Transcriptional regulation of *WNT2B* based on the balance of Hedgehog, Notch, BMP and WNT signals

MASUKO KATOH[1] and MASARU KATOH[2]

[1]M&M Medical BioInformatics, Hongo 113-0033; [2]Genetics and Cell Biology Section, National Cancer Center, Tokyo 104-0045, Japan

Received February 13, 2009; Accepted March 12, 2009

DOI: 10.3892/ijo_00000269

Abstract. We cloned and characterized human WNT2B in 1996, and then others cloned and characterized mouse, chicken, and zebrafish WNT2B orthologs. *WNT2B* is expressed in several types of human cancer, such as basal cell carcinoma, gastric cancer, breast cancer, head/neck squamous cell carcinoma, cervical cancer and leukemia. WNT2B is one of canonical WNTs transducing signals through Frizzled (FZD) and LRP5/LRP6 receptors to ß-catenin-TCF/LEF signaling cascade. Here, refined integrative genomic analyses on *WNT2B* orthologs were carried out to elucidate its transcriptional mechanisms. GLI-, double FOX-, HES/HEY-, bHLH-, and Sp1-binding sites within mammalian *WNT2B* promoter were well conserved. Because *GLI1, FOXA2, FOXC2, FOXE1*, *FOXF1* and *FOXL1* are direct target genes of Hedgehog-GLI2 signaling cascade, Hedgehog signals should induce *WNT2B* upregulation through GLI family members as well as FOX family members. Notch, BMP and Hedgehog signals inhibit *WNT2B* expression via HES/HEY-binding to N-box, whereas BMP and WNT signals inhibit bHLH transcription factor-induced *WNT2B* expression via ID1, ID2, ID3, MSX1 or MSX2. Together these facts indicate that Hedgehog signals and bHLH transcription factors are involved in WNT2B up-regulation, which is counteracted by BMP, WNT and Notch signals. Mesenchymal BMP induces IHH expression in gastrointestinal epithelial cells, and then epithelial Hedgehog induces WNT2B and BMP4 expression in mesenchymal cells. NF-κB signals induce SHH upregulation, and WNT2B is upregulated in inflammatory bowel disease (IBD). BMP-IHH and inflammation-SHH signaling loops are involved in *WNT2B* up-regulation during embryogenesis, adult tissue homeostasis, and carcinogenesis.

Correspondence to: Dr Masaru Katoh, Genetics and Cell Biology Section, National Cancer Center, 5-1-1 Tsukiji, Chuo Ward, Tokyo 104-0045, Japan
E-mail: mkatoh-kkr@umin.ac.jp

Key words: WNT, Hedgehog, BMP, Notch, basal cell carcinoma, gastric cancer, breast cancer, stem cell signaling network, systems biology

Introduction

WNT family members are lipid-modified glycoproteins involved in embryogenesis and carcinogenesis (1-5). We cloned and characterized human WNT2B/WNT13 as the 13th member of the mammalian WNT family in 1996 (6), and others then characterized mouse, chicken, and zebrafish WNT2B orthologs (7-9). Human WNT2B shows 66.9% total amino-acid identity with human WNT2, while mouse Wnt2b shows 71.1% total amino-acid identity with mouse Wnt2. The *WNT2B-ST7L-CAPZA1* locus at human chromosome 1p13.2 and the *WNT2-ST7-CAPZA2* locus at human chromosome 7q31.2 are paralogous regions within the human genome (10). Human *WNT2B* gene consisting of seven exons encodes multiple isoforms due to alternative spicing using alternative promoters (11). WNT2B2 isoform rather than WNT2B1 is evolutionarily conserved.

WNT2B2 functions as a canonical WNT to transduce signal through Frizzled (FZD) receptor and LRP5/6 co-receptor (12). In the absence of canonical WNT signaling, ß-catenin is phosphorylated by Casein kinase 1α (CK1α) and glycogen synthase kinase 3ß (GSK3ß), and then is ubiquitylated by ßTRCP1 (FBXW1)- or ßTRCP2 (FBXW11)-containing ubiquitin-ligase complex for its degradation in the proteasome system (13-17). Canonical WNT signals induce assembly of FZD-Dishevelled complex and LRP5/6-AXIN complex to release ß-catenin from AXIN-APC degradation complex (18-20), which results in stabilization and nuclear translocation of ß-catenin for the transcriptional activation of target genes, such as *MYC* and *CCND1* (21-23).

