Multi-layered prevention and treatment of chronic inflammation, organ fibrosis and cancer associated with canonical WNT/β-catenin signaling activation (Review)

MASARU KATOH

Department of Omics Network, National Cancer Center, Chuo Ward, Tokyo 104-0045, Japan

Abstract. β-catenin/CTNNB1 is an intracellular scaffold protein that interacts with adhesion molecules (E-cadherin/CDH1, N-cadherin/CDH2, VE-cadherin/CDH5 and α-catenins), transmembrane-type mucins (MUC1/CD227 and MUC16/CA125), signaling regulators (APC, AXIN1, AXIN2 and NHERF1/EBP50) and epigenetic or transcriptional regulators (BCL9, BCL9L, CREBBP/CBP, EP300/p300, FOXM1, MED12, SMARCA4/BRG1 and TCF/LEF). Gain-of-function *CTTNB1* mutations are detected in bladder cancer, colorectal cancer, gastric cancer, liver cancer, lung cancer, pancreatic cancer, prostate cancer and uterine cancer, whereas loss-of-function *CTNNB1* mutations are also detected in human cancer. *ABCB1, ALDH1A1, ASCL2, ATF3, AXIN2, BAMBI, CCND1, CD44, CLDN1, CTLA4, DKK1, EDN1, EOMES, FGF18, FGF20, FZD7, IL10, JAG1, LEF1, LGR5, MITF, MSX1, MYC, NEUROD1, NKD1, NODAL, NOTCH2, NOTUM, NRCAM, OPN, PAX3, PPARD, PTGS2, RNF43, SNAI1, SP5, TCF7, TERT, TNFRSF19, VEGFA* and *ZNRF3* are representative β-catenin target genes. β-catenin signaling is involved in myofibroblast activation and subsequent pulmonary fibrosis, in addition to other types of fibrosis. β-catenin and NF-κB signaling activation are involved in field cancerization in the stomach associated with *Helicobacter pylori* (*H. pylori*) infection and in the liver associated with hepatitis C virus (HCV) infection and other etiologies. β-catenin-targeted therapeutics are functionally classified into β-catenin inhibitors targeting upstream regulators (AZ1366, ETC-159, G007-LK, GNF6231, ipafricept, NVP-TNKS656, rosmantuzumab, vanticumab, WNT-C59, WNT974 and XAV939), β-catenin inhibitors targeting protein-protein interactions (CGP049090, CWP232228, E7386, ICG-001, LF3 and PRI-724), β-catenin inhibitors targeting epigenetic regulators (PKF118-310), β-catenin inhibitors targeting mediator complexes (CCT251545 and cortistatin A) and β-catenin inhibitors targeting transmembrane-type transcriptional outputs, including CD44v6, FZD7 and LGR5. Eradicating *H. pylori* and HCV is the optimal approach for the first-line prevention of gastric cancer and hepatocellular carcinoma (HCC), respectively. However, β-catenin inhibitors may be applicable for the prevention of organ fibrosis, second-line HCC prevention and treating β-catenin-driven cancer. The multi-layered prevention and treatment strategy of β-catenin-related human diseases is necessary for the practice of personalized medicine and implementation of precision medicine.

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1. Introduction

The *CTNNB1* gene encodes the intracellular scaffold protein β-catenin (1), which interacts with adhesion molecules (E-cadherin/CDH1, N-cadherin/CDH2, VE-cadherin/CDH5 and α-catenins) (2,3), transmembrane mucins (MUC1/CD227 and MUC16/CA125) (4,5), cytoplasmic signaling regulators (APC, AXIN1, AXIN2, BTRC/βTRCP1, BTRC2/βTRCP2 and NHERF1/EBP50) (6,7), and nuclear transcriptional regulators (BCL9, BCL9L, CREBBP/CBP, EP300/p300, FOXM1, LEF1/TCF7L3, MED12, SMARCA4/BRG1, SPDEF, TCF7/TCF-1, TCF7L1/TCF-3 and TCF7L2/TCF-4) (8-10). Based on protein-protein interactions (PPIs), β-catenin is involved in cell-cell adhesion, cellular signaling and transcriptional regulation (Fig. 1A).

Correspondence to: Dr Masaru Katoh, Department of Omics Network, National Cancer Center, 5-1-1 Tsukiji, Chuo Ward, Tokyo 104-0045, Japan
E-mail: mkatoh-kkr@umin.ac.jp

β-catenin undergoes post-translational modifications, including acetylation, glycosylation, methylation, phosphorylation and ubiquitylation. Oncogenic tyrosine kinases phosphorylate β-catenin at Y654 to release β-catenin from cadherin complexes, whereas canonical WNT signals prevent the phosphorylation of β-catenin at S33, S37, T41 and S45 to release β-catenin from ubiquitylation-mediated degradation (1). The β-TRCP complex is involved in the poly-ubiquitylation of S33/S37/T41/S45-phosphorylated β-catenin and subsequent proteasome-mediated degradation (9,11), whereas USP7 is involved in the de-ubiquitylation and stabilization of β-catenin (12). Stabilized β-catenin is translocated into the nucleus to activate the transcription of TCF/LEF target genes (Fig. 1B). The acetylation of β-catenin at K49 leads to transcriptional activation, whereas the methylation of β-catenin at K49 leads to transcriptional repression (13,14). The functions of β-catenin are regulated by its localization, PPIs and stability based on post-translational modifications.

Representative β-catenin target genes (Fig. 1C) include *ABCB1, ALDH1A1, ASCL2, ATF3, AXIN2, BAMBI, CCND1 (Cyclin D1), CD44, Claudin-1 (CLDN1), CTLA4, DKK1, EDN1, EOMES, FGF18, FGF20, FZD7, GBX1, IL10 (IL-10), Jagged-1 (JAG1), LEF1, LGR5, MITF, MSX1, MYC (c-Myc), NEUROD1, NKD1, NODAL, NOTCH2, NOTUM, NRCAM, osteopontin (OPN), PAX3, PPARD, PTGS2 (COX2), RNF43, SNAI1 (Snail), SP5, TCF7, TERT, TNFRSF19 (Troy), VEGFA (VEGF)* and *ZNRF3* (1,15-28). CTTTGATAT is the consensus DNA-binding motif of TCF-3, whereas CTCGCGAGA is the major DNA-binding motif of TCF-1 (29). By contrast, lysine acetyltransferases CBP and p300 are reported to differentially regulate β-catenin-dependent transcriptional programs in stem cells to propel them towards self-renewal and differentiation, respectively (30). β-catenin target genes are upregulated in a cell context-dependent manner based on the epigenetic status of their regulatory regions and availability of transcriptional regulators (1).

