We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

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

Jae-Ik Han and Ki-Jeong Na
*College of Veterinary Medicine,
 Chungbuk National University
 Cheongju,
 Korea*

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 1 α and then threonine 41, serine 37 and serine 33 by glycogen synthase kinase-3 β (GSK-3 β) 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. Conversely, 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 3 β (GSK-3 β) and axin protein is responsible for regulating the level of β -catenin, via GSK-3 β -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-3 β (GSK-3 β), 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; Stadel *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-3 β 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 viriliation	Biason-Lauber et al., 2004
Wnt7a		Fuhrmann syndrome	Woods et al., 2006
Wnt10a		Odonto-onchy-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 nevus, 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 heterogeneous 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.

4. References

- Adaimy, L., Chouery, E., Megarbane, H., Mroueh, S., Delague, V., Nicolas, E., Belguith, H., de Mazancourt, P. & Megarbane, A. (2007) Mutation in WNT10A is associated with an autosomal recessive ectodermal dysplasia: the odonto-onycho-dermal dysplasia. *American Journal of Human Genetics*: 81(4), 821-828.
- Akiyama, T. (2000) Wnt/ β -catenin signaling. *Cytokine & Growth Factor Review*: 11(4), 273-282.
- Albino, A., Davis, B., & Nanus, D. (1991) Induction of growth factor RNA expression of activated N-rasQ61K on an INK4a-deficient background. *Cancer Research*: 65, 4005-4011.
- Aronsohn, M. G., Carpenter, J. L. (1990) Distal extremity melanocytic nevi and malignant melanomas in dogs. *Journal of the American Animal Hospital Association*: 26(6), 605-612.
- Behrens, J., von Kries, J. P., Kuhl, M., Bruhn, L., Wedlich, D., Grosschedl, R., and Birchmeier, W. (1996) Functional interaction of beta-catenin with the transcription factor LEF-1. *Nature*: 382(6592), 638-642.
- Biason-Lauber, A., Konrad, D., Navratil, F. & Schoenle, E. J. (2004) A WNT4 mutation associated with Mullerian-duct regression and virilization in a 46, XX woman. *The New England Journal of Medicine*: 351(8), 792-798.
- Bjorklund, P., Akerstrom, G. & Westin, G. (2007) An LRP5 receptor with internal deletion in hyperparathyroid tumors with implications for deregulated WNT/ β -catenin signaling. *PLoS medicine*: 4(11), e328.
- Bolon, B., Calderwood Mays, M. B., & Hall, B. J. (1990) Characteristics of canine melanomas and comparison of histology and DNA ploidy to their biologic effect. *Veterinary Pathology*: 27(2), 96-102.
- Bostock, D. E. (1986) Neoplasms of the skin and subcutaneous tissues in dogs and cats. *The British Veterinary Journal*: 142(1), 1-19.
- Boyden, L. M., Mao, J., Belsky, J., Mitzner, L., Farhi, A., Mitnick, M. A., Wu, D., Insogna, K. & Lifton, R. P. (2002) High bone density due to a mutation in LDL-receptor-related protein 5. *The New England Journal of Medicine*: 346(20), 1513-1521.
- Cadigan, K. M., Fish, M. P., Rulifson, E. J. & Nusse, R. (1998) Wingless repression of *Drosophila* frizzled 2 expression shapes the Wingless morphogen gradient in the wing. *Cell*: 93(5), 767-777.