WNT signaling cascades cross-talk with Hedgehog, BMP/TGF-ß, FGF, and Notch signaling cascades to constitute the stem-cell signaling network (24-26). Dysregulation of the stem-cell signaling network due to epigenetic and genetic alterations leads to congenital abnormality and carcinogenesis (27-29).

Human *WNT2B* is expressed in fetal brain, lung, kidney, adult heart, brain, placenta, lung, prostate, testis, ovary, small intestine, colon, and also in several types of human cancer, such as basal cell carcinoma, gastric cancer, breast cancer, head/neck squamous cell carcinoma, cervical cancer, and leukemia (6,11,30-34). *WNT2B* is upregulated in liver and biliary epithelial cells of patients with primary biliary cirrhosis (35), and in colonic mucosa of patients with inflammatory bowel disease (36). *WNT2B* is upregulated in some types of human cancer and in some tissues with chronic inflammation;

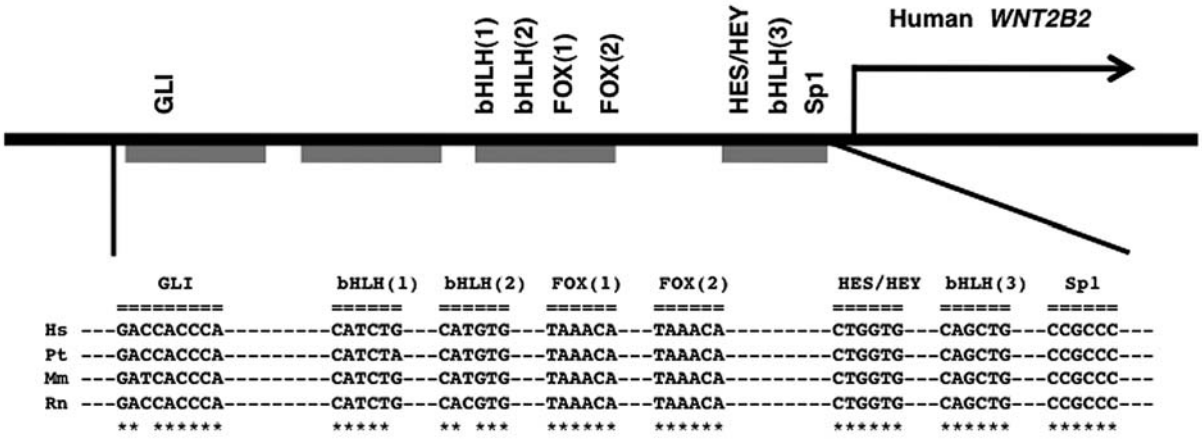

Figure 1. Conserved transcription factor-binding sites within *WNT2B* promoter. Human genome around the *WNT2B2* promoter is shown by the bold bar. Evolutionarily conserved regions are shown by the gray bars. Nucleotide sequences of promoter region of human (Hs), chimpanzee (Pt), mouse (Mm), and rat (Rn) *WNT2B* orthologs are aligned in the bottom. GLI-, double FOX-, HES/HEY-, bHLH-, and Sp1-binding sites within mammalian *WNT2B* promoter are well conserved.

however, the mechanisms of *WNT2B* transcription remain unclear. Here, refined integrative genomic analyses are carried out to elucidate the transcriptional mechanisms of *WNT2B* with an emphasis on the stem-cell signaling network.

Materials and methods

Comparative genomic analyses. Human genome sequences corresponding to human WNT2B2 isoform (NM_024494.2) were searched for by using BLAST programs, as previously described (37-40). Conserved transcription factor-binding sites within the *WNT2B2* promoter were then searched for based on manual inspection, as previously described (41-44).

Regulatory network analyses. Literature on WNT2B, Hedgehog, BMP, and Notch signaling molecules in PubMed and Medline databases was critically evaluated to extract knowledge on the regulation of GLI, FOX, bHLH, ID and MSX family transcription factors. The mechanisms of *WNT2B* transcription were then investigated based on our data of conserved transcription factor-binding sites within the *WNT2B* promoter and in-house knowledgebase of transcription factors regulated by the stem-cell signaling network.

Results

Comparative genomics on WNT2B promoter. Because the region around the *WNT2B2* promoter is GC-rich (45), transcription start sites (TSSs) of human *WNT2B2* mRNA have been predicted to show 'broad peak' pattern, as is usual for other GC-rich promoters. Indeed, NM_024494.2 WNT2B2 RefSeq was extended to the 496-bp 5'-position compared with NM_024494.1 WNT2B2 RefSeq. Comparative integromics analyses of the *WNT2B* promoter were carried out again in this study by using up-to-date in-house knowledgebase on the transcription-factor network.