Inflammation is an immune response to repair tissue damage caused by infectious agents, environmental stimuli and endogenous irritants. The failure to resolve acute inflammation leads to chronic inflammation characterized by the continuous activation of macrophages and lymphocytes in the inflamed tissue microenvironment and elevated levels of the pro-inflammatory cytokines IL-1β, IL-6, IL-17 and TNF-α (31,32). Chronic persistent inflammation then leads to the collapse of homeostatic interactions among epithelial cells, stromal cells and immune cells in the tissue microenvironment, which causes organ fibrosis through the myofibroblast-like transition of tissue-resident fibroblasts, stellate cells or bone marrow-derived fibrocytes, and the subsequent deposition of extracellular matrix (ECM) components, including collagen, fibronectin and hyaluronan (Fig. 2A).

β-catenin signaling dysregulation is involved in chronic inflammation, organ fibrosis, and various types of human cancer (1,33). However, β-catenin-targeted therapy is not yet approved for the treatment of patients with β-catenin-related diseases. As β-catenin is an intracellular protein without intrinsic enzymatic activity, it is difficult to target β-catenin for drug development. In this review, gain- and loss-of-function β-catenin alterations in human cancer types are summarized, and the pathophysiology of β-catenin-related chronic inflammation and/or organ fibrosis are presented with emphases on carcinogenesis in the stomach, liver and lungs. Finally, the development of β-catenin inhibitors targeting its upstream regulators, PPIs and downstream effectors are reviewed.

2. Gain- and loss-of-function β-catenin alterations in human cancer

β-catenin-dependent transcription is aberrantly activated in human cancer due to gain-of-function mutations in the *CTNNB1* gene itself, in addition to genetic alterations in the *APC, AXIN2, RNF43* and *RSPO3* genes involved in the canonical WNT/β-catenin signaling cascade, upregulation of canonical WNT ligands in the tumor microenvironment, or Y654 phosphorylation of β-catenin by oncogenic tyrosine kinases, including BCR-ABL1 fusion, FLT3-ITD mutation and overexpression of MET (34).

Missense mutations at or in-frame deletions around S33, S37, T41 and S45 in β-catenin give rise to gain-of-function β-catenin mutants that are resistant to ubiquitylation-mediated proteasomal degradation and induce the upregulation of oncogenic target genes, including *CCND1* and *MYC*, in adrenocortical tumors, bladder cancer, colorectal cancer, gastric cancer, liver cancer, lung cancer, pancreatic cancer, prostate cancer and uterine cancer (35-40). Aberrant β-catenin-dependent transcriptional activation drives human carcinogenesis through the induction of cancer stem cell (CSC) features, bulk tumor proliferation and the epithelial-to-mesenchymal transition (EMT) in the solid tumors mentioned above.

By contrast, nonsense or frame-shift mutations in β-catenin, including R95*, K335fs, R449fs, E458fs, R474*, R535*, E571* and E642fs, also occur in human cancer, including gastric cancer and head and neck squamous cell carcinoma (37,41-43). In melanoma, decreased β-catenin not only promotes invasion and metastasis through disrupted cell-cell adhesion but also resistance to targeted therapy through MITF/APE1 axis repression (44,45). *Ctnnb1* haploinsufficiency has been shown to promote aggressiveness and metastasis in a mouse model of HER2-positive basal breast cancer (46). β-catenin exerts not only oncogenic but also tumor-suppressor functions in a context-dependent manner.

β-catenin mutations are classified as i) gain-of-function mutations clustered at or around S33, S37, T41 and S45, ii) loss-of-function mutations due to nonsense or frame-shift mutations and iii) other mutations to be further characterized. In addition to these coding mutations, copy number gain (47) and regulatory mutations in the proximal promoter region (48) of the *CTNNB1* gene encoding β-catenin have been reported in prostate cancer and breast cancer, respectively. Owing to the pro- and anti-oncogenic roles of β-catenin, integrative omics analyses, including whole-genome sequencing, transcriptome and immunohistochemical analyses, are necessary to precisely prescribe β-catenin-targeted therapeutics in personalized or precision medicine in the future.

