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Wnt/β-Catenin Signaling Pathway in Canine Skin Melanoma and a Possibility as a Cancer Model for Human Skin Melanoma

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1. Introduction

Cutaneous melanoma is a relatively common skin tumor in the dog, accounting for 5 to 7% of canine skin tumors (Bostock, 1986; Rothwell et al., 1987). This tumor originates from the transformation of the melanocytes, which are present mainly in the epidermis and hair follicles. The transformed melanocytes lose their normal contact with surrounding keratinocytes and tend to proliferate to surrounding tissues (Smith et al., 2002). Breed has been reported to be prognostically significant; more than 75% of melanomas in Doberman pinschers and miniature schnauzers are behaviorally benign, whereas 85% of melanomas in miniature poodles are malignant (Bolon et al., 1990).

Cutaneous melanoma can be behaviorally benign or malignant, and can occur anywhere on the body. Some investigations into the molecular and genetic basis of melanoma were previously performed (Table 1), but the etiology of melanoma is largely unknown. These tumors usually can be diagnosed by simple fine-needle aspiration cytology; however, histologic examination is important to determine the potential for malignancy (Aronsohn & Carpenter 1990; Bolon et al., 1990).

The therapeutic treatment for local cutaneous melanoma in the dog is surgical excision. It shows an excellent prognosis after surgical excision of benign tumors, whereas the prognosis of tumors with malignant criteria is guarded or poor; metastatic rates of 30 to 75% have been reported after the surgery (Withrow & Vail 2007). Systemic chemotherapy for malignant melanoma has shown little promise. Some agents, including mitoxantrone (Ogilvie et al., 1991), doxorubicin (Moore, 1993), dacarbazine (Gillick & Spiegle, 1987), and carboplatin (Rassnick et al., 2001) have been used for treatment. However, in general, the effects of these drugs have been poor and the durations of the effects have been shortlived. A few researches have been conducted to develop effective therapeutic targets in the mechanism of melanoma progression and/or metastasis; however, there is no effective strategy until the present time (von Euler et al., 2008; Han et al., 2010; Thamm et al., 2010).

Factor	Normal function	Abnormality	Reference
p53 gene	: activate DNA repair protein : hold the cell cycle at the G1/S phase : initiate apoptosis if the DNA damage proves to be irreversible	: exclusion of p53 from the nucleus	Koenig et al., 2002
Metallothionein	: capture harmful oxidant radicals	: inactivates p53 functions	Dincer et al., 2001
RB-1 gene	: hold the cell cycle at the G1/S phase	: exclusion of RB-1 from the nucleus	Koenig et al., 2002
P16/P21/P27	: inhibits the activity of CDK2 and CDK4	: loss or reduction of ink-4a gene	Koenig et al., 2002
PTEN gene	: inhibits the AKT signaling pathway	: loss or reduction of PTEN expression	Koenig et al., 2002
N-RAS	: a member of the RAS signal transduction	: mutation of N-RAS gene	Mayr et al., 2003
VEGF	: important signaling protein in vasculogenesis and angiogenesis	: improves the angiogenesis in tumors	Rawlings et al., 2003

Table 1. Cutaneous melanoma-related molecular and genetic factors in dogs.

2. Wnt/β-catenin signaling pathway

2.1 Normal regulation of the Wnt/ β-catenin signaling pathway

2.1.1 Wnt signaling: ligands and receptors

The Wnt genes encode a group of 19 secreted cysteine rich glycoproteins that act as ligands to activate receptor-mediated signaling pathways that control cell differentiation, cell proliferation, and cell motility (Chlen & Moon, 2007). Wnt proteins are defined by sequence rather than by functional properties. Because it is difficult to solubilize active Wnt molecules, the purification of Wnts is complicated. Its insoluble nature is caused by the lipid modification causing hydrophobic state. For example, murine Wnt3a, the first identified Wnt protein, undergoes two kinds of lipid modification; first is the addition of palmitate to cysteine 77 causing diminishing the ability to activate β-catenin signaling and second is the addition of palmitoleoyl to serine 209 causing Wnt3a accumulation in the endoplasmic reticulum (Willert et al., 2003; Takada et al., 2006; Galli et al., 2007; Komekado et al., 2007). Until now, *Drosophila* Wingless (Wg) is the most investigated Wnt molecule *in vivo*. Those researches indicate that the hydrophobicity and membrane localization of Wg are lost when Porcupine (Porc) gene is eliminated (Zhai et al., 2004; Takeda et al., 2006; Hausmann et al., 2007). Porc encodes a transmembrane ER protein responsible for Wg lipid modification. Consequently, it suggests that Porc is a important mediator of both lipid modification and membrane targeting of Wg.