BLAST programs using the NM_024494.2 WNT2B2 RefSeq as a query sequence revealed that the TSS of human *WNT2B2* mRNA was located within AL354760.11 and AC140714.1 genome sequences. BLAST programs next revealed that the distal promoter region (-2447 ~ -2043 position from TSS) and the proximal promoter region (-701 ~ -213 position from TSS) were well conserved between human *WNT2B* genome sequence and mouse *Wnt2b* genome sequence AC166156.4 (Fig. 1).

Consensus transcription factor-binding sites within the conserved promoter regions were searched for with manual inspection based on in-house knowledgebase. Double bHLH-binding sites [bHLH(1) and bHLH(2)] and double FOX-binding sites [FOX(1) and FOX(2)] within the distal promoter region of human *WNT2B* gene were conserved in mouse *Wnt2b* promoter (Fig. 1). HES-binding site, bHLH-binding site [bHLH(3)], and Sp1-binding site within the proximal promoter region of human *WNT2B* gene were also conserved in mouse *Wnt2b* promoter (Fig. 1).

Conservation of transcription factor-binging sites in other mammalian species was then searched for. Rat *Wnt2b* gene was located within AC106372.5 genome sequence, as previously described (45). Chimpanzee *WNT2B* gene was located within NW_001229591.1 genome sequence. The bHLH(1)-binding site was not conserved in chimpanzee *WNT2B* promoter, whereas the bHLH(2)-binding site was not conserved in rat *Wnt2b* promoter. Together these facts indicate that FOX(1)-, FOX(2)-, HES-, bHLH(3)-, and Sp1-binding sites were conserved in human *WNT2B*, chimpanzee *WNT2B*, mouse *Wnt2b*, and rat *WNT2B* promoters (Fig. 1).

Hedgehog signaling cascades and WNT2B. Hedgehog signals are transduced through Patched family receptors to activate Smoothened signal transducer, which results in stabilization and nuclear accumulation of GLI family members for transcriptional activation of Hedgehog target genes (29,46-48). Hedgehog signaling cascade is aberrantly activated in basal cell carcinoma (49-51), gastric cancer (52,53), breast cancer (54), and other tumors. *WNT2B* is expressed in basal cell carcinoma (32), gastric cancer (6), breast cancer (31), and other tumors, as mentioned above. Because Hedgehog signaling activation and *WNT2B* expression co-existed in several types of human cancer, we investigated the causal link between Hedgehog signaling activation and *WNT2B* expression.

Consensus GLI-binding site was located at the position -4636 ~ -4628 from the human *WNT2B* TSS (Fig. 1). The