3. Activation of β-catenin in chronic gastritis and gastric cancer associated with *Helicobacter pylori* infection

Helicobacter pylori (*H. pylori*) is a Gram-negative, helical rod-shaped microaerophilic bacterium that specifically
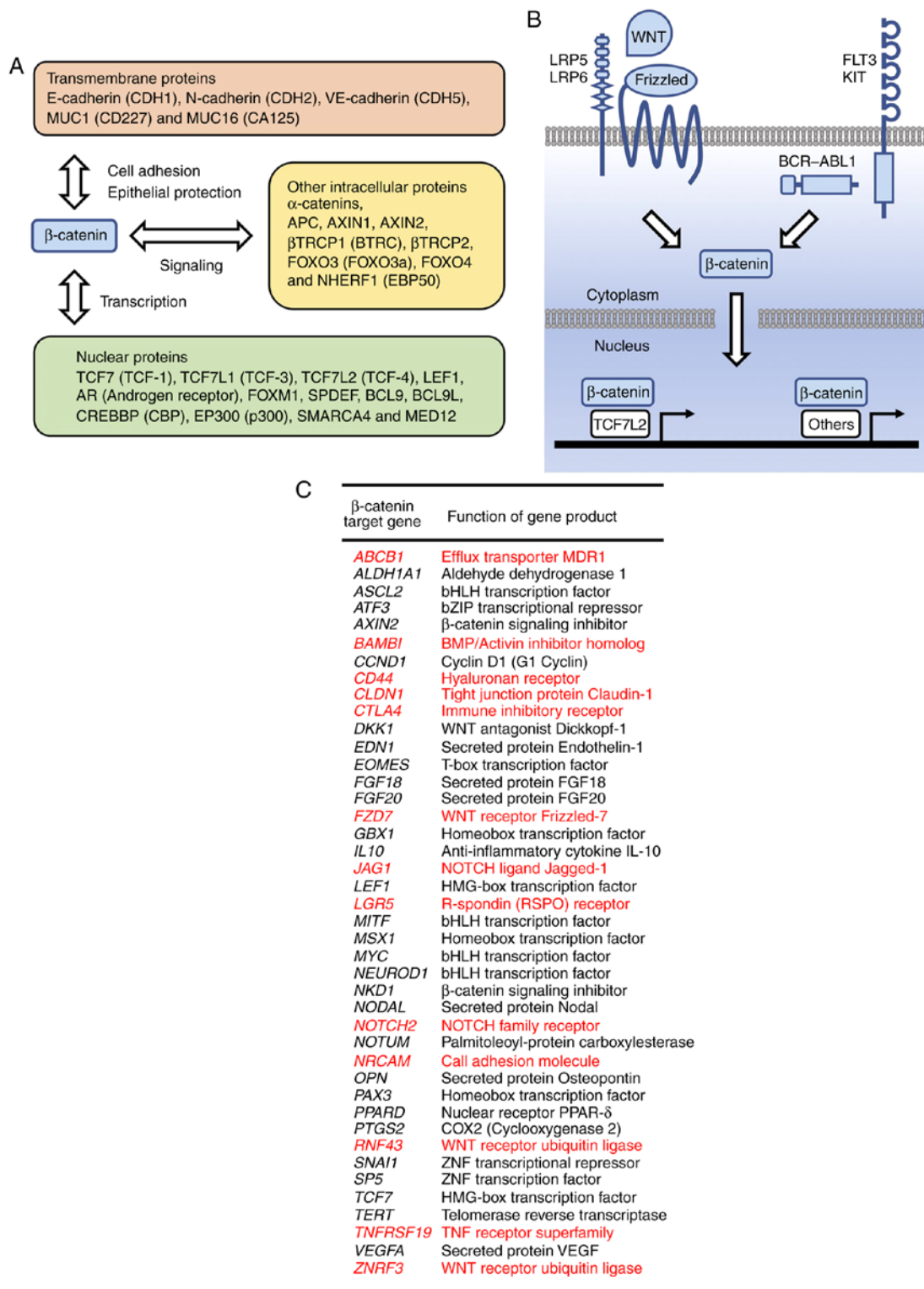
Figure 1. Overview of β-catenin functions at a glance. (A) Protein-protein interactions of β-catenin. β-catenin is a scaffold protein that interacts with adhesion molecules (E-cadherin, N-cadherin and VE-cadherin), transmembrane-type mucins (MUC1 and MUC16), signaling regulators (APC, AXIN1, AXIN2 and NHERF1) and epigenetic or transcriptional regulators (BCL9, BCL9L, CREBBP, EP300, FOXM1, LEF1, MED12, SMARCA4, TCF7, TCF7L1 and TCF7L2). β-catenin is involved in cell adhesion, intracellular signaling and transcription. The functions of β-catenin are regulated by its localization, protein-protein interactions and stability based on post-translational modifications. (B) β-catenin signaling into the nucleus. Canonical WNT signals prevent β-catenin phosphorylation at S33, S37, T41 and S45 to release β-catenin from ubiquitylation-mediated degradation, whereas oncogenic tyrosine kinases phosphory-late β-catenin at Y654 to release β-catenin from cadherin complexes. Stabilized β-catenin is translocated into the nucleus to activate the transcription of TCF/LEF-target genes and transcription dependent on other transcription factors in a cellular context-dependent manner based on epigenetic states and the availability of transcriptional regulators at the regulatory regions of target genes. (C) Transcriptional targets of β-catenin. *ABCB1, ALDH1A1, ASCL2, ATF3, AXIN2, BAMBI, CCND1, CD44, CLDN1, CTLA4, DKK1, EDN1, EOMES, FGF18, FGF20, FZD7, GBX1, IL10, JAG1, LEF1, LGR5, MITF, MSX1, MYC, NEUROD1, NKD1, NODAL, NOTCH2, NOTUM, NRCAM, OPN, PAX3, PPARD, PTGS2, RNF43, SNAI1, SP5, TCF7, TERT, TNFRSF19, VEGFA* and *ZNRF3* are representative β-catenin target genes. β-catenin target genes encoding transmembrane proteins, including CD44v6, FZD7 and LGR5, are shown in red. Transmembrane proteins upregulated by the β-catenin signaling are rational targets of antibody-based drugs, including monoclonal antibodies, antibody-drug conjugates, bi-specific antibodies and chimeric antigen receptor-modified T cells.
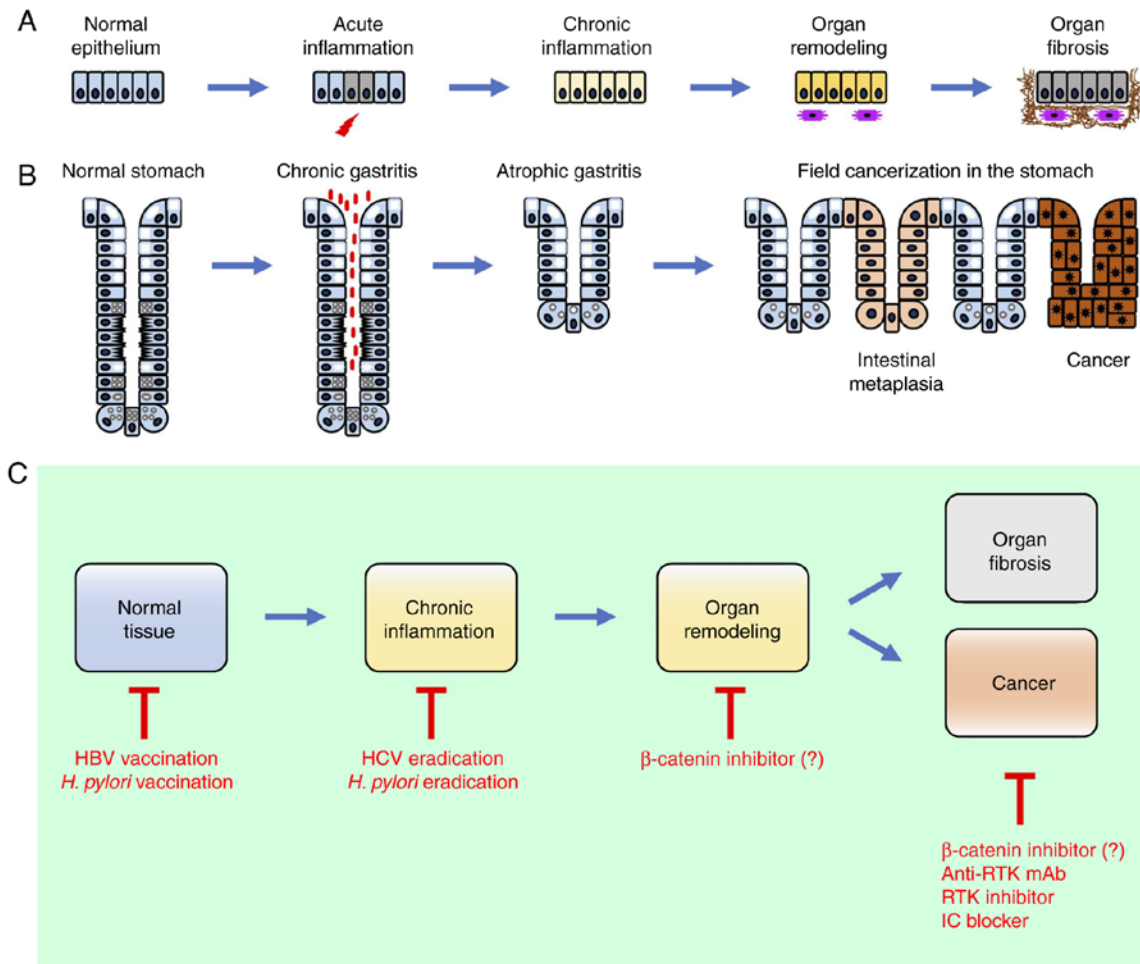
Figure 2. Precision medicine of chronic inflammation, organ fibrosis and cancer associated with aberrant β-catenin signaling activation. (A) Chronic persistent inflammation and fibrosis. The failure to resolve acute inflammation leads to chronic inflammation, organ remodeling and fibrosis with the subsequent deposition of extracellular matrix. β-catenin is involved in the activation of myofibroblast-like cells during organ remodeling and fibrosis. (B) Field cancerization in the stomach associated with *H. pylori* infection. Decades of persistent *H. pylori* infection lead to the sequential progression of chronic gastritis, atrophic gastritis, intestinal metaplasia and gastric cancer. During chronic active gastritis, *H. pylori* injects CagA into epithelial cells to activate MET and β-catenin signaling to promote epithelial proliferation. In a subset of human gastric cancer, the canonical WNT/β-catenin signaling cascade is aberrantly activated due to gain-of-function mutations in the *CTNNB1* gene or loss-of-function mutations in the *APC* or *RNF43* gene. β-catenin is involved in *H. pylori*-related chronic active gastritis and gastric cancer. (C) Multi-layered prevention and treatment of β-catenin-related human diseases. Vaccines are available for the prevention of cancer-associated infections with HBV and *H. pylori*. The eradication of HCV and *H. pylori* is an optimal first-line prevention of field cancerization in the liver and stomach, respectively. Investigational β-catenin inhibitors are expected to be applicable for organ fibrosis prevention, second-line HCC prevention and treating β-catenin-driven cancer. The multi-layered prevention and treatment strategy of β-catenin-related human diseases is realistic for the practice of personalized medicine at present and necessary for the implementation of precision medicine in the future. *H. pylori, Helicobacter pylori*; HBV, hepatitis B virus; HCV, hepatitis C virus; RTK, receptor tyrosine kinase; IC, immune checkpoint; mAb, monoclonal antibody.