In Vertebrates, there are two kinds of Wnt signaling pathway; β-catenin-dependent (canonical) and β-catenin-independent (non-canonical) signaling pathways. Canonical or β-catenin-dependent signaling pathway is also called as the Wnt/β-catenin signaling

pathway. Two distinct receptor families are important for the Wnt/β-catenin signaling pathway: the Frizzled (Fz) seven transmembrane receptors and the LDL receptor-related proteins 5 and 6 (LRP5 and LRP6) (He et al., 2004; Logan and Nusse, 2004). In Wnt/Fz interaction, Wnt proteins bind directly to the cysteine-rich domain of Fz receptor; however, without a cognate ligand, the complex of Wnt/Fz cannot activate Wnt signaling, indicating Fz activation is ligand dependent. For participating to Wnt signaling, LRPs need to transport to the cell surface by a specific molecule called Boca in *Drosophila* or Mesd in mice (Culi & Mann, 2003; Hsieh et al., 2003). Two LRPs act different functions at different developmental process; LRP6 is more important for embryogenesis while LRP5 is critical for adult bone homeostasis. In most data, Wnt induces the formation of Fz-LRP5/6 complex to activate Wnt signaling pathway.

2.1.2 Wnt signaling: off state

Cytoplasmic β-catenin phosphorylation and degradation is the characteristic feature (Fig. 1). The Axin protein coordinates sequential phosphorylation of β-catenin at serine 45 by CK 1α and then threonine 41, serine 37 and serine 33 by glycogen synthase kinase-3β (GSK-3β) through the interaction with separate domains of Axin (Kimelman & Xu, 2006). After then, the E3 ubiquitin ligase β-Trcp binds to serine 33 and 37 of β-catenin, and leads to β-catenin ubiquitination and degradation. GSK3 and CK1 also phosphorylate Axin and Adenomatous polyposis coli (APC), resulting in the enhancement of β-catenin phosphorylation and degradation through increased association between Axin/APC and β-catenin (Kimelman & Xu, 2006; Huang & He, 2008). Additional aspects on Axin complex deserve further discussion.

1. Serine/threonine phosphatases, PP1 and PP2A, counteract the role of GSK3 and/or CK1 in the Axin complex. PP1 promote the dissociation of the Axin complex through the dephosphorylation of Axin while PP2A dephosphorylates β-catenin. Both reactions result in reduced β-catenin degradation (Luo et al., 2007; Su et al., 2008).
2. Axin concentration is different among each component in *Xenopus*, indicating that Axin controls the rate of the complex assembly (Lee et al., 2003). However, it is not sure whether the different concentration of Axin in each component is universal to other organisms.

APC is a part of the Axin complex causing β-catenin phosphorylation. APC also inhibit the dephosphorylation of β-catenin, and thereby enhancing β-catenin degradation (Su et al., 2008). APC and Axin compete for same β-catenin, and APC also remove phosphorylated β-catenin from Axin for degradation and for making Axin available for another β-catenin phosphorylation (Xing et al., 2003; Kimelman & Xu, 2006). APC also promote to remove β-catenin from the nucleus and suppress β-catenin target genes.

Interestingly, APC can promote Wnt signaling through the acceleration of Axin degradation (Lee et al., 2003; Takacs et al., 2008). It depends on the APC amino acid terminal that is not involved in β-catenin degradation. Conversly, Axin can also promote APC degradation (Choi et al., 2004). However, the mechanisms of both APC and Axin degradation are not known.

2.1.3 Wnt signaling: on state

Wnt/β-catenin signaling pathway is important in many developmental processes including the formation of neural crest-derived melanocytes (Larue & Delmas 2006). In neural-crest