- Chamberlain, A. J., Fritschi, L. & Kelly, J. W. (2003) Nodular melanoma: patient's perceptions of presenting features and implications for earlier detection. *Journal of the American Academy of Dermatology*: 48(5), 694-701.
- Chen, H. J., Lin, C. M., Lin, C. S., Perez-Olle, R., Leung, C. L. & Liem, R. K. (2006) The role of microtubule actin cross-linking factor 1 (MACF1) in the Wnt signaling pathway. *Genes & development*: 20(14), 1933-1945.
- Chien, A. J. & Moon, R. T. (2007) WNTS and WNT receptors as therapeutic tools and targets in human disease processes. *Frontiers in Bioscience*: 12, 448-457.
- Chin, L., Garraway, L. A., and Fisher, D. E. (2006) Malignant melanoma: genetics and therapeutics in the genomic era. *Genes & Development*: 20(16), 2149-2182.
- Choi, J., Park, S. Y., Costantini, F., Jho, E. H. & Joo, C. K. (2004) Adenomatous polyposis coli is down-regulated by the ubiquitin-proteasome pathway in a process facilitated by Axin. *The Journal of Biological Chemistry*: 279(47), 49188-49198.
- Clevers, H. (2006) Wnt/ β -catenin signaling in development and disease. *Cell*: 127(3), 469-80.
- Cliffe, A., Hamada, F. & Bienz, M. (2003) A role of Dishevelled in relocating Axin to the plasma membrane during wingless signaling. *Current Biology*: 13(11), 960-966.
- Culi, J. & Mann, R. S. (2003) Boca, an endoplasmic reticulum protein required for wingless signaling and trafficking of LDL receptor family members in *Drosophila*. *Cell*: 112(3), 343-354.
- Danilcovitch-Miagkova, A., Miagkov, A., Skeel, A., Nakaigawa, N., Zbar, B. & Leonard, E. J. (2001) Oncogenic mutants of RON and MET receptor tyrosine kinases causes activation of the beta-catenin pathway. *Molecular and Cellular Biology*: 21(17), 5857-5868.
- Davidson, G., Wu, W., Shen, J., Bilic, J., Fenger, U., Stanek, P., Glinka, A. & Niehrs, C. (2005) Casein kinase 1 gamma couples Wnt receptor activation to cytoplasmic signal transduction. *Nature*: 438(7069), 867-872.
- Delmas, V., Beermann, F., Martinuzzi, S., Carreira, S., Ackermann, J., Kumasaka, M., Denat, L., Goodall, J., Luciani, F., Viros, A., Demirkan, N., Bastian, B. C., Goding, C. R. & Larue, L. (2007) β -catenin induces immortalization of melanocytes by suppressing p16INK4a expression and cooperates with N-Ras in melanoma development. *Genes & Development*: 21(22), 2923-2935.
- Demunter, A., Libbrecht, L., Degreef, H., De Wolf-Peeters, C., a& van den Oord, J. J. (2002) Loss of membranous expression of β -catenin is associated with tumor progression in cutaneous melanoma and rarely caused by exon 3 mutations. *Modern Pathology*: 15(4), 454-461.
- Dincer, Z., Jasani, B., & Haywood, S. (2001) Metallothionein expression in canine and feline mammary and melanocytic tumours. *Journal of Comparative Pathology*: 125(2-3), 130-136.
- Ding, Y., Xi, Y., Chen, T., Wang, J. Y., Tao, D. L., Wu, Z. L., Li, Y. P., Li, C., Zeng, R. & Li, L. (2008) Caprin-2 enhances canonical Wnt signaling through regulating LRP5/6 phosphorylation. *The Journal of Cell Biology*: 182(5), 865-872.
- Dunn, K. J., Williams, B. O., Li, Y., & Pavan, W. J. (2000) Neural crest-directed gene transfer demonstrates Wnt1 role in melanocyte expansion and differentiation during mouse development. *Proceedings of the National Academy of Sciences of the United States of America*: 97(18), 10050-10055.