colonizes the human stomach through interactions between bacterial BabA and HopQ adhesins to host ABO blood antigens and CEACAM, respectively (49,50). *H. pylori* secretes urease for ammonia production from urea to survive in an microenvironment of high acidity, and they deliver CagA, VacA, γ-glutamyl transpeptidase and other virulence factors to the gastric microenvironment to elicit epithelial polarity dysregulation and mucosal damage, leading to pro-inflammatory cytokine secretion and immune tolerance (51,52). Cytokine-mediated T helper cell (Th)1 and Th17 responses induce anti-*H. pylori* acquired immunity within *H. pylori*-colonized microenvironments, whereas the dendritic cell (DC)-mediated expansion of regulatory T (Treg) cells leads to immune evasion within the gastric microenvironment and cross-tolerance to allergens in extra-gastric microenvironments (51,53).

In human organoid culture systems infected with *H. pylori*, CagA is injected into epithelial cells through the type IV secretion system and associates with the HGF receptor (MET) and hyaluronan receptor (CD44) to promote epithelial proliferation, in part through β-catenin signaling activation (54-56). By contrast, in a mouse model with artificial *H. pylori* infection, Rspo3 is upregulated to expand Lgr5+ gastric stem/progenitor cells (57). As WNT2B (WNT-13) was originally cloned and characterized as a canonical WNT ligand derived from the human stomach (58,59), RSPO3 can enhance canonical WNT/β-catenin signaling activation through the release of Frizzled family WNT receptors from RNF43/ZNRN3-mediated repression (1,60) and thus promote epithelial proliferation and gastric hyperplasia. The WNT/β-catenin signaling cascade is aberrantly activated in human gastric cancer due to gain-of-function mutations in the

CTNNB1 gene, as mentioned above, and to loss-of-function mutations in the *APC* and *RNF43* genes (37). Together, these findings indicate that β-catenin serves key roles in *H. pylori*-related chronic active gastritis and gastric cancer.