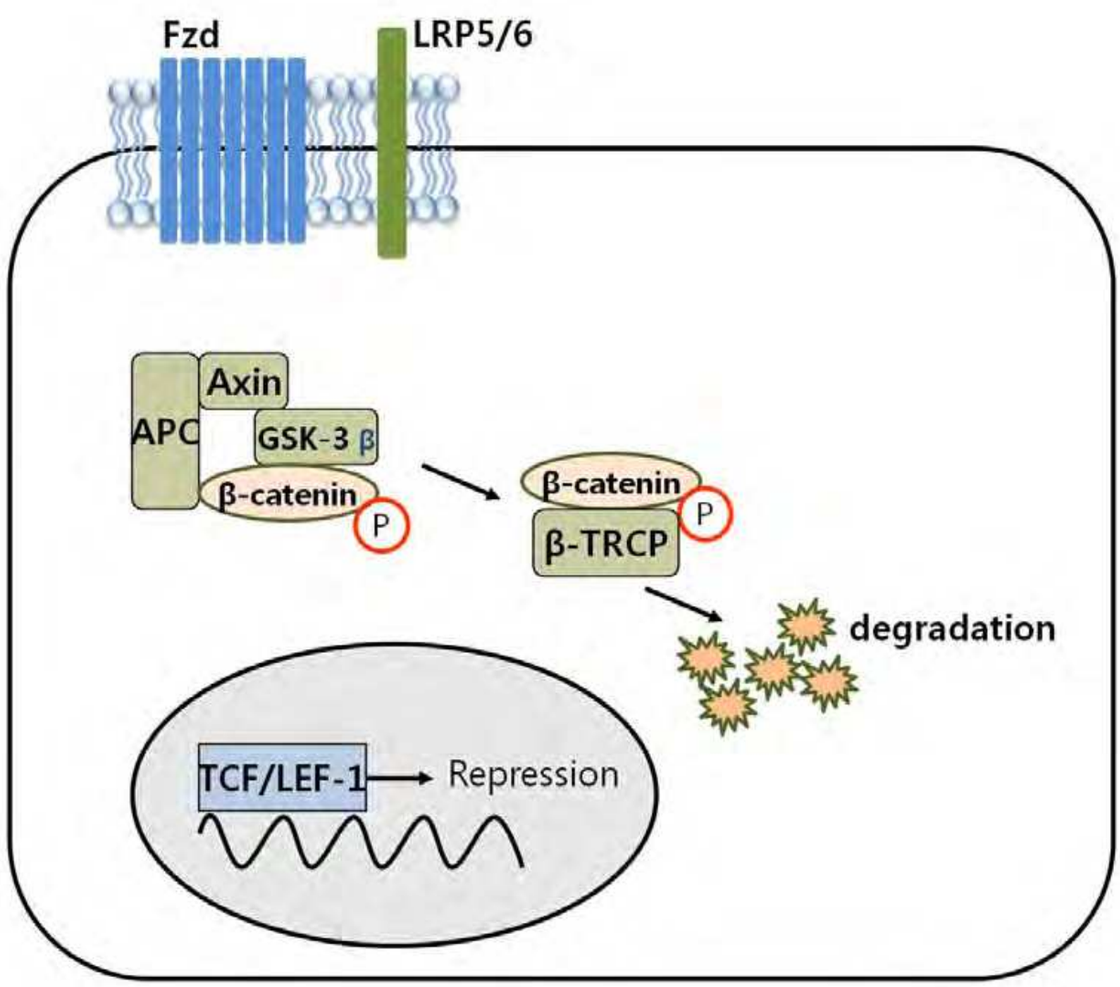

Fig. 1. Regulation of Wnt/β-catenin signaling pathway. In the absence of Wnt signals, the cellular concentration of free β-catenin is low, because a complex of the adenomatous polyposis coli (APC), glycogen synthase kinase 3β (GSK-3β) and axin protein is responsible for regulating the level of β-catenin, via GSK-3β-mediated phosphorylation of specific serin and threonine residues in β-catenin.

emigration and expansion during the embryogenesis, this pathway has been implicated in the migration and differentiation of the melanoblast by β-catenin dependent manner (Fig. 2) (Dunn *et al.* 2000; Ikeya *et al.* 1997). A hallmark of the activation of the pathway is the accumulation of β-catenin protein in the cytoplasm. Wnt signals influence the proteins that regulate β-catenin stability through several mechanisms and thereby induce the activation of Wnt target gene through the nuclear translocation of β-catenin as follows;

1. After the signaling of Wnt proteins, the receptor complex transduces a signal to several intracellular proteins that include Dishevelled (Dsh) through a direct binding between Dsh and Fz. Dsh is a ubiquitously expressed cytoplasmic protein and interacts with a C-terminal cytoplasmic Lys-Thr-X-X-X-Trp motif of Fz (Umbhauer et al., 2000). During the process, Dsh is also phosphorylated by several protein kinases such as Par1 (Yanagawa et al., 1995; Sun et al., 2001). Wnt-induced LRP phosphorylation is also important for the receptor activation. LRP5 and LRP6 have five repetitive Pro-Pro-Pro-(SerTrp)Pro [PPP(S/T)P] motifs, which are involved in constitutive β-catenin signaling (Tamai et al., 2004; MacDonald et al., 2008). GSK3 and CK1 are responsible for PPP(S/T)P phosphorylation after the stimulation of Wnt proteins (Davidson et al., 2005; Zeng et al., 2005). These dual phosphorylated motifs become a binding site for the Axin complex and recruit Axin to LRP6 under Wnt stimulation. Zeng et al. (2008) indicates that GSK3 is responsible for most PPP(S/T)P phosphorylation in GSK α/β null cell lines. Consequently, Axin/GSK3 interaction mediates LRP6 phosphorylation, resulting in the accumulation of β-catenin in the cytoplasm.
2. As described above, the receptors transduce a signal to several intracellular proteins that include Dishevelled (Dsh). Activated Dsh acts as a suppressor of the proteasome-mediated degradation, which is controlled by a complex of glycogen synthase kinase-3β (GSK-3β), Axin, Adenomatous polyposis coli (APC), and β-TrCP. In particular, Wnt signals promote to detach Axin from the complex and thereby, induce β-catenin stabilization (Cliffe et al., 2003; Tamai et al., 2004). Consequently, stabilized β-catenin accumulates in the cytoplasm.
3. In vertebrates, Caprin-2, a cytoplasmic protein, binds to LRP6 and promotes its phosphorylation by GSK3 (Ding et al., 2008). In addition, Caprin-2 promotes the formation of LRP6-Axin-GSK3 complex.
4. Microtubule actin cross-linking factor 1 (Macf1) is a member of the protein that links the cytoskeleton to junctional proteins. It seems that this protein is a transporter of Axin to LRP6. Its function may be vertebrate-specific (Chen et al., 2006).
5. Cytoplasmic β-catenin can enter and retain in the nucleus (Henderson & Fagotto, 2002; Stadeli et al., 2006). Though the mechanism of the movement is not well understand, Henderson and Fagotto (2002) suggests that nuclear pore protein interacts directly with β-catenin, resulting in the movement to the nucleus. A recent study indicates that JNK2 and Rac1 constitute a cytoplasmic complex with β-catenin and thereby promote its nuclear translocation (Wu et al., 2008).
6. In the nucleus, β-catenin interacts with transcription factors such as lymphoid enhancer-binding factor 1/T cell-specific transcription factor (LEF/TCF) DNA-binding proteins. In the absence of Wnt signal, TCF acts as a repressor of Wnt target genes, however, β-catenin convert the TCF repressor into a transcriptional activator complex and thereby activates the transcription of the target genes including c-myc and cyclin D1 that cause a cell proliferation and differentiation. The target genes of Wnt/β-catenin signaling pathway are summarized in Table 2.