- Ikeya, M., Lee, S. M., Johnson, J. E., McMahon, A. P., & Takada, S. (1997) Wnt signaling required for expansion of neural crest and CNS progenitors. *Nature*: 389(6654), 966-970.
- Florez, J. C., Jablonski, K. A., Bayley, N., Pollin, T. I., de Bakker, P. I., Shuldiner, A. R., Knowler, W. C., Nathan, D. M. & Altshuler, D. (2006) TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. *The New England Journal of Medicine*: 355(3), 241-250.
- Galli, L. M., Barnes, T. L., Secrest, S. S., Kadowaki, T. & Burrus, L. W. (2007) Porcupine-mediated lipid-modification regulates the activity and distribution of Wnt proteins in the chick neural tube. *Development (Cambridge, England)*: 134(18), 3339-3348.
- Gama, A., Paredes, J., Gärtner, F., Alves, A. & Schmitt, F. (2008) Expression of E-cadherin, P-cadherin and β -catenin in canine malignant mammary tumours in relation to clinicopathological parameters, proliferation and survival. *The Veterinary Journal*: 177(1), 45-53.
- Gillick, A., & Spiegle, M. (1987) Dacarbazine treatment of malignant melanoma in a dog. *Canadian Veterinary Journal*: 28, 204.
- Gong, Y., Slee, R. B., Fukai, N., Rawadi, G., Roman-Roman, S., Reginato, A. M., Wang, H., Cundy, T., Glorieux, F. H., Lev, D., Zacharin, M., Oexle, K., Marcelino, J., Suwairi, W., Heeger, S., Sabatakos, G., Apte, S., Adkins, W. N., Allgrove, J., Arslan-Kirchner, M., Batch, J. A., Beighton, P., Black, G. C., Boles, R. G., Boon, L. M., Borrone, C., Brunner, H. G., Carle, G. F., Dallapiccola, B., De Paepe, A., Floege, B., Halfhide, M. L., Hall, B., Hennekam, R. C., Hirose, T., Jans, A., Jüppner, H., Kim, C. A., Keppler-Noreuil, K., Kohlschütter, A., LaCombe, D., Lambert, M., Lemyre, E., Letteboer, T., Peltonen, L., Ramesar, R. S., Romanengo, M., Somer, H., Steichen-Gersdorf, E., Steinmann, B., Sullivan, B., Superti-Furga, A., Swoboda, W., van den Boogaard, M. J., van Hul, W., Vikkula, M., Votruba, M., Zabel, B., Garcia, T., Baron, R., Olsen, B. R. & Warman, M. L. (2001) LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell*: 107(4), 513-523.
- Gross, T. L., Ihrke, P. J., Walder, E. J. & Affolter, V. K. (2005) In Skin diseases of the dog and cat: clinical and histopathologic diagnosis, 2nd ed. Blackwell publishing: Oxford 813-836.
- Haass, N. K., Smalley, K. S. M., Li, L. & Herlyn, M. (2005) Adhesion, migration and communication in melanocytes and melanoma. *Pigment Cell Research*: 18(3), 150-159.
- Hamderson, B. R. & Fagotto, F. (2002) The ins and outs of APC and beta-catenin nuclear transport. *EMBO reports*: 3(9), 834-839.
- Han, J. I., Kim, D. Y. & Na, K. J. (2009) Increased expression of MET and RON receptor tyrosine kinases in canine cutaneous melanotic tumor. *Journal of Veterinary Clinics*: 26(5), 429-432.
- Han, J. I., Kim, D. Y. & Na, K. J. (2010) Dysregulation of the Wnt/ β -catenin signaling pathway in canine cutaneous melanotic tumor. *Veterinary Pathology*: 47(2), 285-291.
- Hausmann, G., Banziger, C. & Basler, K. (2007) Helping Wingless take flight: how WNT proteins are secreted. *Nature reviews*: 8(4), 331-336.
- He, X., Semenov, M., Tamai, K. & Zeng, X. (2004) LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: arrows point the way. *Development (Cambridge, England)*: 131(8), 1663-1677.