Decades of persistent *H. pylori* infection lead to field cancerization in the stomach (Fig. 2B) through the sequential progression of chronic active gastritis, fundic gland atrophy, intestinal metaplasia and gastric cancer (61-63). Although *H. pylori* eradication in relatively older patients with irreversible gastric atrophy and intestinal metaplasia may not contribute to the prevention of gastric carcinogenesis due to preexisting genetic and epigenetic alterations in the premalignant lesions, *H. pylori* eradication in relatively younger patients with chronic active gastritis and/or reversible atrophy is optimal for the prevention of gastric carcinogenesis (Fig. 2C). A triple or quadruple regimen (proton-pump inhibitor, amoxicillin and clarithromycin with or without metronidazole) is prescribed for the eradication of *H. pylori* (64-67). To avoid the prevalence of drug-resistant *H. pylori,* the quadruple regimen is recommended for *H. pylori* eradication in Canada, Europe and the US.

By contrast, atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab are representative immune checkpoint inhibitors that are approved for the treatment of patients with certain types of cancer (34,68). As *H. pylori* eradication eliminates *H. pylori*-related chronic inflammation and *H. pylori*-specific immune evasion, and reduces non-specific immune evasion caused by the DC-mediated Treg expansion and IL-10 elevation in the gastric microenvironment, *H. pylori* eradication may synergize with immune checkpoint inhibitors for the treatment of advanced gastric cancer with chronic active gastritis.

4. Activation of β-catenin in liver fibrosis and hepatocellular carcinoma

Chronic liver inflammation associated with hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, alcohol abuse, non-alcoholic fatty liver disease and other etiologies leads to liver fibrosis due to the myofibroblast-like transition of hepatic stellate cells or other mesenchymal cells and subsequent accumulation of excessive ECM (31,33). Liver cirrhosis is the most advanced stage of liver fibrosis, which is characterized by impaired liver functions and complications, including ascites, hepatic encephalopathy and upper gastrointestinal bleeding. Persistent liver inflammation leads to field cancerization in the liver through the sequential progression of chronic hepatitis, liver fibrosis and hepatocellular carcinoma (HCC) (69), similar to *H. pylori*-related field cancerization in the stomach (Fig. 2C).

The canonical WNT/β-catenin signaling cascade is involved in the development and homeostasis of the liver (70,71). Canonical WNT/β-catenin signals promote the proliferation of LGR5$^+$ hepatocyte progenitors in the peri-venous zone of hepatic lobules, whereas non-canonical WNT and other signals promote the proliferation of cholangiocyte progenitors in the peri-portal zone of hepatic lobules (71-73). Canonical Wnt-dependent Lgr5$^+$ liver stem/progenitor cells in an organoid culture have successfully been applied in transplantation therapy for liver failure in a rat model (74).

HCV is a single-stranded RNA virus that infects hepatocytes to produce Core, NS3/4A, NS5A, NS5B and other viral proteins, and HCV upregulates the expression of β-catenin and MYC in hepatocytes (69). HBV is a partially double-stranded DNA virus that infects hepatocytes to produce HBx, pre-S, S and other viral proteins, and HBx upregulates the expression of EPCAM, β-catenin and MYC and activates NF-κB signaling in hepatocytes (69). The RSPO-dependent activation of the WNT/β-catenin signaling cascade is involved in the activation of hepatic stellate cells to promote liver fibrosis (75), whereas a β-catenin inhibitor (PRI-724) has been shown to prevent HCV-related liver fibrosis in a mouse model (76). By contrast, the WNT/β-catenin signaling cascade is aberrantly activated in human HCC due to gain-of-function mutations in the *CTNNB1* gene and loss-of-function mutations in the *APC* and *AXIN1* genes (35). Additionally, gain-of-function β-catenin mutations (S33Y or S45Y) and the overexpression of Met have been shown to synergistically promote liver tumorigenesis in a mouse model (77), whereas an oncolytic adenovirus Ad.wnt-E1A(Δ24 bp)-TSLC1 has been shown to effectively target liver cancer cells with aberrant β-catenin-TCF/LEF signaling activation and repress *in vivo* tumorigenesis and metastasis (78). β-catenin plays key roles in multiple processes of chronic inflammation-related liver pathophysiology, including hepatocyte proliferation, stellate-cell activation, liver fibrosis and liver tumorigenesis.

The eradication of HCV is predicted to be an optimal approach to prevent HCC; as such, the eradication of *H. pylori* may be used to prevent gastric cancer. Direct-acting antivirals, including HCV NS3/4A protease inhibitors (glecaprevir and paritaprevir), HCV NS5A inhibitors (ledipasvir, ombitasvir, pibrentasvir and velpatasvir) and HCV NS5B RNA polymerase inhibitors (dasabuvir and sofosbuvir), have been developed for the eradication of HCV. For example, glecaprevir/pibrentasvir and velpatasvir/sofosbuvir are combination drugs that are approved for the treatment of HCV genotypes 1, 2, 3, 4, 5 and 6 (79,80). Studies in Italy and Spain revealed that the occurrence and recurrence of HCC were not prevented by HCV eradication (81,82), whereas a study in Japan revealed that the occurrence of HCC was successfully prevented by HCV eradication (83). As complications of non-viral etiologies of chronic liver inflammation, ethnic or genetic backgrounds, stages of liver fibrosis, and genomic or epigenetic alterations in premalignant lesions may affect the outcomes of HCV eradication, further investigations in larger cohorts are necessary to address the controversy regarding the rate of HCC development following HCV eradication.

5. Activation of β-catenin in pulmonary fibrosis and lung cancer

Fibrosis is a common pathology of chronic inflammation in the liver and other organs, including the lungs, heart and kidneys (31,32). Irreversible pulmonary fibrosis, cardiac fibrosis or renal fibrosis leads to organ destruction and subsequent decompensation, which is the final serious condition in patients with non-cancerous diseases. For example, cardiac fibrosis is caused by the transformation of cardiac fibroblasts into myofibroblasts and leads to myocardial stiffness and ventricular dysfunction (32), whereas pulmonary fibrosis

is caused by chronic inflammation associated with cancer therapy, cigarette smoking, connective tissue diseases, environmental pollution, infection, pulmonary hypertension and idiopathic pulmonary fibrosis (84,85).