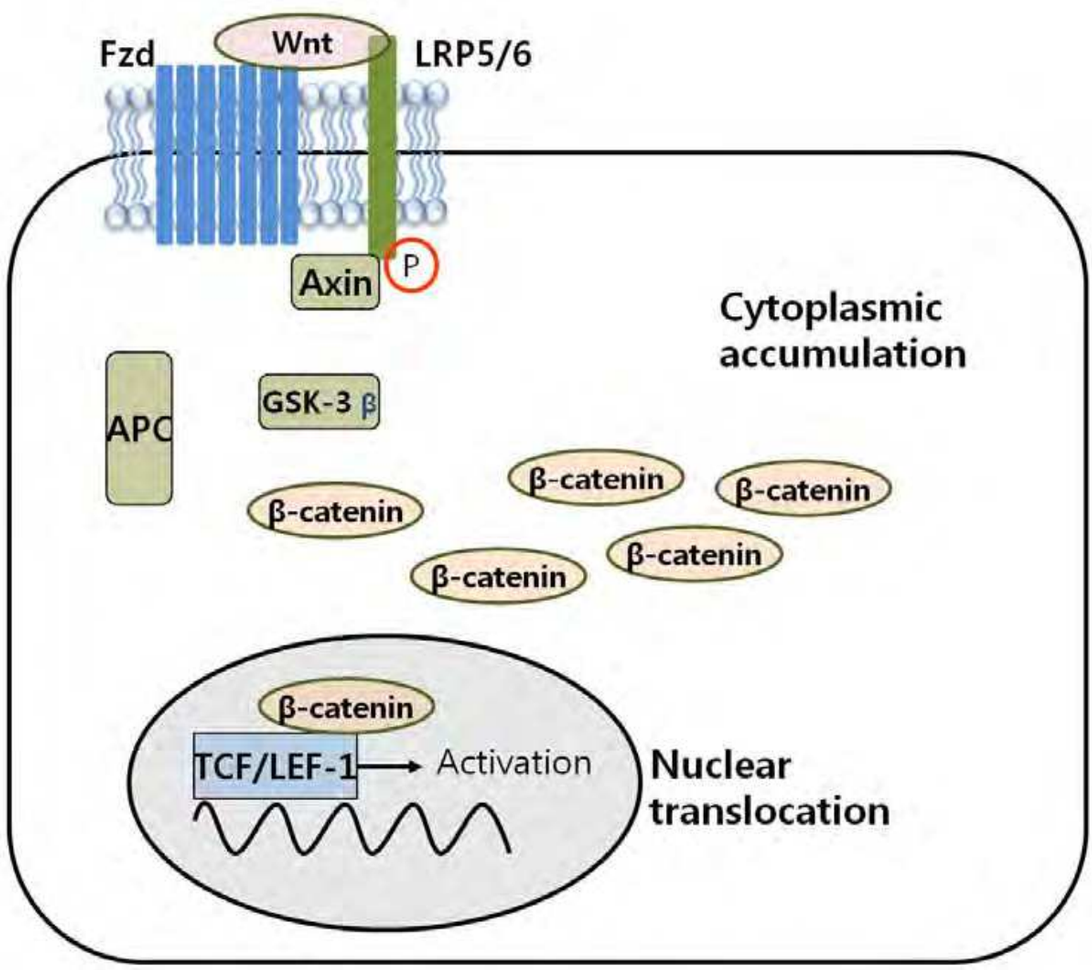

Fig. 2. Regulation of Wnt/β-catenin signaling pathway. Upon Wnt signaling, the activity of GSK-3β is inhibited by Dsh, hence β-catenin is accumulated in the cytoplasm. The accumulated β-catenin can enter the nucleus and activates the target genes such as *LEF-1*, c-myc and cyclin D1.