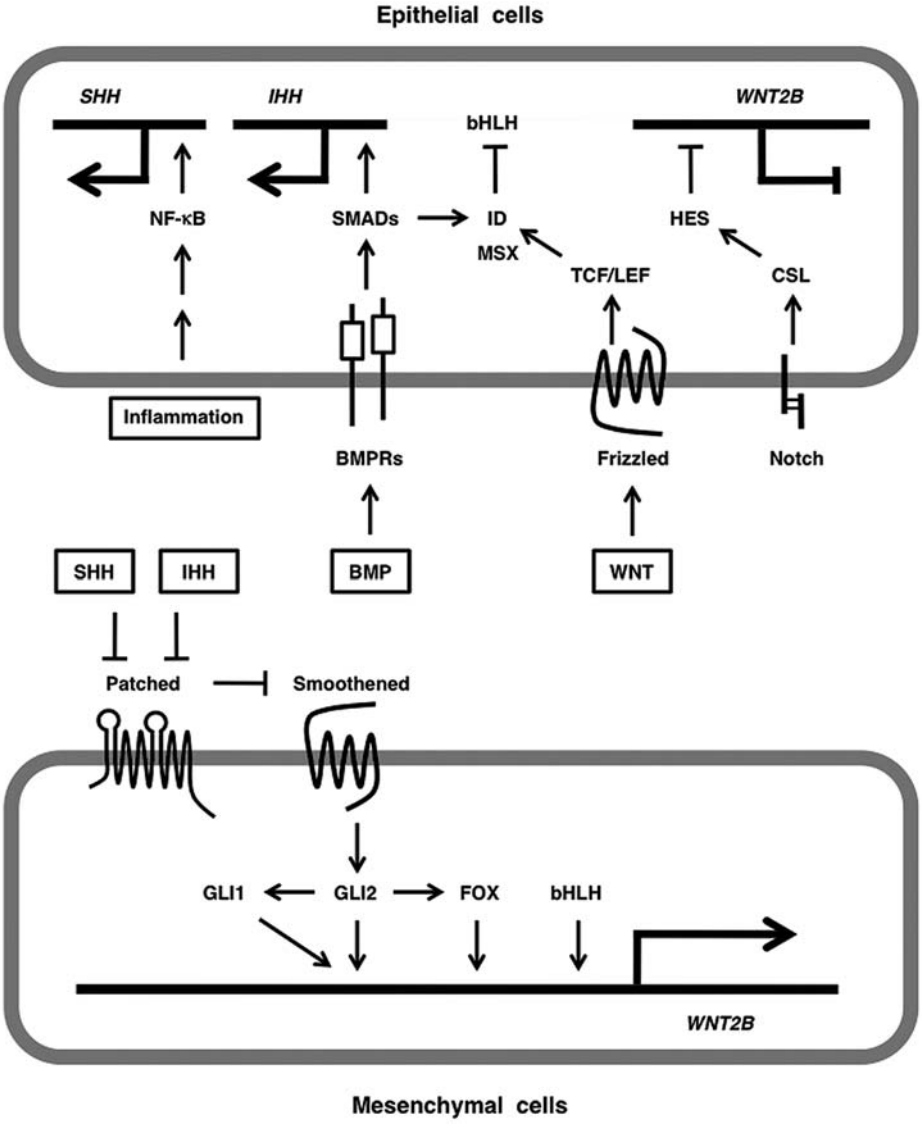

Figure 2. BMP-IHH-WNT2B and Inflammation-SHH-WNT2B signaling loops. Mesenchymal BMP induces *IHH* expression via SMADs in gastrointestinal epithelial cells, and inflammation induces *SHH* expression via NF-κB in epithelial cells. *WNT2B* expression is repressed in gastrointestinal epithelial cells by BMP and WNT signals via ID and MSX family members, and also by Notch signals via HES/HEY family members. IHH and SHH activate Hedgehog signaling cascades in mesenchymal cells to upregulate *WNT2B* expression via GLI and FOX family members, in cooperation with bHLH transcription factors.

GLI-binding site at about 5 kb upstream of human *WNT2B* TSS was completely conserved in chimpanzee *WNT2B* and rat *WNT2b* promoters, and was almost conserved in mouse *WNT2b* promoter except one base substitution (Fig. 1). *GLI1, FOXA2, FOXC2, FOXE1, FOXF1* and *FOXL1* are direct target genes of Hedgehog-GLI signaling cascade (29), and double FOX-binding sites within human *WNT2B* promoter were completely conserved in chimpanzee *WNT2B*, rat *WNT2b*, and mouse *Wnt2b* promoters, as mentioned above. Hedgehog signals should induce *WNT2B* upregulation through GLI and FOX family members (Fig. 2).

BMP signaling cascades and WNT2B. BMP signals are transduced through BMP receptors to SMAD1, SMAD5 or SMAD8 effectors to regulate transcription of target genes in cooperation with SMAD4 (55). *ID1, ID2, ID3, MSX1, MSX2, HES1, HEY1,* and *IHH* are representative target genes of BMP signaling cascades (56-58). ID1, ID2 and ID3 are HLH transcription factors functioning as inhibitors of tissue-specific bHLH transcription factors. MSX1 and MSX2 are homeobox transcription factors functioning as inhibitors of tissue-specific bHLH transcription factors. HES1 and HEY1 are N-box-binding transcriptional repressors to downregulate tissue-specific bHLH transcription factors. BMP signals downregulate *WNT2B* expression due to the repression of bHLH-induced transcription via ID1, ID2, ID3, MSX1, MSX2, HES1 or HEY1.

In adult mouse intestine, *Wnt2b* is expressed in mesenchymal cells (59), whereas *Indian Hedgehog* (*Ihh*) is expressed in differentiated epithelial enterocytes (60). We previously underscored the role of BMP-IHH signaling loop in the gastrointestinal homeostasis and carcinogenesis (61). Because epithelial IHH is able to induce mesenchymal WNT2B expression as mentioned above, we propose the BMP-IHH-WNT2B signaling loop in this study.