Airway damage-induced canonical WNT/β-catenin signaling activation in alveolar epithelial type II cells promotes the activation and remodeling of interstitial fibroblasts; transient remodeling leads to resolution, whereas persistent remodeling leads to pulmonary fibrosis (31,85). Canonical WNT/β-catenin signaling activation in pulmonary endothelial cells activates perivascular fibroblasts to undergo a myofibroblast-like transition, which also leads to ECM accumulation and increased tissue stiffness, further promoting pulmonary fibrosis (86,87). Pulmonary injuries also induce the chemokine-dependent recruitment of monocytes and their subsequent transition into monocyte-derived alveolar macrophages that express higher levels of pro-inflammatory and pro-fibrotic genes than tissue-resident alveolar macrophages (88). However, β-catenin inhibitors, including ICG-001 and XAV939, ameliorate chronic lung injury and prevent the progression to severe pulmonary fibrosis (89,90). The canonical WNT/β-catenin signaling cascade is involved in the pathogenesis of pulmonary fibrosis.

Genetic alterations in the canonical WNT/β-catenin signaling regulators are relatively rare in human lung cancer (91). However, lung CSCs differentiate into WNT-producing supporting cells to maintain the stemness of CSCs and promote the expansion of bulk tumor cells (92). The upregulation of RSPO2 or RSPO3 leads to canonical WNT/β-catenin signaling activation in patient-derived xenograft (PDX) models of human lung cancer (93), and nuclear β-catenin staining is associated with poor prognosis in patients with lung cancer (94,95). Despite relatively infrequent genetic alterations, the canonical WNT/β-catenin signaling cascade is involved in multi-step tumorigenesis in the human lungs through WNT- and RSPO-dependent paracrine signaling.

Receptor tyrosine kinases (RTKs), including ALK, DDR2, EGFR, FGFR1, FGFR2, HER2, MET, NTRK1, RET and ROS1, are aberrantly activated in human lung cancer due to gene amplification, gene fusions or point mutations (96-99). Although ALK inhibitors (alectinib and ceritinib), an ALK/ROS1 inhibitor (crizotinib) and EGFR inhibitors (afatinib, erlotinib, gefitinib and osimertinib) are approved for the treatment of patients with lung cancer, drug resistance and recurrence are difficult to avoid due to acquired mutations in the targeted RTKs, the by-passed activation of other RTKs and β-catenin signaling activation (34). Therapy-related chronic inflammation, in addition to cancer-cell plasticity and intra-tumor heterogeneity, lead to resistance to RTK-targeted therapeutics, in part through canonical WNT signaling activation.

6. Therapeutics targeting β-catenin for preventing organ fibrosis or treating cancer

β-catenin is involved in chronic inflammation, organ fibrosis and carcinogenesis; however, β-catenin lacking intrinsic enzymatic activity is a difficult target for drug development. Antibody-based or decoy-receptor drugs targeting ligands or receptors involved in canonical WNT signaling and small-molecule compounds targeting porcupine (PORCN), tankyrase (TNKS) and β-catenin PPIs have been developed as β-catenin inhibitors for preclinical studies and/or clinical trials (34). In addition to these investigational drugs, small-molecule compounds targeting epigenetic/transcriptional regulators involved in β-catenin-dependent transcription and antibody- or peptide-based drugs binding to β-catenin-target gene products have also been suggested as β-catenin inhibitors. β-catenin-targeted therapeutics are functionally classified as follows: i) β-catenin inhibitors targeting upstream regulators, ii) β-catenin inhibitors targeting PPIs, iii) β-catenin inhibitors targeting epigenetic regulators, iv) β-catenin inhibitors targeting mediator complexes, and v) β-catenin inhibitors targeting transcriptional outputs (Fig. 3). Follows is a discussion of the pros and cons of each β-catenin inhibitor class.

β-catenin inhibitors targeting upstream regulators. Anti-FZD1/2/5/7/8 monoclonal antibody (mAb) (vantictumab) (100), anti-FZD5 mAb (IgG-2919) (101), anti-RSPO3 mAb (rosmantuzumab) (102), FZD8-Fc (ipafricept) (103), PORCN inhibitors (ETC-159, GNF6231, WNT-C59 and WNT974) (104-107) and TNKS inhibitors (AZ1366, G007-LK, NVP-TNKS656 and XAV939) (108-111) are therapeutics targeting upstream regulators of β-catenin (Fig. 3). The on-target effects on β-catenin-independent WNT signaling cascades are potential risks for anti-FZD mAbs, FZD8-Fc and PORCN inhibitors, whereas the on-target effects on WNT-independent signaling cascades are potential risks for TNKS inhibitors (34). ETC-159, ipafricept, rosmantuzumab, vantictumab and WNT974 are in clinical trials for the treatment of cancer patients.

β-catenin inhibitors targeting PPIs. CGP049090 (112), CWP232228 (113), E7386 (114), ICG-001 (89), LF3 (115) and PRI-724 (116) are representative therapeutics targeting β-catenin PPIs (Fig. 3). CGP049090, CWP232228 and LF3 inhibit the PPI between β-catenin and TCF, whereas E7386, ICG-001 and PRI-724 inhibit the PPI between β-catenin and CREBBP. Although E7386, ICG-001 and PRI-724 are claimed to repress CREBBP-dependent stemness-related transcription and reciprocally enhance EP300-dependent differentiation-related transcription, this hypothesis remains to be generalized for various types of primary tumors with complex genetic alterations. In addition, the specificities of therapeutics targeting β-catenin PPI remain to be elucidated. E7386 is in a clinical trial for cancer patients, whereas PRI-724 is in clinical trials for patients with cancer or liver fibrosis.