Target gene	Changes in target gene expression	Mediator	Reference
Fz	Suppress	Wnt	Muller et al., 1999
Dfz2	Suppress	Wnt	Cadigan et al., 1998
Dfz3	Activate	Wnt	Sato et al., 1999
Fz7	-	Wnt	Willert et al., 2002
LRP	Suppress	Wnt	Wehrli et al., 2000
Axin2	Suppress	β-catenin	Jho et al., 2002
β-TCRP	Suppress	β-catenin	Spiegelman et al., 2000
TCF1	Suppress	TCF	Roose et al., 2001
LEF1	Activate	β-catenin	Hovanes et al., 2001

Table 2. The target genes of Wnt/β-catenin signaling pathway.

2.2 Dysregulation of the Wnt/ β-catenin signaling pathway

2.2.1 Wnt signaling in human diseases

In human medicine, mutations of the Wnt/β-catenin signaling pathway have been introduced as a cause of many hereditary disorders, cancer, and other diseases (Table 3). These include mutations in several components of Wnt signaling pathway such as ligands and receptors. Also, the loss of E-cadherin or the abruption of cadherin-catenin complex by MET/RON receptor tyrosine kinases (RTKs) can cause the abnormal accumulation of β-catenin into the cells (Danikovitch-Miagkova *et al*. 2001; Nelson and Nusse 2004).

Gene	Function	Disease	References
Wnt3	Ligands	Tetra-amelia	Niemann et al., 2004
Wnt4		Mullerian-duct regression and virilization	Biason-Lauber et al., 2004
Wnt7a		Fuhrmann syndrome	Woods et al., 2006
Wnt10a		Odonto-onchyo-dermal hypoplasia	Adaimy et al., 2007
LRP5	Receptor	Hyperparathyroid tumor High bone mass Osteoporosis-pseudoglioma FEVR eye vascular defects	Gong et al., 2001; Boyden et al., 2002; Little et al., 2002; Toomes et al., 2004; Bjorklund et al., 2007
LRP6		Early coronary disease and osteoporosis	Mani et al., 2007
Axin1	Facilitates β-catenin degradation	Caudal duplication, cancer	Satoh et al., 2000; Oates et al., 2006
Axin2		Tooth agenesis, cancer	Liu et al., 2000; Lammi et al., 2004
APC	Facilitates β-catenin degradation	Familial adenomatous polyposis, cancer	Kinzler et al., 1991; Nishisho et al., 1991
β-catenin	Signal transducer	Cancer	Korinek et al., 1997; Morin et al., 1997
TCF	Transcriptional partner of β-catenin	Type II diabetes (?)	Florez et al., 2006; Grant et al., 2006

Table 3. Human diseases caused by mutations of the Wnt/β-catenin signaling pathway

Association of dysregulated Wnt/β-catenin signaling pathway with human cancer has also been documented through constitutively activated β-catenin signaling. Dysfunction of APC/Axin/GSK3 complex or β-catenin mutation (especially in exon 3) blocks its degradation and consequently, accumulated β-catenin leads to excessive cell proliferation that predisposes cells to tumorigenesis. Particularly, in human skin melanoma, dysregulated Wnt/β-catenin signaling pathway is essential for metastasis. In this tumor, the transformation of normal melanocytes into melanoma cells is a multistep process (Albino et al., 1991; Haass et al., 2005; Meier et al., 2000; Shih & Herlyn 1993). The first step, considered as benign, is associated with the formation of a nevus and the radial growth phase (RGP). During RGP, melanocytes tend to proliferate superficially to the basement membrane of the

epidermis. During the next stage, the vertical growth phase (VGP), the cells bypass senescence to proliferate actively in a vertical manner in the dermis, crossing the basement membrane. At this stage, the cells migrate and become clearly invasive (Fig. 3). In RGP and VGP, the alteration of Wnt/β-catenin signaling pathway has been considered to act fundamental roles (Sanders et al. 1999; Larue and Beermann 2007). However, in human, only infrequent mutation has been found in genes encoding the components, such as APC and β-catenin. Therefore, it is presumed that Wnt/β-catenin signaling is probably activated by changes in the expression of genes encoding the components directly involved in the signaling pathway or associated with the regulation of this pathway (Larue and Delmas 2006).