Based on these facts, it was concluded that BMP signals directly downregulate *WNT2B* expression in intestinal epithelial cells through the impediment of the bHLH-driven transcription,

and also that BMP signals indirectly upregulate *WNT2B* expression in intestinal mesenchymal cells through Hedgehog-mediated transcription (Fig. 2).

Canonical WNT signaling cascades and WNT2B. Canonical WNT signals are transduced through FZD and LRP5/6 receptors to activate transcription of target genes via the ß-catenin-TCF/LEF complex, as mentioned above. MYC is a key target of canonical WNT signaling activation in colorectal cancer (22). MYC is one of bHLH-LZ transcription factors binding to the CACGTG motif to regulate cellular proliferation and differentiation (62). Manual inspection in this study revealed that consensus TCF/LEF- or MYC-binding site within *WNT2B* promoter was not conserved in mammals (data not shown). WNT and BMP signals synergistically induce upregulation of *ID2, MSX1,* and *MSX2* mRNAs (63). Because ID2, MSX1 and MSX2 are involved in the inhibition of bHLH-mediated transcription as mentioned above, it was predicted that canonical WNT signals downregulate *WNT2B* expression via ID and MSX family members (Fig. 2).

Notch signaling cascades and WNT2B. Notch ligands induce Notch signaling activation through the NICD-CSL complex, and *HES1, HES5, HEY1, HEY2* and *HEYL* are representative target genes of Notch signaling cascades (64-67). Manual inspection in this study revealed that the consensus CSL-binding site within *WNT2B* promoter was not conserved among mammals (data not shown). On the other hand, HES/HEY-binging N-box within proximal promoter region of *WNT2B* was conserved in mammals (Fig. 1). Together these facts indicate that Notch signals downregulate *WNT2B* expression via HES/HEY family members (Fig. 2).

Chronic inflammation and WNT2B. Chronic inflammation in tumor microenvironment is advantageous for tumor progression, because mediators or effectors of chronic inflammation support the proliferation and survival of tumor cells (68,69). NF-κB and STAT3 are representative transcription factors involved in inflammation-associated carcinogenesis. Because *WNT2B* is upregulated in chronic inflammation-associated diseases such as primary biliary cirrhosis (35) and inflammatory bowel disease (35,36), we next investigated the causal link between chronic inflammation and *WNT2B* expression. Consensus STAT3-binding site was not identified conserved in the *WNT2B* promoter region in this study (data not shown), while *in silico* prediction of NF-κB-binding site is not practical at present. Recently, *Sonic Hedgehog* (*Shh*) was identified as an NK-κB target gene (70). Because epithelial Hedgehog induces *WNT2B* upregulation in mesenchymal cells as mentioned above, we propose the inflammation-SHH-WNT2B signaling loop (Fig. 2).

Discussion

Refined integrative genomic analyses on *WNT2B* orthologs were carried out to elucidate the transcriptional mechanisms of *WNT2B* in this study. GLI- and double FOX-binding sites within the distal promoter region as well as HES/HEY-, bHLH- and Sp1-binding sites within the proximal promoter region were well conserved in mammalian *WNT2B* orthologs (Fig. 1).

GLI-binding site in human *WNT2B* promoter was completely conserved in chimpanzee *WNT2B* and rat *Wnt2b* promoters, and was almost conserved in mouse *Wnt2b* promoter except one base substitution (Fig. 1). Double FOX-binding sites within human *WNT2B* promoter were completely conserved in chimpanzee *WNT2B*, rat *Wnt2b*, and mouse *Wnt2b* promoters (Fig. 1). Hedgehog signals initially stabilize the GLI2 activator to upregulate primary Hedgehog target genes, such as *GLI1, FOXA2, FOXC2, FOXE1, FOXF1* and *FOXL1*. Hedgehog-GLI2-induced GLI1 upregulation augments the Hedgehog signaling quantitatively as well as qualitatively (29). Based on the conserved GLI- and double FOX-binding sites within distal *WNT2B* promoter region, it was concluded that Hedgehog signals should induce *WNT2B* upregulation through GLI and FOX family members (Fig. 2).