β-catenin inhibitors targeting epigenetic regulators. Epigenetic components that permit access of the β-catenin complex to the promoter and enhancer regions of its target genes are downstream regulators of β-catenin-dependent transcription (Fig. 3). JMJD2A (KDM4A), JMJD2B (KDM4B) and JMJD2C (KDM4C) are Jumonji domain-containing enzymes that demethylate histone H3 at K9 and K36 (H3K9 and H3K36) (117,118). JMJD2C associated with β-catenin and chromatin is required for the expression of *CCND1* and cell growth in colorectal cancer cells (119). Mouse Jmjd2a and Jmjd2c are required for the self-renewal of embryonic stem
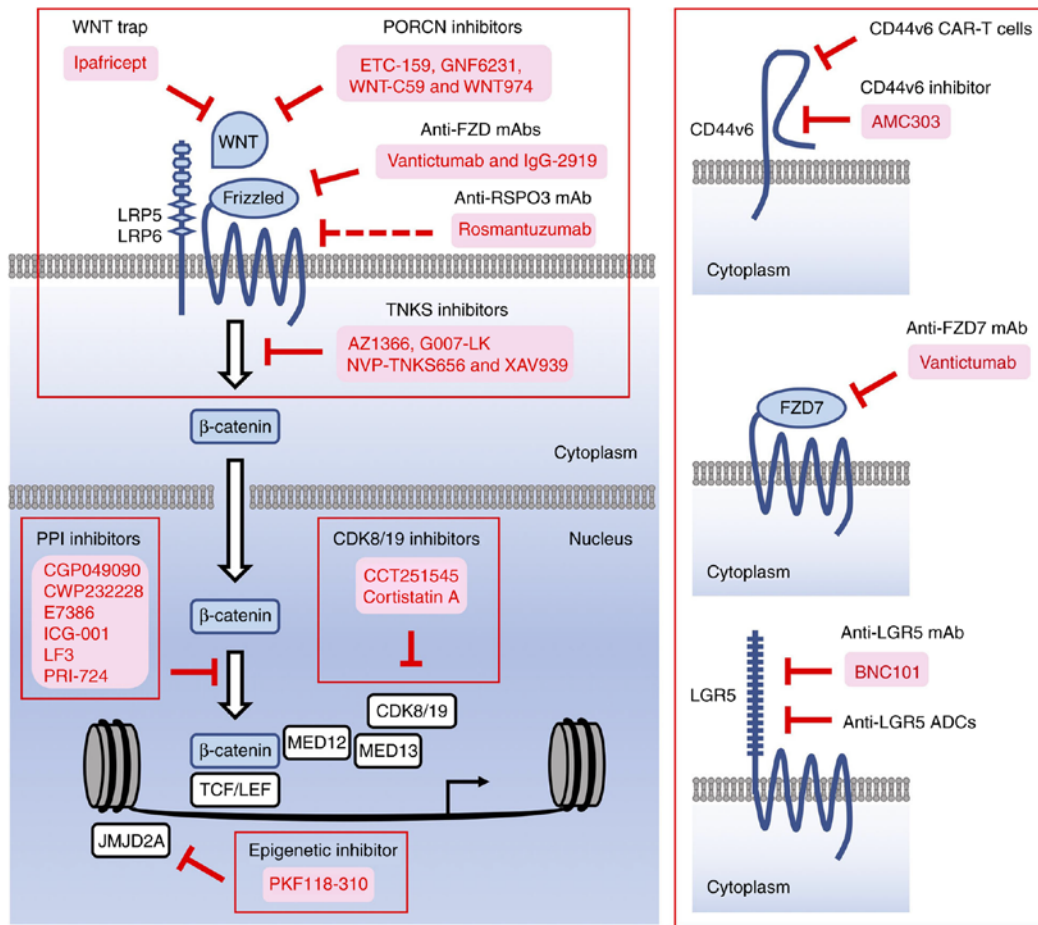
Figure 3. Investigational β-catenin inhibitors and mechanisms of action. β-catenin-targeted therapeutics are functionally classified as i) β-catenin inhibitors targeting upstream regulators (AZ1366, ETC-159, G007-LK, GNF6231, ipafricept, NVP-TNKS656, rosmantuzumab, vantictumab, WNT-C59, WNT974 and XAV939), ii) β-catenin inhibitors targeting PPIs (CGP049090, CWP232228, E7386, ICG-001, LF3 and PRI-724), iii) β-catenin inhibitors targeting epigenetic regulators (PKF118-310), iv) β-catenin inhibitors targeting mediator complexes (CCT251545 and cortistatin A), and v) β-catenin inhibitors targeting transcriptional outputs [CD44v6 chimeric antigen receptor-modified T cells, CD44v6 inhibitor AMC303, anti-FZD7 mAb cross-reacting with FZD1, FZD2, FZD5 and FZD8 (vantictumab), anti-LGR5 mAb BNC101 and anti-LGR5 ADCs]. AMC303, BNC101, ETC-159, ipafricept, PRI-724, rosmantuzumab, vantictumab and WNT974 are in clinical trials, whereas other investigational β-catenin inhibitors are in preclinical stages. PPIs, protein-protein interactions; ADCs, antibody-drug conjugates; PORCN, porcupine; TNKS, tankyrase; mAb, monoclonal antibody.

cells (ESCs) (120), and Jmjd2c associated with a mediator complex is required for the lineage-specific gene expression and multi-lineage differentiation of ESCs (121). PKF118-310 was initially identified as a compound that inhibits β-catenin-dependent transcription via inhibition of the interaction between β-catenin and TCF7L2, and PKF118-310 has been re-discovered as a JMJD2A inhibitor (8,122,123). PKF118-310 has been shown to exert antitumor effects on colorectal cancer and prostate cancer *in vitro* and breast cancer and HCC *in vivo* (122,124,125). PKF118-310 also exerts antifibrotic effects in mouse models of dermal fibrosis (126). Other epigenetic regulators, including EZH2 (127,128), KDM1A (LSD1) (129) and PRMT5 (130), are also involved in canonical WNT/β-catenin signaling activation in certain contexts. As epigenetic regulators are desirable targets in the field of clinical oncology (127,131-134), EZH2 inhibitors, including GSK2816126 and tazemetostat/EPZ-6438), KDM1A inhibitors, including GSK2879552 and pargyline, and PRMT5 inhibitors, including GSK3235025/EPZ015666 and PJ-68, have been developed; however, the mechanisms of action of these investigational drugs on β-catenin-dependent transcription

require further clarification to identify biomarkers for patient selection. PKF118-310 is a promising compound to be optimized for the treatment of patients with β-catenin-dependent fibrosis and cancer.