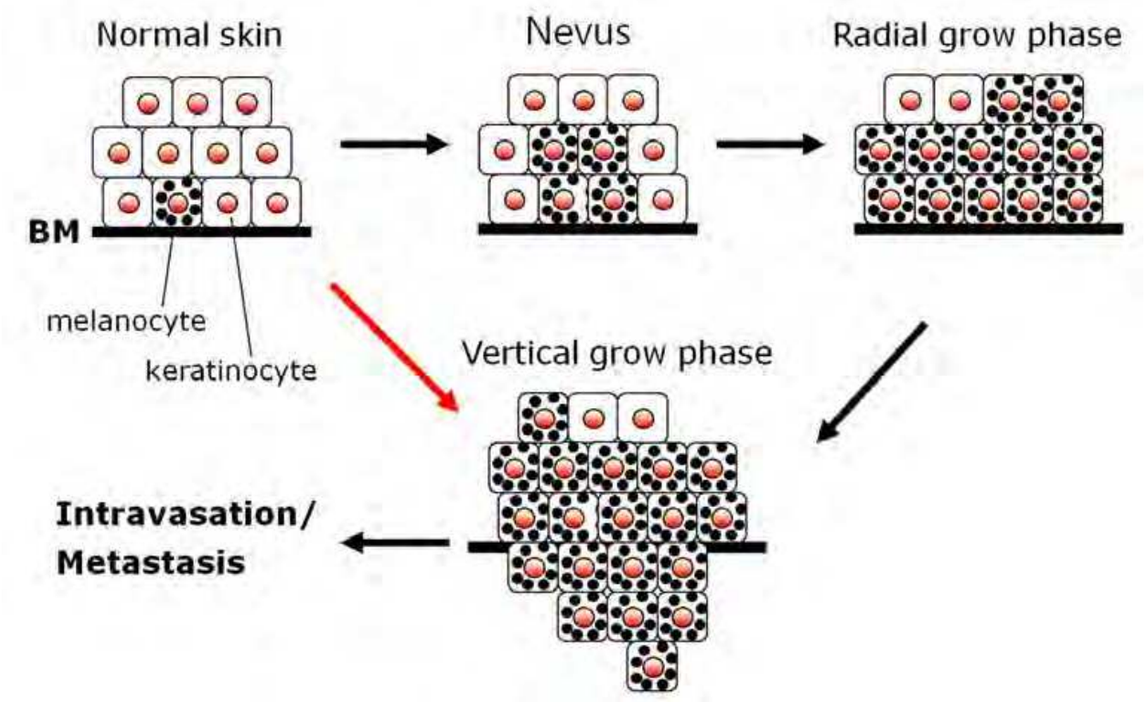

Fig. 3. Cutaneous melanomagenesis in human. After the formation of nervi, constitutively activated β-catenin results in the progress of RGP and VGP, inducing tumor cell metastasis. BM, basement membrane.

2.2.2 Wnt signaling in canine diseases

In dogs, abnormalities of the Wnt/β-catenin signaling pathway have been investigated in mammary tumor and skin melanoma (Gama et al., 2008; Han et al., 2010). In both studies, decreased membrane β-catenin expression was consistently observed, indicating the disruption of intercellular adhesion (Fig. 4). On plasma membrane level, β-catenin acts as a bridge that links cadherin to the cytoskeleton in the plasma membrane of the normal cell (Demunter et al. 2002; Sanders et al. 1999). Thus, the loss of cadherin molecule or the disruption of cadherin-catenin complex can induce the release of β-catenin into the cytoplasm. The loss of E-cadherin and the activated MET/RON receptor tyrosine kinases (RTKs) have been reported to cause the cytoplasmic release of β-catenin in human melanoma and normal canine kidney cells (Danilkovitch-Miagkova et al. 2001; Demunter et

al. 2002; Sanders et al. 1999). In the study of canine skin melanoma, the authors observed significantly increased β-catenin expression in mRNA level (Han et al., 2010). It seems that the increased synthesis of β-catenin can also induce the cytoplasmic accumulation, besides the translocation of membrane β-catenin. Wnt factor has been considered to increase the synthesis of β-catenin in human (Danilkovitch-Miagkova et al. 2001; Larue and Delmas 2006). However, the expression level of β-catenin in protein level is needed to confirm our hypothesis as increased RNA synthesis does not always equate with increased protein synthesis. The authors also examined consistently decreased expression of membrane E-cadherin in all canine skin melanoma tissues, indicating the disruption of intercellular adhesion (Fig. 5, unpublished). However, the authors couldn't conclude the relationship between E-cadherin and β-catenin because of low sample number. In another study, the authors observed that only 28% of tumor tissues revealed overexpressed MET/RON RTKs indicating that those RTKs were not a major contributing factor for increased β-catenin expression in the cytoplasm (Han et al., 2009). As a next study, the authors are examining the mutation of β-catenin gene. GSK3/APC/Axin complex recognizes the amino acid sequence encoded by exon 3 of β-catenin gene and initiates phosphorylation, followed by degradation of β-catenin.