- Hovanes, K., Li, T. W., Munguia, J. E., Truong, T., Milovanovic, T., Lawrence Marsh, J., Holcombe, R. F. & Waterman, M. L. (2001) Beta-catenin-sensitive isoforms of lymphoid enhancer factor-1 are selectively expressed in colon cancer. *Nature Genetics*: 28(1), 53-57.
- Hsieh, J. C., Lee, L., Zhang, L., Wefer, S. & Brown, K. (2003) Mesd encodes an LRP5/6 chaperone essential for specification of mouse embryonic polarity. *Cell*: 112(3), 355-367.
- Huang, H. & He, X. (2008) Wnt/beta-catenin signaling: new (and old) players and new insights. *Current opinion in cell biology*: 20(2), 119-125.
- Jho, E. H., Zhang, T., Domon, C., Joo, C. K., Freund, J. N. & Costantini, F. (2002) Wnt/beta-catenin/Tcf signaling induces the transcription of Axin2, a negative regulator of the signaling pathway. *Molecular and Cellular Biology*: 22(4), 1172-1183.
- Kimelman, D. & Xu, W. (2006) beta-catenin destruction complex: insights and questions from a structural perspective. *Oncogene*: 25(57), 7482-7491.
- Kinzler, K. W., Nilbert, N. C., Vogelstein, B., Bryan, T. M., Levy, D. B., Smith, K. J., Preisinger, A. C., Hamilton, S. R., Hedge, P., Markhan, A., Carlson, M., Joslyn, G., Groden, J., White, R., Miki, Y., Miyoshi, Y., Nishisho, I. & Nakamura, Y. (1991) Identification of a gene located at chromosome 5q21 that is mutated in colorectal cancers. *Science*: 251(4999), 1366-1370.
- Koenig, A., Bianco, S. R., Fosmire, S., Wojcieszyn, J., and Modiano, J. F. (2002) Expression and significance of p53, Rb, p21/waf-1, p16/ink4a, and PTEN tumor suppressors in canine melanoma. *Veterinary Pathology*: 39(4), 458-472.
- Komekado, H., Yamamoto, H., Chiba, T. & Kikuchi, A. (2007) Glycosylation and palmitoylation of Wnt-3a are coupled to produce an active form of Wnt-3a. *Genes to Cells*: 12(4), 521-534.
- Korinek, V., Barker, N., Morin, P. J., van Wichen, D., de Weger, R., Kinzler, K. W., Vogelstein, B. & Clevers, H. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC^{-/-} colon carcinoma. *Science*: 275(5307), 1784-1787.
- Lammi, L., Arte, S., Somer, M., Jarvinen, H., Lahermo, P., Thesleff, I., Pirinen, S. & Nieminen, P. (2004) Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. *American Journal of Human Genetics*: 74(5), 1043-1050.
- Larue, L. & Beermann, F. (2007) Cutaneous melanoma in genetically modified animals. *Pigment Cell Research*: 20(6), 485-497.
- Larue, L., and Delmas, V. (2006) The WNT/ β -catenin pathway in melanoma. *Frontiers in Biosciences*: 11, 733-742.
- Lee, E., Salic, A., Kruger, R., Heinrich, R. & Kirschner, M. W. (2003) The roles of APC and Axin derived from experimental and theoretical analysis of the Wnt pathway. *PLoS Biology*: 1(1), E10.
- Little, R. D., Carulli, J. P., Del Mastro, R. G., Dupuis, J., Osborne, M., Folz, C., Manning, S. P., Swain, P. M., Zhao, S. C., Eustace, B., Lappe, M. M., Spitzer, L., Zweier, S., Braunschweiger, K., Benchekroun, Y., Hu, X., Adair, R., Chee, L., FitzGerald, M. G., Tulig, C., Caruso, A., Tzellas, N., Bawa, A., Franklin, B., McGuire, S., Nogues, X., Gong, G., Allen, K. M., Anisowicz, A., Morales, A. J., Lomedico, P. T., Recker, S. M., Van Eerdewegh, P., Recker, R. R. & Johnson, M. L. (2002) A mutation in the LDL-