β-catenin inhibitors targeting mediator complexes. Mediator complexes that assemble transcription factors, cofactors and other regulators of RNA polymerase II-mediated mRNA synthesis are involved in the β-catenin-dependent transcription of oncogenic targets, including *CCND1* and *MYC* (135-137) (Fig. 3). β-catenin binds to MED12, which associates with MED13, cyclin C (CCNC) and CDK8/19 to form the kinase module of the mediator complex. As CDK8 and CDK19 are key components of the mediator complex, CCT251545 (138,139) and cortistatin A (140,141) have been characterized as CDK8/19 inhibitors that suppress β-catenin-dependent transcription and the *in vivo* tumorigenesis of colorectal cancer, breast cancer and acute myeloid leukemia. CDK8/19 phosphorylates mediator complex components (CCNC, MED12, MED13, MED14 and MED26), epigenetic regulators (BCL9, BPTF, BRD9, KDM3A, MLL2, SETD1A and SIRT1) and

transcription factors or cofactors (ATF7, FOXC1, KLF12 and STAT1) (141). Additionally, mediator complexes are involved in β-catenin-dependent transcription and transcription dependent on other transcription factors (136,137). Due to the unknown on-target effects associated with the various functions of CDK9/18 and mediator complexes, the application of CDK9/18 inhibitors for the treatment of patients with WNT-driven cancer has been suspended at the preclinical stage.

β-catenin inhibitors targeting transcriptional outputs. *ABCB1, BAMBI, CD44, CLDN1, CTLA4, FZD7, JAG1, LGR5, NOTCH2, NRCAM, RNF43, TNFRSF19* and *ZNRF3* are representative β-catenin target genes that encode transmembrane proteins (Fig. 1C). For example, the CD44v6 isoform that functions as a positive regulator of canonical WNT, CXCL12 (SDF1), FGF2, HGF, OPN and VEGF signaling in CSCs is involved in malignant phenotypical characteristics, including the EMT, tumor cell invasion and metastasis, therapeutic resistance and recurrence (142-145). FZD7 is a seven-transmembrane receptor, which transduces canonical and non-canonical WNT signaling in a context-dependent manner, whereas LGR5 is a seven-transmembrane receptor, which transduces RSPO signaling and potentiates WNT signaling through FZD receptors (8,24,34,146-149). Other transmembrane-type β-catenin signaling outputs are also involved in various pathophysiological aspects of human diseases.

As transmembrane proteins expressed on tumor cells are appropriate targets for the development of peptide-based drugs (142), mAbs, antibody-drug conjugates (ADCs), bi-specific antibodies (bsAbs) and chimeric antigen receptor-modified T cells (150-155), drugs targeting CD44v6, FZD7 and LGR5 are under development as functional β-catenin inhibitors. CD44v6 CAR-T cells (156) and anti-LGR5 ADCs (157,158) and are in preclinical stages, whereas the phase I clinical trial of anti-CD44v6 ADC (bivatuzumab mertansine) for patients with head and neck squamous cell carcinoma was terminated due to severe on-target skin toxicities (159). A peptide-based CD44v6 inhibitor (AMC303) (160) is in a phase I clinical trial for the treatment of patients with advanced solid tumors (ClinicalTrials.gov Identifier: NCT03009214); anti-FZD7 mAb (vantictumab), which cross-reacts with FZD1, FZD2, FZD5 and FZD8 (100), is in phase I clinical trials for cancer patients, as mentioned above (ClinicalTrials.gov Identifier: NCT01957007 and NCT01973309); anti-LGR5 mAb (BNC101) (161) is also in a phase I clinical trial for cancer patients (ClinicalTrials.gov Identifier: NCT02726334). Antibody- or peptide-based drugs are promising options for the treatment of β-catenin-driven human diseases; however, further evaluation of the benefits, costs and on-target toxicities are necessary prior to clinical application.

7. Multi-layered prevention and treatment of β-catenin-related diseases

Clinical medicine, particularly clinical oncology, is moving toward genomics-based personalized medicine due to the development of nucleotide sequence technologies. Such personalized medicine is expected to further evolve into omics- and clinical record-based precision medicine with relatively inexpensive costs due to increasing medical expenses in aging societies (162). Genomics-based testing platforms, including MSK-IMPACT (43), FoundationOne (163) and Oncomine Comprehensive Panel (164), and organoid- or PDX-based drug screening (165-167) are useful tools for the prescription of targeted therapeutics; however, there remain unmet medical needs for patients with refractory cancer driven by gain-of-function mutations in non-enzymatic oncogenes, including *CTNNB1* and *KRAS*, or loss-of-function mutations in tumor-suppressor genes, including *APC* and *TP53*.

β-catenin signaling is involved in myofibroblast activation and subsequent organ fibrosis (Fig. 2A), whereas the activation of β-catenin and NF-κB signaling is involved in field cancerization in the liver associated with HBV, HCV and other etiologies, and field cancerization in the stomach associated with *H. pylori* infection (Fig. 2B). Vaccines against HBV and *H. pylori* are available for the prevention of cancer-associated infections (168,169). The eradication of HCV and *H. pylori* are optimal choices for the first-line prevention of HCC and gastric cancer, respectively (Fig. 2C); however, pathogen eradication is not always successful and may occur too late to reverse the process of field cancerization. β-catenin inhibitors are expected to be applicable for organ fibrosis prevention, second-line HCC prevention and treating β-catenin-driven cancer (Fig. 2C). Although β-catenin without intrinsic enzymatic activity is difficult to target in drug development, several classes of investigational β-catenin inhibitors (Fig. 3) are in preclinical stages or clinical trials for treating patients with β-catenin-related diseases. The multi-layered prevention and treatment strategy of β-catenin-related human diseases is realistic at present and necessary for the implementation of precision medicine in the future.

Availability of data and materials

Not applicable.

Authors' contributions

MK analyzed the literatures, designed and wrote the study, and produced the figures.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

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