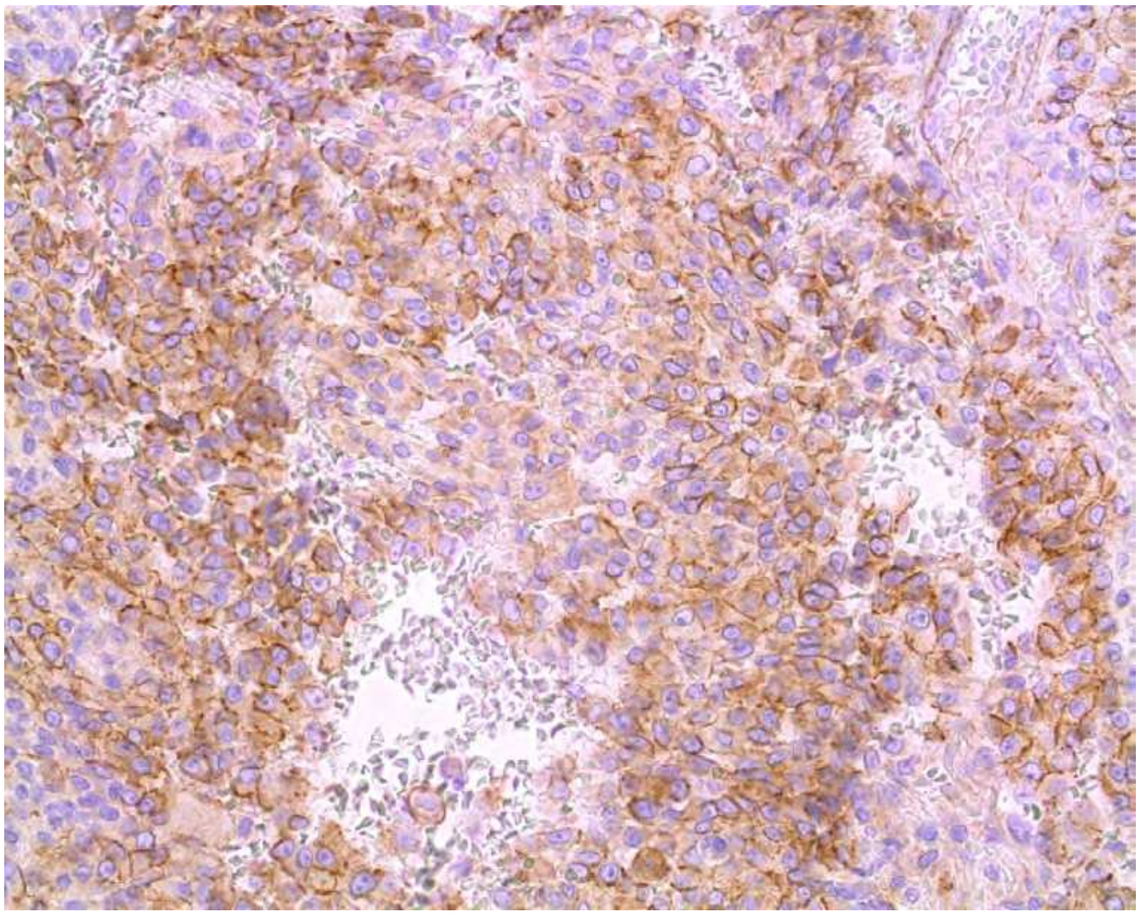

Fig. 4. Immunohistochemistry for β-catenin in canine skin melanoma showing variable membrane expression and cytoplasmic translocation of β-catenin (authors' study).