- receptor-related protein 5 gene results in the autosomal dominant high-bone-mass trait. *American Journal of Human Genetics*: 70(1), 11-19.
- Liu, W., Dong, X., Mai, M., Seelan, R. S., Taniguchi, K., Krishnadath, K. K., Halling, K. C., Cunningham, J. M., Boardman, L. A., Qian, C., Christensen, E., Schmidt, S. S., Roche, P. C., Smith, D. I. & Thibodeau, S. N. (2000) Mutations in AXIN2 cause colorectal cancer with defective mismatch repair by activating beta-catenin/TCF signaling. *Nature Genetics*: 26(2), 146-147.
- Logan, C. Y. & Nusse, R. (2004) The Wnt signaling pathway in development and disease. *Annual Review of Cell and Developmental Biology*: 20, 781-810.
- Longstreet, J. (1988) Cutaneous malignant melanoma and ultraviolet radiation: a review. *Cancer Metastasis Reviews*: 7(4), 321-333.
- Luo, W., Peterson, A., Garcia, B. A., Coombs, G., Kofahl, B., Heinrich, R., Shabanowitz, J., Hunt, D. F., Yost, H. J. & Virshup, D. M. (2007) Protein phosphatase 1 regulates assembly and function of the beta-catenin degradation complex. *The EMBO Journal*: 26(6), 1511-1521.
- MacDonald, B. T., Yokota, C., Tamai, K., Zeng, X. & He, X. (2008) Wnt signal amplification via activity, cooperativity, and regulation of multiple intracellular PPPSP motifs in the Wnt co-receptor LRP6. *The Journal of Biological Chemistry*: 283(23), 16115-16123.
- Mani, A., Radhakrishnan, J., Wang, H., Mani, A., Mani, M. A., Nelson-Williams, C., Carew, K. S., Mane, S., Najmabadi, H., Wu, D. & Lifton, R. P. (2007) LRP6 mutation in a family with early coronary disease and metabolic risk factors. *Science*: 315(5816), 1278-1282.
- Mayr, B., Schaffner, G., and Reifinger, M. (2003) N-ras mutations in canine malignant melanomas. *Veterinary Journal*: 165(2), 169-171.
- Meier, F., Nesbit, M. & Hsu, M. (2000) Human melanoma progression in skin reconstructs. Biological significance of bFGF. *The American Journal of Pathology*: 156(1), 193-200.
- Moore, A. S. (1993) Recent advances in chemotherapy for nonlymphoid malignant neoplasms. *Compendium on Continuing Education for the Practicing Veterinarian*: 15, 1039-1050.
- Muller, H., Samanta, R. & Wieschaus, E. (1999) Wingless signaling in the *Drosophila* embryo: zygotic requirements and the role of the frizzled genes. *Development*: 126(3), 577-86.
- Nelson, W. J. & Nusse, R. (2004) Convergence of Wnt, β -catenin, and cadherin pathways. *Science*: 303(5663), 1483-7.
- Niemann, S., Zhao, C., Pascu, F., Stahl, U., Aulepp, U., Niswander, L., Weber, J. L. & Muller, U. (2004) Homozygous WNT3 mutation causes tetra-amelia in a large consanguineous family. *American Journal of Human Genetics*: 74(3), 558-563.
- Nishisho, I., Nakamura, Y., Miyoshi, Y., Miki, Y., Ando, H., Horii, A., Koyama, K., Utsunomiya, J., Baba, S. & Hedge, P. (1991) Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. *Science*: 253(5020), 665-669.
- Oates, N. A., van Vliet, J., Duffy, D. L., Kroes, H. Y., Martin, N. G., Boomsma, D. I., Campbell, M., Coulthard, M. G., Whitelaw, E. & Chong, S. Increased DNA methylation at the AXIN1 gene in a monozygotic twin from a pair discordant for a caudal duplication anomaly. *American Journal of Human Genetics*: 79(1), 155-162.
- Ogilvie, G. K., Obradovich, J. E., Elmslie, R. E. (1991) Efficacy of mitoxantrone against various neoplasms in dogs. *Journal of the American Veterinary Medical Association*: 198(9), 1618-1621.

- Omholt, K., Platz, A., Ringborg, U., Hansson, J. (2001) Cytoplasmic and nuclear accumulation of β -catenin is rarely caused by *ctnnb1* exon 3 mutations in cutaneous malignant melanoma. *International Journal of Cancer*: 92(6), 839-842.
- Rassnick, K. M., Ruslander, D. M., Cotter, S. M. (2001) Use of carboplatin for treatment of dogs with malignant melanoma: 27 cases (1989-2000). *Journal of the American Veterinary Medical Association*: 218(9), 1444-1448.
- Rawlings, N. G., Simko, E., and Bechuk, T. (2003) Localization of integrin $\alpha v \beta 3$ and vascular endothelial growth factor receptor-2 (KDR/Flk-1) in cutaneous and oral melanomas of dog. *Histology and Histopathology*: 18(3), 819-826.
- Roose, J., Huls, G., van Beest, M., Moerer, P., van der Horn, K., Goldschmeding, R., Loqtenberg, T. & Clevers, H. (1999) Synergy between tumor suppressor APC and the beta-catenin-Tcf4 target Tcf1. *Science*: 285(5435), 1923-1926.
- Rothwell, T. L. W., Howlett, C. R., Middleton, D. J., Griffiths, D. A., and Duff, B. C. (1987) Skin neoplasms of dogs in Sydney. *Australian Veterinary Journal*: 64(6), 161-164.
- Sanders, D. S. A., Blessing, K., Hassan, G. A. R., Bruton, R., Marsden, J. R. & Jankowski, J. (1999) Alterations in cadherin and catenin expression during the biological progression of melanocytic tumours. *Molecular Pathology*: 52(3), 151-157.
- Sato, A., Kojima, T., Ui-Tei, K., Miyata, Y. & Saigo, K. (1999) Dfrizzled-3, a new *Drosophila* Wnt receptor, acting as an attenuator of Wingless signaling in wingless hypomorphic mutants. *Development*: 126(20), 4421-4430.
- Satoh, S., Daigo, Y., Furukawa, Y., Kato, T., Miwa, N., Nishiwaki, T., Kawasoe, T., Ishiguro, H., Fujita, M., Tokino, T., Sasaki, Y., Imaoka, S., Murata, M., Shimano, T., Yamaoka, Y. & Nakamura, Y. (2000) AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1. *Nature Genetics*: 24(3), 245-250.
- Shin, I. M. & Herlyn, M. (1993) Role of growth factors and their receptors in the development and progression of melanoma. *The Journal of Investigative Dermatology*: 100(2 Suppl), 196S-203S.
- Smith, S. H., Goldschmidt, M. H. & McManus, P. M. (2002) A comparative review of melanocytic neoplasm. *Veterinary Pathology*: 39(6), 651-678.
- Spiegelman, V. S., Slaga, T. J., Pagano, M., Minamoto, T., Ronai, Z. & Fuchs, S. Y. (2000) Wnt/beta-catenin signaling induces the expression and activity of betaTrCP ubiquitin ligase receptor. *Molecular Cell*: 5(5), 877-882.
- Stadeli, R., Hoffmans, R. & Basler, K. (2006) Transcription under the control of nuclear Arm/beta-catenin. *Current Biology*: 16(10), R378-385.
- Su, Y., Fu, C., Ishikawa, S., Stella, A., Kojima, M., Shitoh, K., Schreiber, E. M., Day, B. W. & Lie, B. (2008) APC is essential for targeting phosphorylated-catenin to the SCF (beta-TrCP) ubiquitin ligase. *Molecular Cell*: 32(5), 652-661.
- Sun, T. Q., Lu, B., Feng, J. J., Reinhard, C., Jan T. N., Fantl, W. J. & Williams, L. T. (2001) PAR-1 is a Dishevelled-associated kinase and a positive regulator of Wnt signaling. *Nature Cell Biology*: 3(7), 628-636.
- Takacs, C. M., Baird, J. R., Hughes, E. G., Kent, S. S., Henchabane, H., Paik, R. & Ahmed, Y. (2008) Dual positive and negative regulation of wingless signaling by adenomatous polyposis coli. *Science*: 319(5861), 333-336.