HES/HEY- and bHLH-binding sites in human *WNT2B* promoter were completely conserved in chimpanzee *WNT2B*, rat *Wnt2b*, and mouse *Wnt2b* promoters (Fig. 1). Notch and BMP signals upregulate HES/HEY family members to repress *WNT2B* transcription, whereas BMP and WNT signals upregulate ID and MSX family members to impede bHLH-induced *WNT2B* upregulation. Notch, BMP, and WNT signals synergistically repress *WNT2B* transcription due to the impediment of the bHLH-induced *WNT2B* transcription (Fig. 2).

We emphasized the BMP-IHH signaling loop to maintain the homeostasis of stem-cell signaling network (61), and Kasperczyk *et al* reported the NF-κB-SHH signaling loop during chronic inflammation (70). These facts were combined with the results of this study to propose that the BMP-IHH and inflammation-SHH signaling loops are involved in *WNT2B* upregulation during embryogenesis, adult tissue homeostasis, and carcinogenesis.

References

1. Katoh M: *WNT* and *FGF* gene clusters. Int J Oncol 21: 1269-1273, 2002.
2. Katoh M: Regulation of WNT signaling molecules by retinoic acid during neuronal differentiation in NT2 cells: Threshold model of WNT action. Int J Mol Med 10: 683-687, 2002.
3. Nusse R: Wnts and Hedgehogs: lipid-modified proteins and similarities in signaling mechanisms at the cell surface. Development 130: 5297-5305, 2003.
4. Moon RT, Kohn AD, De Ferrari GV and Kaykas A: WNT and ß-catenin signalling: diseases and therapies. Nat Rev Genet 5: 691-701, 2004.
5. Clevers H: Wnt/ß-catenin signaling in development and disease. Cell 127: 469-480, 2006.
6. Katoh M, Hirai M, Sugimura T and Terada M: Cloning, expression and chromosomal localization of *Wnt13*, a novel member of the *Wnt* gene family. Oncogene 13: 873-876, 1996.
7. Zakin LD, Mazan S, Maury M, Martin N, Guénet JL and Brûlet P: Structure and expression of *Wnt13*. Mech Dev 73: 107-116, 1998.
8. Jasoni C, Hendrickson A and Roelink H: Analysis of chicken *Wnt-13* expression demonstrates coincidence with cell division in the developing eye and is consistent with a role in induction. Dev Dyn 215: 215-224, 1999.
9. Fischer S, Draper BW and Neumann CJ: The zebrafish *fgf24* mutant identifies an additional level of Fgf signaling involved in vertebrate forelimb initiation. Development 130: 3515-3524, 2003.
10. Katoh M: WNT2B: comparative integromics and clinical applications. Int J Mol Med 16: 1103-1108, 2005.
11. Katoh M, Kirikoshi H, Saitoh T, Sagara N and Koike J: Alternative splicing of the *WNT2B*/*WNT13* gene. Biochem Biophys Res Commun 275: 209-216, 2000.
12. Katoh M, Kirikoshi H, Terasaki H and Shiokawa K: *WNT2B2* mRNA, upregulated in primary gastric cancer, is a positive regulator of the WNT- ß-catenin-TCF signaling pathway. Biochem Biophys Res Commun 289: 1093-1098, 2001.

