta-catenin is produced throughout melanocyte formation during development and in mature melanocytes (71). However, the Wnt/beta-catenin pathway has not been definitively demonstrated to be required for *Mitf* expression throughout development of the melanocyte lineage (72). Thus, aberrant Wnt/beta-catenin cascades may ultimately lead to the deregulation of Mitf-M expression, with effects on crucial cell functions (differentiation, proliferation, survival) during development and in adult life. The crucial importance of Wnt/beta-catenin signaling in melanocytes is highlighted by the essential role of its downstream *Mitf-M* target gene.

5.2.3.3.2. Dct

The production of dopachrome tautomerase (Dct), an early melanoblast marker, is regulated by the Wnt/beta-catenin pathway. In mouse mutants lacking beta-catenin neural-crest derivatives, no Dct is detected in the cells (43, 70). Dct gene transcription is regulated by a complex containing MITF and LEF1 (Yasumoto *et al.*, 2002). LEF1 also interacts with Pax3 and the Groucho-related corepressor Grg4 in melanocytes. In the presence of activated beta-catenin, Grg4 and Pax3 are removed from the Dct promoter and no longer interact with LEF1, resulting in the loss of Pax3-mediated repression (70). These findings led Lang *et al.* to propose a model in which Pax3 is a key factor in the determination of melanocyte fate and inhibition of the differentiation program in stem cells. Wnt/beta-catenin activation in stem cells relieves Pax3-mediated repression, allowing *Dct* expression and Mitf-mediated activation of the transcription of target genes encoding proteins involved in differentiation.

5.2.3.3.3. Brn-2

The POU domain transcription factor Brn-2 has been implicated in the control of proliferation and is strongly upregulated in melanoma (73-75). The downregulation of Brn-2 production in melanoma cells is associated with changes in morphology and a loss of melanocytic and neural crest markers, including Mitf and tyrosinase (73, 74). Decreases in Brn-2 production are also associated with a loss of tumorigenicity of these cells in nude mice (73). It has therefore been suggested that Brn-2 plays an important role in the proliferation and determination of the melanocyte lineage. The absence of Brn-2 from early melanoblasts (embryonic day 11.5 in mouse) strongly suggests that Brn-2 is not important at this period of the development in this lineage (75). However, Brn-2 may nonetheless be involved in melanoblast stem cell renewal in the niche of the hair bulbs. An active LEF/TCF binding site has been identified in the *Brn-2* promoter (75). This is of particular interest because it implies that beta-catenin can induce a protein (Brn-2) involved in cell proliferation and a protein (Mitf) involved in cell differentiation that inhibits cell proliferation.

5.2.3.3.4. Nr-CAM

The Nr-CAM (neuronal cell adhesion molecule) gene was identified by microarray analysis as a target gene of beta-catenin (76). This gene is strongly expressed in melanoma cells and this strong expression is correlated with enhanced motility and tumorigenesis.

6. CONCLUSION

Several studies have shown that the Wnt/beta-catenin pathway regulates melanocyte development. The identification of Wnt/beta-catenin target genes in the melanocyte lineage and their associated specific functions has shown that this pathway is involved in a number of processes in cells, including proliferation, survival, motility and differentiation. The deregulation of this pathway is often seen in melanoma, but the molecular and cellular mechanisms involved are unclear. In particular, mutations in the beta-catenin and APC genes have been identified in melanoma but at too low a frequency to account for activation of the Wnt/beta-catenin pathway in one third of the melanomas analyzed. Multiple proteins regulate the Wnt/beta-catenin cascade, extracellularly, at the membrane, in the cytoplasm and in the nucleus. Little is known about the identity and production profiles of these proteins involved in regulating signaling in the melanocyte lineage. The way in which these regulators affect the Wnt/beta-catenin pathway in melanocyte homeostasis and during melanoma formation is an important issue that has received little attention to date. Gain-and-loss-of-function experiments with various components of the Wnt/beta-catenin cascade in cell culture or animal models will be of particular value for evaluating the contribution of each protein to malignant transformation.

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Abbreviations: APC: adenomatous polyposis coli, ICAT: inhibitor of β-catenin and Tcf; LEF1: lymphoid-enhancing factor 1, Mitf: microphthalmia-associated transcription factor, Fzd: Frizzed, LDL: low-density lipoprotein receptor-related protein family, IGF: insulin-like growth factor, TLE: transducin-like enhancer, CBP: CREB binding protein, CREB: the cyclic-AMP responsive factor, Dkk: Sfrp, Wif and Cerberus, Gsk3: glycogen synthase kinase, Dsh: Dishevelled, bFGF: basic fibroblast growth factor, ET: endothelin, MSH: melanocyte-stimulating hormone, SCF: stem cell factor, HGF: hepatocyte growth factor, DKK: dickkopf, PI3K: phosphoinositide3-kinase, Sox10: SRY Box containing gene 10, Pax3: paired homeodomain transcription factor, PDK1: phosphoinositide-dependent kinase 1, PDK2: phosphoinositide-dependent kinase 2, RGP: radial growth phase, VGP: vertical growth phase,

Key Words: APC, ICAT, LEF1, IGF, Gsk, cAMP, CBP, SCF, PDK, MSH, Sox, DKK, RGP, VGP, Pax, FGF, Dkk, Sfrp, CREB, Adenomatous Polyposis, Frizzled, Transcription factor, Insulin, Kinase, Hepatocyte, Melanocyte, Development, Tumor, Skin, Wnt, Beta catenin, Review

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