- Takada, R., Satomi, Y., Kurata, T., Ueno, N., Norioka, S., Kondoh, H., Takao, T. & Takada, S. (2006) Monounsaturated fatty acid modification of Wnt protein: its role in Wnt secretion. *Developmental Cell*: 11(6), 791-801.
- Tamai, K., Zeng, X., Liu, C., Zhang, X., Harada, Y., Chang, Z. & He, X. (2004) A mechanism for Wnt coreceptor activation. *Molecular Cell*: 13(1), 149-156.
- Tang, A., Eller, M. S., Hara, M., Yaar, M., Hirohashi, S., & Gilchrist, B. A. (1994) E-cadherin is the major mediator of human melanocyte adhesion to keratinocytes in vitro. *Journal of Cell Science*: 107(Pt 4), 983-992.
- Thamm, D. H., Huelsmeyer, M. K., Mitzey, A. M., Qurollo, B., Rose, B. J. & Kurzman, I. D. (2010) RT-PCR-based tyrosine kinase display profiling of canine melanoma: IGF-1 receptor as a potential therapeutic target. *Melanoma Research*: 20(1), 35-42.
- Toomes, C., Bottomley, H. M., Jackson, R. M., Towns, K. V., Scott, S., Mackey, D. A., Craig, J. E., Jiang, L., Yang, Z., Trembath, R., Woodruff, G., Gregory-Evans, C. Y., Gregory-Evans, K., Parker, M. J., Black, G. C., Downey, L. M., Zhang, K. & Inglehearn, C. F. (2004) Mutations in LRP5 or FZD4 underlie the common familial exudative vitreoretinopathy locus on chromosome 11q. *American Journal of Human Genetics*: 74(4), 721-730.
- Umbhauer, M., Djiane, A., Goisset, C., Penzo-Mendez, A., Riou, J. F., Boucaut, J. C. & Shi, D. L. (2000) The C-terminal cytoplasmic Lys-Thr-X-X-X-Trp motif in frizzled receptors mediates Wnt/beta catenin signaling. *EMBO Journal*: 19(18), 4944-4954.
- Vail, D. M. & MacEwen, E. G. (2000) Spontaneously occurring tumors of companion animals as models for human cancer. *Cancer Investigation*: 18(8), 781-792.
- von Euler, H., Sadeghi, A., Carlsson, B., Rivera, P., Loskog, A., Segall, T., Korsgren, O. & Tötterman, T. H. (2008) Efficient adenovector CD40 ligand immunotherapy of canine malignant melanoma. *Journal of Immunotherapy*: 31(4), 377-384.
- Wehrli, M., Dougan, S. T., Caldwell, K., O'Keefe, L., Schwartz, S., Vaizel-Ohayon, D., Schejter, E., Tomlinson, A. & DiNardo, S. (2000) arrow encodes an LDL-receptor-related protein essential for Wingless signaling. *Nature*: 407(6803), 527-530.
- Willert, J., Epping, M., Pollack, J., Brown, P. & Nusse, R. (2002) A transcriptional response to Wnt protein in human embryonic carcinoma cells. *BMC Developmental Biology*: 2, 8.
- Willert, K., Brown, J. D., Danenberg, E., Duncan, A. W., Weissman, I. L., Reya, T., Yates, J. R. 3rd. & Nusse, R. (2003) Wnt proteins are lipid-modified and can act as stem cell growth factors. *Nature*: 423(6938), 448-452.
- Woodhead, A. D., Setlow, R. B. & Tanaka, M. (1999) Environmental factors in nonmelanoma and melanoma skin cancer. *Journal of Epidemiology*: 9(6 Suppl), S102-S114.
- Woods, C. G., Stricker, S., Seemann, P., Stern, R., Cox, J., Sherridan, E., Roberts, E., Springell, K., Scott, S., Karbani, G., Sharif, S. M., Toomes, C., Bond, J., Kumar, D., Al-Gazali, L. & Mundlos, S. (2006) Mutations in WNT7A cause a range of limb malformations, including Fuhrmann syndrome and Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome. *American Journal of Human Genetics*: 79(2), 402-408.
- Xing, Y., Clements, W. K., Kimelman, D. & Xu, W. (2003) Crystal structure of a beta-catenin/axin complex suggests a mechanism for the beta-catenin destruction complex. *Genes & development*: 17(22), 2753-2764.
- Xu, Q., Wang, Y., Dabdoub, A., Smallwood, P. M., Williams, J., Woods, C., Kelly, M. W., Jiang, L., Tasman, W., Zhang, K. & Nathans, J. (2004) Vascular development in the