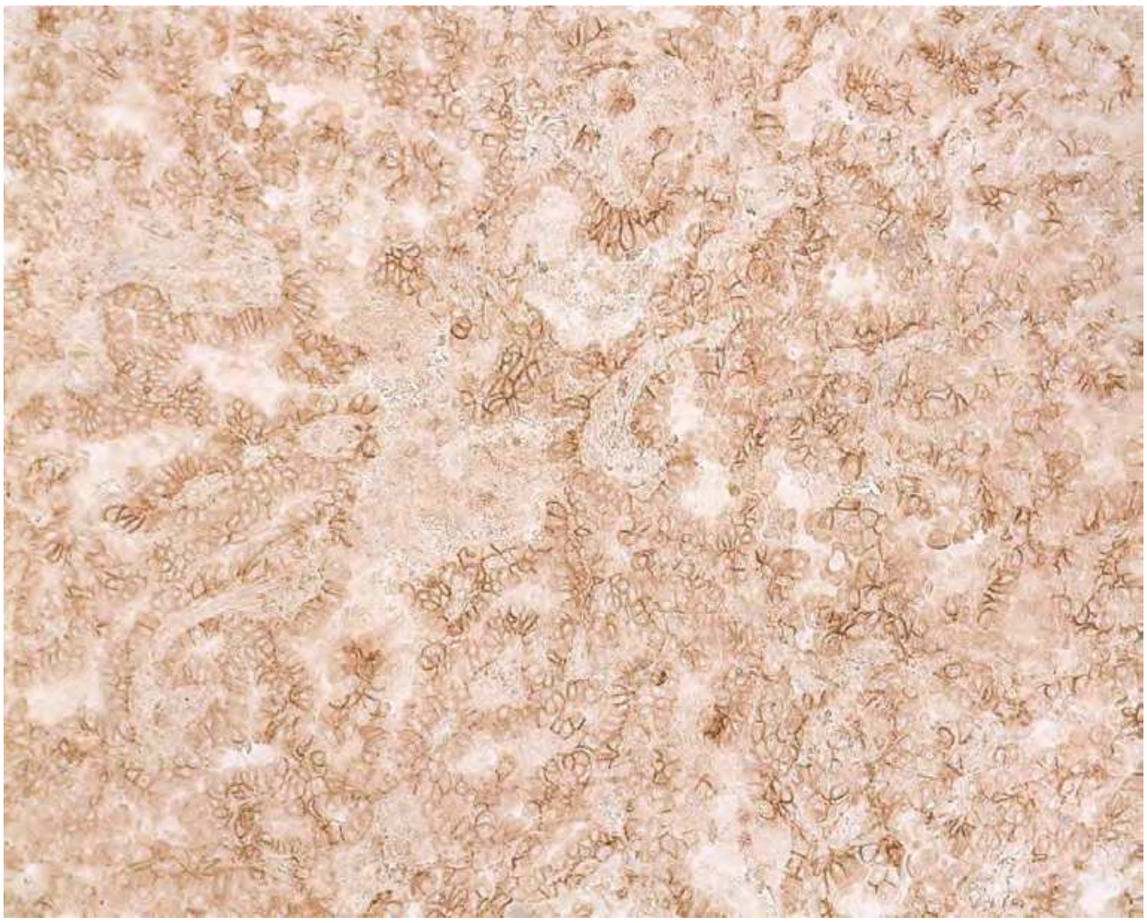

Fig. 5. Immunohistochemistry for E-cadherin in canine skin melanoma showing variable membrane expression of E-cadherin (authors' study).

3. Spontaneous canine skin melanoma as a model for human melanoma

Spontaneous tumors in companion animals are suitable models for human cancer. They share a similar lifestyle with human (their owner), and have a relatively high incidence of tumors, large body size and shorter life span (Vail & MacEwen, 2000). Their tumors are also spontaneously occurring and genetically heterogenous in contrast to the tumor of experimental animals induced by chemical or transplantation. In companion animals, tumors that have a potential to be a model for human are mammary carcinoma, osteosarcoma, melanoma, lymphoma and leukemia.

Although a lot of investigations and therapeutic trials have been conducted, the incidence and deaths by skin melanoma continue to increase in human, particularly Caucasian population (Longstreet, 1988; Woodhead et al., 1999). In human, melanoma classifies four subtypes; superficial spreading melanoma (SSM), nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma. SSM is the most common type of melanoma, accounting for about 70% of all diagnosed cases. The most aggressive type is, however, nodular melanoma. Nodular melanoma is the second common type, accounting for 15% of all diagnosed cases. Usually, it develops in people aged 60 and older. Because of high

incidence of the alteration in Wnt/β-catenin signaling pathway, a genetically modified mouse model has been developed (Delmas et al. 2007). However, the location of melanocytes in mice differs from that in the human skin and a mouse model does not spontaneously develop melanoma (Larue and Beermann 2007). Whereas, in normal skin of the dog, the melanocyte is mainly present in the basal layer of the epidermis and hair follicle similar to that of the human. In addition, the age incidence, histopathology and biological behavior, which rapidly progression to vertical growth phase (VGP) without radial growth phase (RGP) in canine cutaneous melanoma are very similar to the feature of human cutaneous nodular melanoma (Chamberlain et al. 2003; Gross et al. 2005; Smith et al. 2002). It suggests that the canine cutaneous melanoma could be a suitable model for therapeutic trial by correcting the altered Wnt/β-catenin signaling pathway.

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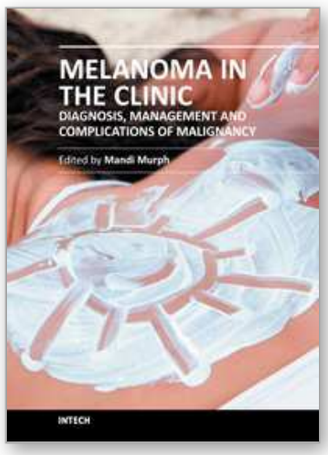

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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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