13. Jiang J and Struhl G: Regulation of the Hedgehog and Wingless signalling pathways by the F-box/WD40-repeat protein Slimb. Nature 391: 493-496, 1998.
14. Winston JT, Strack P, Beer-Romero P, Chu CY, Elledge SJ and Harper JW: The $SCF^{ß\text{-}TRCP}$-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IκBα and ß-catenin and stimulates IκBα ubiquitination *in vitro*. Genes Dev 13: 270-283, 1999.
15. Koike J, Sagara N, Kirikoshi H, Takagi A, Miwa T, Hirai M and Katoh M: Molecular cloning and genomic structure of the *ßTRCP2* gene on chromosome 5q35.1. Biochem Biophys Res Commun 269: 103-109, 2000.
16. Saitoh T and Katoh M: Expression profiles of *ßTRCP1* and *ßTRCP2*, and mutation analysis of *ßTRCP2* in gastric cancer. Int J Oncol 18: 959-964, 2001.
17. Spiegelman VS, Tang W, Katoh M, Slaga TJ and Fuchs SY: Inhibition of HOS expression and activities by Wnt pathway. Oncogene 21: 856-860, 2002.
18. Wong HC, Bourdelas A, Krauss A, *et al*: Direct binding of the PDZ domain of Dishevelled to a conserved internal sequence in the C-terminal region of Frizzled. Mol Cell 12: 1251-1260, 2003.
19. Tolwinski NS, Wehrli M, Rives A, Erdeniz N, DiNardo S and Wieschaus E: Wnt signal can be transmitted through LRP5/6 and Axin independently of GSK3ß activity. Dev Cell 4: 407-418, 2003.
20. Katoh M and Katoh M: WNT signaling pathway and stem cell signaling network. Clin Cancer Res 13: 4042-4045, 2007.
21. Korinek V, Barker N, Morin PJ, *et al*: Constitutive transcriptional activation by a ß-catenin-Tcf complex in APC-/- colon carcinoma. Science 275: 1784-1787, 1997.
22. He TC, Sparks AB, Rago C, *et al*: Identification of *c-MYC* as a target of the APC pathway. Science 281: 1509-1512, 1998.
23. Tetsu O and McCormick F: ß-catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature 398: 422-426, 1999.
24. Garciadiego-Cazares D, Rosales C, Katoh M and Chimal-Monroy J: Coordination of chondrocyte differentiation and joint formation by α5ß1 integrin in the developing appendicular skeleton. Development 131: 4735-4742, 2004.
25. Katoh M: WNT signaling in stem cell biology and regenerative medicine. Curr Drug Targets 9: 565-570, 2008.
26. Bailey J, Singh PK and Hollingsworth MA: Cancer metastasis facilitated by developmental pathways: Sonic hedgehog, Notch, and bone morphogenetic proteins. J Cell Biochem 102: 829-839, 2007.
27. Katoh M: Dysregulation of stem cell signaling network due to germline mutation, SNP, *Helicobacter pylori* infection, epigenetic change, and genetic alteration in gastric cancer. Cancer Biol Ther 6: 832-839, 2007.
28. Katoh M: Cancer genomics and genetics of *FGFR2*. Int J Oncol 33: 233-237, 2008.
29. Katoh Y and Katoh M: Hedgehog signaling, epithelial-to-mesenchymal transition, and miRNA. Int J Mol Med 22: 271-275, 2008.
30. Van den Berg DJ, Sharma AK, Bruno E and Hoffman R: Role of members of the *Wnt* gene family in human hematopoiesis. Blood 92: 3189-3202, 1998.
31. Katoh M: Differential regulation of *WNT2* and *WNT2B* expression in human cancer. Int J Mol Med 8: 657-660, 2001.
32. Bonifas JM, Pennypacker S, Chuang PT, *et al*: Activation of expression of Hedgehog target genes in basal cell carcinomas. J Invest Dermatol 116: 739-742, 2001.
33. Rhee CS, Sen M, Lu D, *et al*: Wnt and Frizzled receptors as potential targets for immunotherapy in head and neck squamous cell carcinomas. Oncogene 21: 6598-6605, 2002.
34. Benhaj K, Akcali KC and Ozturk M: Redundant expression of canonical Wnt ligands in human breast cancer cell lines. Oncol Rep 15: 701-707, 2006.
35. Tanaka A, Leung PS, Kenny TP, *et al*: Genomic analysis of differentially expressed genes in liver and biliary epithelial cells of patients with primary biliary cirrhosis. J Autoimmun 17: 89-98, 2001.
36. You J, Nguyen AV, Albers CG, Lin F and Holcombe RF: Wnt pathway-related gene expression in inflammatory bowel disease. Dig Dis Sci 53: 1013-1019, 2008.
37. Katoh Y and Katoh M: Conserved POU-binding site linked to SP1-binding site within *FZD5* promoter. Int J Oncol 30: 751-755, 2007.
38. Katoh M and Katoh M: Comparative integromics on *FZD7* orthologs. Int J Mol Med 19: 529-533, 2007.
39. Katoh Y and Katoh M: Comparative genomics on *PROM1* gene encoding stem cell marker CD133. Int J Mol Med 19: 967-970, 2007.
40. Katoh M and Katoh M: Conserved POU/OCT- and GATA-binding sites in 5'-flanking promoter region of mammalian *WNT8B* orthologs. Int J Oncol 30: 1273-1277, 2007.
41. Katoh M and Katoh M: Comparative integromics on *JMJD1C* gene encoding histone demethylase. Int J Oncol 31: 219-223, 2007.
42. Katoh Y and Katoh M: Comparative integromics on JMJD2A, JMJD2B and JMJD2C. Int J Mol Med 20: 269-273, 2007.
43. Katoh M and Katoh M: Comparative integromics on non-canonical WNT or planar cell polarity signaling molecules. Int J Mol Med 20: 405-409, 2007.
44. Katoh Y and Katoh Y: Integrative genomic analyses on GLI2. Int J Oncol 33: 881-886, 2008.
45. Katoh M: Molecular evolution of *WNT2B* orthologs. Int J Oncol 26: 1135-1139, 2005.
46. Beachy PA, Karhadkar SS and Berman DM: Tissue repair and stem cell renewal in carcinogenesis. Nature 432: 324-331, 2004.
47. Hooper JF and Scott MP: Communicating with Hedgehogs. Nat Rev Mol Cell Biol 6: 306-317, 2005.
48. Katoh Y and Katoh M: Hedgehog signaling pathway and gastrointestinal stem cell signaling network. Int J Mol Med 18: 1019-1023, 2006.
49. Hahn H, Wicking C, Zaphiropoulos PG, *et al*: Mutations of the human homologue of *Drosophila patched* in the nevoid basal cell carcinoma syndrome. Cell 85: 841-851, 1996.
50. Johnson RL, Rothman AL, Xie J, *et al*: Human homolog of *patched*, a candidate gene for the basal cell nevus syndrome. Science 272: 1668-1671, 1996.
51. Epstein EH: Basal cell carcinomas: attack of the Hedgehog. Nat Rev Cancer 8: 743-754, 2008.
52. Berman DM, Karhadkar SS, Maitra A, *et al*: Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumors. Nature 425: 846-851, 2003.
53. Katoh Y and Katoh M: Hedgehog signaling in gastric cancer. Cancer Biol Ther 4: 1050-1054, 2005.
54. Kubo M, Nakamura M, Tasaki A, *et al*: Hedgehog signaling pathway is a new therapeutic target for patients with breast cancer. Cancer Res 64: 6071-6074, 2004.
55. Hardwick JC, Kodach L, Offerhaus J and van den Brink GR: BMP signaling in colorectal cancer. Nat Rev Cancer 8: 806-812, 2008.
56. Hollnagel A, Oehlmann V, Heymer J, Rüther U and Nordheim A: *Id* genes are direct targets of BMP induction in embryonic stem cells. J Biol Chem 274: 19838-19845, 1999.
57. Dahlqvist C, Blokzijl A, Chapman G, *et al*: Functional Notch signaling is required for BMP4-induced inhibition of myogenic differentiation. Development 130: 6089-6099, 2003.
58. Seki K and Hata A: *Indian Hedgehog* gene is a target of the BMP signaling pathway. J Biol Chem 279: 18544-18549, 2004.
59. Gregorieff A, Pinto D, Begthel H, Destrée O, Kielman M and Clevers H: Expression pattern of WNT signaling components in the adult intestine. Gastroenterology 129: 626-638, 2005.
60. Van den Brink GR, Bleuming SA, Hardwick JC, *et al*: Indian Hedgehog is an antagonist of Wnt signaling in colonic epithelial cell differentiation. Nat Genet 36: 277-282, 2004.
61. Katoh M: Networking of WNT, FGF, Notch, BMP, and Hedgehog signaling pathways during carcinogenesis. Stem Cell Rev 3: 30-38, 2007.
62. Meyer N and Penn LZ: Reflecting on 25 years with MYC. Nat Rev Cancer 8: 976-990, 2008.
63. Willert J, Epping M, Pollack JR, Brown PO and Nusse R: A transcriptional response to Wnt protein in human embryonic carcinoma cells. BMC Dev Biol 2: 8, 2002.
64. Artavanis-Tsakonas S, Rand MD and Lake RJ: Notch signaling: cell fate control and signal integration in development. Science 284: 770-776, 1999.
65. Radtke F and Raj K: The role of Notch in tumorigenesis: oncogene or tumor suppressor? Nat Rev Cancer 3: 765-767, 2003.
66. Katoh M and Katoh M: Notch signaling in gastrointestinal tract. Int J Oncol 30: 247-251, 2007.
67. Katoh M and Katoh M: Integrative genomic analyses on HES/HEY family. Int J Oncol 31: 461-466, 2007.
68. Karin M: NF-κB in cancer development and progression. Nature 441: 431-436, 2006.
69. Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. Nature 454: 436-444, 2008.
70. Kasperczyk H, Baumann B, Debatin KM and Fulda S: Characterization of sonic hedgehog as a novel NF-κB target gene that promotes NF-κB-mediated apoptosis resistance and tumor growth *in vivo*. FASEB J 23: 21-33, 2009.