- retina and inner ear: control by Norrin and Frizzled-4, a high-affinity ligand-receptor pair. *Cell*: 116(6), 883-895.
- Yanagawa, S., van Leeuwen, F., Wodarz, A., Klingensmith, J. & Nusse, R. (1995) The disheveled protein is modified by wingless signaling in *Drosophila*. *Genes & Development*: 9(9), 1087-1097.
- Zeng, X., Huang, H., Tamai, K., Zhang, X., Harada, Y., Yokota, C., Almeida, K., Wang, J., Doble, B., Woodgett, J., Wynshaw-Boris, A., Hsieh, J. C. & He, X. (2008) Initiation of Wnt signaling: control of Wnt coreceptor Lrp6 phosphorylation/activation via frizzled, disheveled and axin functions. *Development (Cambridge, England)*: 135(2), 873-877.
- Zeng, X., Tamai, K., Doble, B., Li, S., Huang, H., Habas, R., Okamura, H., Woodgett, J. & He, X. (2005) A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation. *Nature*: 438(7069), 873-877.
- Zhai, L., Chaturvedi, D. & Cumberledge, S. (2004) *Drosophila* Wnt-1 undergoes a hydrophobic modification and is targeted to lipid rafts; a process that requires Porcupine. *The Journal of Biological Chemistry*: 279(32), 33220-33227.

IntechOpen

Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy

Edited by Prof. Mandi Murph

ISBN 978-953-307-571-6

Hard cover, 310 pages

Publisher InTech

Published online 23, August, 2011

Published in print edition August, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jae-Ik Han and Ki-Jeong Na (2011). Wnt/ β -Catenin Signaling Pathway in Canine Skin Melanoma and a Possibility as a Cancer Model for Human Skin Melanoma, Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy, Prof. Mandi Murph (Ed.), ISBN: 978-953-307-571-6, InTech, Available from: <http://www.intechopen.com/books/melanoma-in-the-clinic-diagnosis-management-and-complications-of-malignancy/wnt-catenin-signaling-pathway-in-canine-skin-melanoma-and-a-possibility-as-a-cancer-model-for-human->

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen