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Subject Review

The Links between Transcription, β-catenin/JNK Signaling, and Carcinogenesis

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Abstract

Interactions between transcription and signaling are fundamentally important for understanding both the structure and function of genetic pathways and their role in diseases such as cancer. The finding that β-catenin/TCF4 and JNK/c-Jun cooperate has important implications in carcinogenesis. Previously, we found that binding of c-Jun and β-catenin/TCF4 to the *c-jun* promoter is dependent upon JNK activity, thus one role for this complex is to contribute to the repression and/or activation of genes that may mediate cell maintenance, proliferation, differentiation, and death, whereas deregulation of these signals may contribute to carcinogenesis. Here we address the functional links reported between activated β-catenin/JNK signaling pathways, their component genes, and their common targets, and discuss how alterations in the properties of these genes lead to the development of cancer. (Mol Cancer Res 2009;7(8):1189–96)

Introduction

Cancer is a genomic disease and is associated with genetic and epigenetic alterations. Accumulation of these alterations during carcinogenesis activates proto-oncogenes and inactivates tumor suppressors (1, 2). The mammalian Wnt gene family consists of 19 members and encodes secreted glycoproteins. These glycoproteins control many cellular processes such as cell proliferation, apoptosis, and differentiation in the adult and during embryonic development (refs. 3-5, and see the Wnt signaling site: http://www.stanford.edu/~rnusse/wntwindow.html). Wnt signaling is important because several of its signal transduction target genes are implicated in various cancer types and developmental disorders.

Wnt signaling has traditionally been classified as either canonical or noncanonical, with the former more extensively characterized. Here the binding of Wnts to Frizzled and LRP5/6 receptors stabilizes the cytoplasmic β-catenin that subsequently becomes translocated to the nucleus, where it interacts with transcription factors regulating the target gene expression. In fact, some Wnt pathway mutations, such as loss of the *adenomatous polyposis coli* (*APC*) gene is sufficient to give rise to a tumor. This mutation may, by abnormally activating Wnt signaling, also switch on associated pathways: Notch, Eph/ephrin, BMP, Hedgehog, and MAPK, as observed in the APC^{Min} mouse model of intestinal carcinogenesis (1, 2).

c-Jun NH2-terminal kinase (JNK) is a member of the mitogen-activated protein kinases (MAPK) and is involved in noncanonical Wnt signaling and planar cell polarity. It is activated in response to growth factors, inhibition of DNA and protein synthesis, environmental stress and inflammatory cytokines, all of which regulate cell proliferation, differentiation, and apoptosis (6, 7).

Previously we described the link between canonical (β-catenin/TCF4) and noncanonical (JNK/c-Jun) Wnt-signaling pathways in intestinal tumorigenesis (8). This relationship has been supported by recent studies using alternative approaches (9-13). However, the links between the β-catenin/TCF4 and JNK/c-Jun pathways are still poorly understood, and the identities of the downstream targets and/or effectors of JNK/Wnt remain largely unknown. Moreover, little is known about the effect of phosphorylation by JNK on the functions of these targets in the development of cancer.

Wnt/MAPK Pathways

Activation of the Wnt-signaling pathway stimulates growth and mediates developmental and carcinogenic signaling between cells (2, 14). In the absence of the Wnt signal, β-catenin levels are regulated by a multiprotein complex that phosphorylates β-catenin targeting its degradation (Fig. 1; ref. 15). This β-catenin degradation complex consists of the APC tumor-suppressor protein Axin and GSK-3β (16). Upon docking of Wnt to Frizzled and LRP5/6 receptors, a cascade of events (canonical Wnt signaling) is relayed that destabilizes the degradation complex. β-catenin levels accumulate and translocate to the nucleus where β-catenin functions as a coactivator for the lymphoid-enhancing factor/T-cell factor (LEF/TCF) family of transcription factors (17). However, the components of this HMG box family, LEF-1, TCF1, TCF3, and TCF4, have a virtually identical DNA-binding domain and a β-catenin interaction

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domain (18), and this family of nuclear transcription factors remain the predominant partners of β-catenin.

Wnt signaling can also activate noncanonical, β-catenin-independent pathways (Fig. 1). Several noncanonical pathways have been identified, including activation of JNK (19, 20). JNKs are serine/threonine kinases that belong to the group of MAP kinases activated by phosphorylation of the threonine and tyrosine residues in the conserved Thr-X-Tyr motif (21). This phosphorylation is catalyzed by the MAPK kinases (MKK), which are in turn activated by a serine/threonine phosphorylation catalyzed by the MAPKK kinases (MEKK). JNK activation, which can occur via many types of cellular stresses or extracellular signals, plays an essential role in organogenesis during mouse development by regulating cell proliferation, survival, and apoptosis. JNK activation is also involved in mRNA stabilization, cell migration, and cytoskeleton integrity (22-26).

Recent reports proposed Wnt signaling output is dictated by receptor complement present and is dependent on the cell type (27, 28). However, more evidences of crosstalk between Wnt downstream signals through the β-catenin and JNK pathways have now appeared. For example, it is well known that abnormal stimulation of the Wnt pathway through, for instance, transgenic expression of Wnt1 (*int-1*) or Wnt10b triggers tumorigenesis in mice (29, 30). Wnt5a inhibits the canonical Wnt pathway by promoting β-catenin degradation in a GSK3β-independent manner (31). Also, Wnt5a induces JNK activation in a Ror2-dependent manner to regulate cell migration (22). However, Wnt7a promotes JNK activation and c-Jun phosphorylation in lung cancer

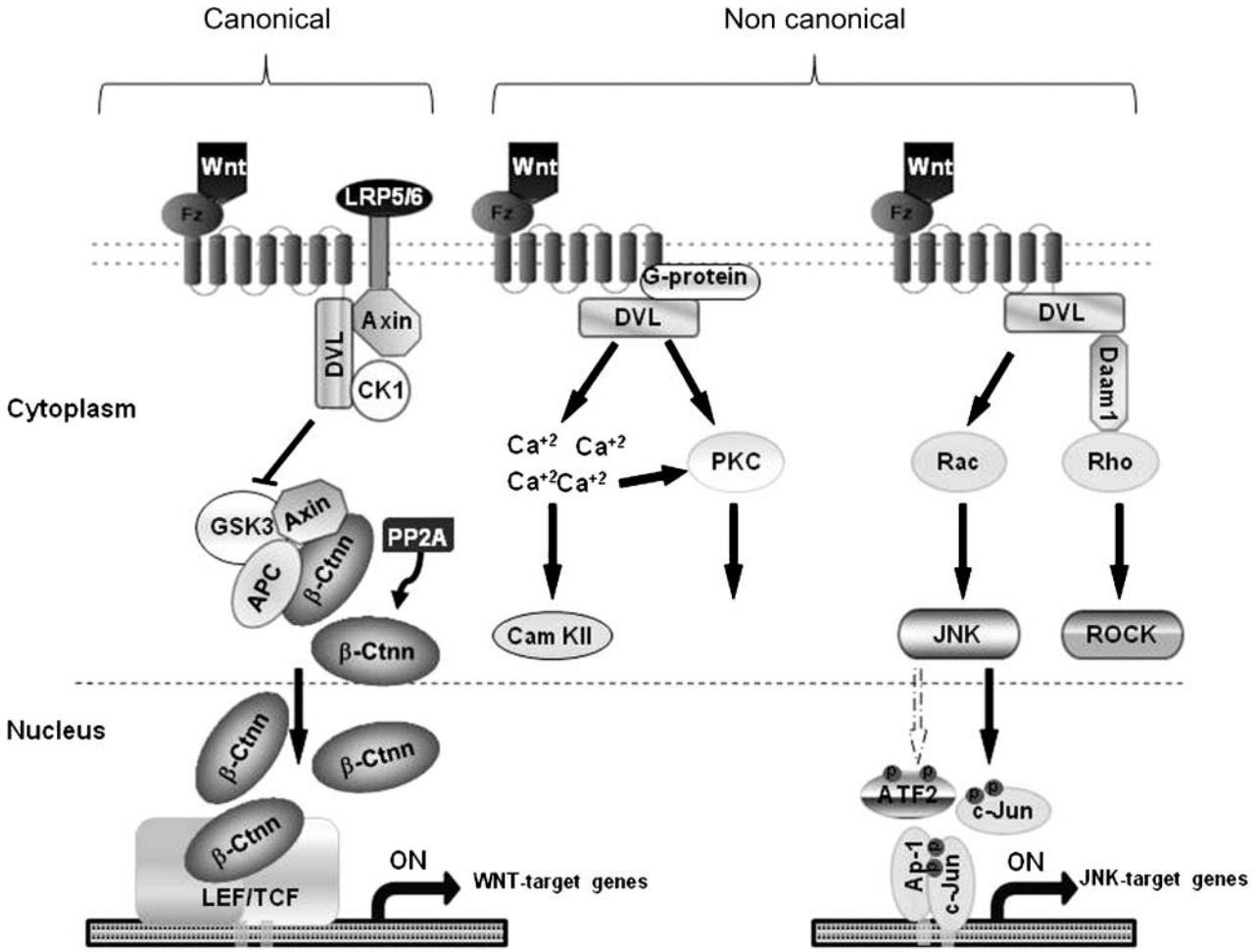

FIGURE 1. Schematic representation of canonical and noncanonical Wnt pathway components. The canonical signaling is initiated (*left*) by association of Wnt with its coreceptors Lrp5/6 and Frizzled (*Fz*) at the plasma membrane, leading to the inhibition of β-catenin (β-*Ctnn*) degradation complex (Axin/APC/GSK3-β), which permits the accumulation of β-catenin and its translocation to the nucleus to activate target gene transcription by associating with Lef/Tcf transcription factors. The heterotrimeric protein phosphates 2A (PP2A) may also regulate β-catenin stability as antagonists of the serine kinases and are required for the elevation of β-catenin levels, which are dependent on Wnt. In colorectal cancer, mutations of β-catenin itself, inactivation of the APC protein, or Wnt pathway inhibition of GSK3-β kinase lead to the inappropriate formation of β-catenin/Tcf4 complexes. Fz family receptors are also able to trigger the noncanonical Wnt pathways. The noncanonical Wnt pathways are: the Wnt/$Ca2^+$ pathway (*middle*) and the planar cell polarity pathway (*right*). The Wnt/$Ca2^+$ pathway, most likely, signals through G-heterotrimeric proteins to assemble intracellular $Ca2^+$, and to stimulate PKC. In the planar cell polarity pathway, two independent pathways, which are initiated by dishevelled (*DVL*), result in the activation of Rho and Rac GTPases. Activation of Rho involves Daam-1, which results in the activation of the Rho-associated kinase ROCK. However, Rac activation is Daam-1 independent and stimulates JNK activity and consequently phosphorylates AP-1 transcription factors.

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Table 1. Summary of β-catenin/TCF4 and JNK/c-Jun Common Target Genes with Promoters Contained in Binding Sites of AP-1 and TCFs, Which Were Analyzed and Transcriptionally Induced in Cancers

β-catenin/JNK Target Genes	Reference
c-myc	Yochum et al. (110)
c-jun	Nateri et al. (8)
cyclin-D1	Toualbi et al. (100)
Mmp7	Crawford et al. (116)
Mmp26	Marchenko et al. (119)
Osteopontin(Eta-1)	El-Tanani et al. (112)
Cd44	Nateri et al. (8), Van der Flier et al. (108)
Wnt2	Le Floch et al. (10)

NOTE: These studies show JNK/β-catenin pathways cooperatively enhance their transcriptional activities including *c-jun* promoter itself, *c-myc, cyclin D*1, *Mmp*7, *Mmp*26, *Wnt*2, *Eta*-1, and *Cd*44.

cells (23). Moreover, in adult bone marrow mononuclear cells, Wnt3a promotes "stemness," proliferation, and hematopoietic commitment, and Wnt11 induces cardiomyogenic differentiation in a JNK-dependent manner (24).

On the other hand, Dsh/Dvl and Axin are essential elements in both canonical and noncanonical pathways, because they activate the Wnt/JNK signaling pathway and interact with β-catenin. These interactions take place through different domains in the protein sequence (25). Axin induces JNK activity through its MEKK1 binding and self-association domains (26), but these domains are not required for the degradation of β-catenin in *Xenopus* axis determination (32). Moreover, the DIX domain of Dsh is essential for β-catenin signaling, but it is not required for the planar cell polarity pathway in *Drosophila* (33). This suggests that Wnt cascade might switch at the Axin and Dsh/Dvl level and the dual role of these transducers might indicate cross-signaling interaction between the Wnt pathways, as well as other signaling pathways. However, the significance of this interaction in human development and disease remains largely unknown.

Wnt and JNK pathways can also coordinate to activate certain genes that are common targets for both pathways. For example, transgenic mice with high levels of c-myc or cyclin D1, both Wnt targets, also develop tumorigenesis (34, 35). This activation could take place, at least in part, through the union of β-catenin/TCF4 and c-Jun/AP-1, which form a transcriptional complex that induce the expression of these common target genes (Table 1). These targets will be discussed further in this article.

JNK Signaling

Among the three JNK isoenzymes, JNK3 is restricted to expression in brain whereas the JNK1 and JNK2 proteins are ubiquitously expressed (21). JNK family members are involved in diverse biological phenomena through the phosphorylation and regulation of many types of proteins, among them, transcription factors, such as ATF2, Elk-1, stat3 (6, 36, 37), and c-Myc (38), as well as members of the Bcl-2 family (Bcl-2, Bcl-xL, Bim, and BAD), IRS-1, Itch, and Tau (39-43). Inactivation of single *jnk* genes in mice failed to exert marked developmental defects, whereas the double knockout of *jnk1* and *jnk2* resulted in embryonic lethality because of neural tube defects (44, 45). Moreover, mice embryos with the $jnk1^{-/+}$;$jnk2^{-/+}$ genotypes showed delayed epithelial development in the epidermis, intestines, and lungs accompanied by decreased EGF signaling (46). Although *jnk3* has been shown to be mutated in brain tumors (47), its role in carcinogenesis has not been extensively studied (48).

The diversity of JNK target genes has defined differential functions for JNK, and the analyses of pathways regulated by JNK have shown that JNK is indispensable for both cell proliferation and apoptosis. It seems that, depending on the stimulus and the cell type, the activation of JNKs might give rise to cell proliferation or apoptosis (6, 36).

Recently, there are accumulating data supporting a key role of JNK activity in cell survival, proliferation, and carcinogenesis. JNK activity is induced by oncogenes in certain tumor types (49-51). Ras-transformed MEFs lacking both *jnk1* and *jnk2* had a reduced growth rate (52). Growth inhibition was also reported using myeloma and breast cancer cells treated with JNK inhibitors, and antisense oligonucleotides (53, 54). In addition, the small GTPase Ral, a putative proximal regulator of the JNK pathway, is required for murine skin carcinogenesis (55). Other studies showed that JNK1 is required for BCR/Abl-mediated transformation of pre-B cells *in vitro* and *in vivo* (56). Thus, there is growing evidence supporting a protumorigenic role for the JNKs, and the idea that blocking JNK signaling may be of therapeutic benefit in treating cancer led to the development of small molecule JNK inhibitors (57, 58).

Several studies provide information on the molecular targets through which JNKs may promote cell transformation. TGFβ1 can activate JNK1, which in turn phosphorylates cyclin-dependent kinase inhibitor p21/WAF1, a transcriptional target of p53 and cell cycle regulator, and increases its stability through a SMAD-independent mechanism (59, 60). Also, JNK is implicated in androgen-independent prostate cancer in which, after leptin stimulation, JNK mediates STAT3 activation through Ser-727 phosphorylation (37).

JNKs phosphorylate c-Jun on Ser63, Ser73, Thr91, and Thr93 within the transcriptional activation domain. Phosphorylation of JNK was markedly increased in response to oncogene over-expression (49, 50, 61), and this phosphorylation is also required for activated *Ras*-induced skin tumorigenesis *in vivo* (62). Furthermore, c-Jun contributes to early stages of carcinogen-induced hepatocellular carcinoma by antagonizing the action of p53 (63), and transgenic mice expressing an oncogenic form of *jun* developed fibrosarcomas at sites of wound healing (64). Additionally, in human melanoma, the ERK signaling pathway upregulates JNK and activates c-Jun and its downstream targets, including cyclin D1 and RACK1, which in turn enables protein kinase C (PKC) to phosphorylate and enhance JNK activity (65). We have also identified TCF4 and β-catenin as novel partners of c-Jun. These three proteins form a complex in a JNK-dependent manner (Fig. 2), and if phosphorylation was prevented through mutation of the JNK phosphorylation sites the extent of intestinal tumorigenesis in the APC^{Min} mouse model was delayed (8). Similarly, JNKs phosphorylate the androgen receptor in prostate cancer cells, leading to nuclear export and inhibition of androgen-receptor-dependent transcriptional responses (66). In lung cancer cells, the JNK pathway may contribute to cellular transformation by down-regulating tumor suppressors such as p53 or nuclear receptors that promote epithelial differentiation. Retinoic acid receptor α (RARα), involved in

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normal epithelial cell growth and differentiation, is phosphorylated on several residues by JNKs leading to its enhanced degradation (67). ATF2 transcription factor is phosphorylated by JNK, and its transcriptional activity depends on its heterodimerization with c-Jun (68). Inhibiting ATF2 interferes with, and slows the progression of, melanoma development (69), and over-expression of ATF2 is required for progression and growth of mouse skin tumors (70). However, other studies show that ATF2 can also elicit skin tumor suppressor function, and the loss of the transcriptional activity of ATF2 enhances the induced skin tumorigenesis that is associated with an increase in the expression of β-catenin, EGFR, phospho-JNK, phospho-c-Jun, and cyclin D (71). Additionally, DNA topoisomerase I, which is required for EGF receptor expression and cell proliferation of HT-1080 cells, has recently been identified as a JNK-dependent interaction partner with c-Jun (72). Also, JNKs have been shown to directly phosphorylate Smad2 and -3 on sites within their linker regions where phosphorylation is associated with increased nuclear localization of Smad3 and phospho-c-Jun. Moreover, the induction of JNK activity increased the progression and extension of colon cancer (73).

We previously showed that induction of JNK activity is antagonized by an SCF-E3-Ligase FBXW7 tumor suppressor (74, 75). Moreover, Pdcd4 tumor suppressor inhibits the activity of JNK (76) and down-regulation of Pdcd4, which is frequently down-regulated in human colon cancer tissues, and in colon cancer HT29 cells, it produces activation of β-catenin/Tcf-dependent and AP-1-dependent transcription (77). Taken together this activity provides additional evidence for a role of JNKs and their targets in cell transformation and tumor development (51).

JNK Null Mice and Tumorigenesis: a Controversial Partnership

Many of the studies already discussed suggest that JNK signaling has a protumorigenic activity. This role is supported by some *in vivo* studies in which $Jnk1^{-/-}$ mutant mice exhibited a marked decrease in gastric tumor development caused by *N*-methyl-*N*-nitrosourea, in comparison with wild-type controls. Of note, p21 expression was similar between wild-type and $JNK1^{-/-}$ mice. The impaired carcinogenesis was associated with decreased cell transformation and proliferation (78). Moreover, $JNK1^{-/-}$ mice were much less susceptible to diethylnitrosamine-induced hepatocarcinogenesis, and the absence of JNK1 resulted in decreased expression of cyclin D and vascular endothelial growth factor, as well as reduced cell proliferation and tumor neovascularization (79).

In contrast to these findings, others found that $JNK1^{-/-}$ mice develop spontaneous intestinal tumors that were associated with down-regulation of p21 in intestinal epithelial cells (80), and recently the same group showed that JNK activity negatively regulates β-catenin signaling through GSK3β pathway and that the β-catenin alteration is probably responsible for the intestinal tumor formation in $JNK1^{-/-}$ mice (81). Furthermore, $JNK1^{-/-}$ mice developed more UVA-induced papillomas than either $JNK^{+/+}$ or $JNK2^{-/-}$ mice, which was associated with suppressed Myt1 phosphorylation and decreased caspase-3 cleavage. This suggests that the JNK1-mediated phosphorylation of Myt1 plays an important role in UVA-induced apoptosis and the prevention of skin carcinogenesis (82). She and colleagues also described that $Jnk1^{-/-}$ mice are more susceptible to TPA-induced skin tumor development than wild-type mice (83); contrasting completely with JNK2, which primarily functions as a key regulator of carcinogenesis, as evidenced by the multiplicity of papillomas induced by TPA in $Jnk2^{-/-}$ mice compared with wild-type mice (84), which support a critical role for JNK2 in the tumor promotion process. Of relevance, fibroblasts lacking *jnk2* unexpectedly show higher JNK activity and c-Jun phosphorylation (85, 86), and JNK2 can also phosphorylate and induce nuclear translocation of β-catenin (87).

These findings suggest that JNKs can have tumor-promoting or tumor-suppressing functions, depending on the cell type and/or organ or the stimuli, and provide mechanistic insights into the distinct roles of the different JNK isoforms.

However, it is of note that $Jnk1^{-/-}$ mice, reported by Tong and colleagues (80), are conventional knock-outs that lack JNK1 in all cell types, and it may be that the loss of JNK1 function in immune cells led to prolonged inflammation or reduced immune surveillance, thus contributing to tumor development. Indeed, $jnk1^{-/-}$ mice had reduced immunity, and *jnk1*-deficient

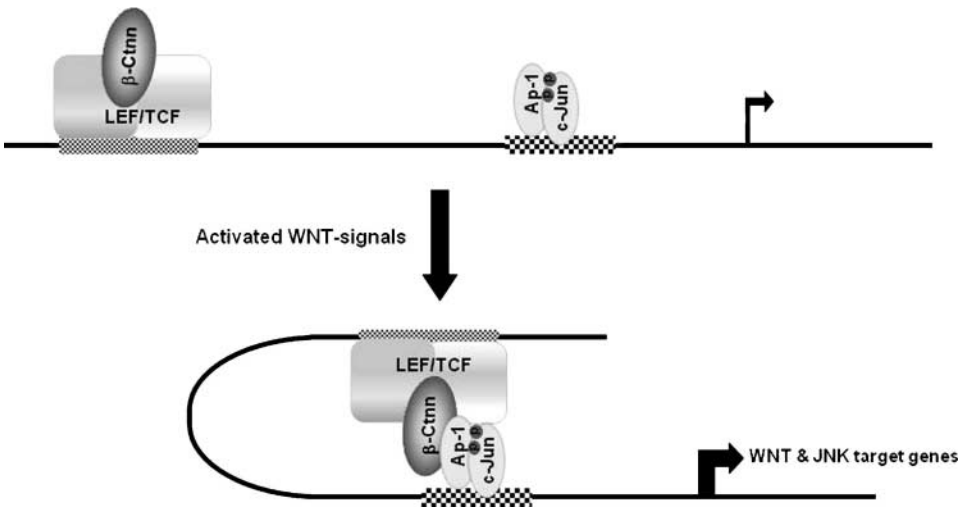

FIGURE 2. Schematic representation of a JNK-dependent interaction on *c-jun* promoter between phosphorylated c-Jun and β-catenin/TCF4, which consequently activates c-Jun transcription. This activation requires both the TCF and AP-1 sites of the *c-jun* promoter acting in *cis* and depends on amino-terminal c-Jun serine residue phosphorylation (8).

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T cells show abnormal T-helper cell differentiation and cytokine production (88, 89). As neither general JNK activity nor phosphorylation of its substrates (e.g., ATF2, c-Jun) have been analyzed in a conditionally ablated *jnk1* null mouse, it remains unclear whether it has a functional role in tumor development. So far genetic changes in JNK1 have not been identified in human tumors. Therefore, to investigate the significance of JNK1 activation, a tissue-specific transgenic mouse allowing a constitutively active JNKK2-JNK1 fusion protein (90), thereby stimulating JNK and phosphorylating its substrates, is required.

AP-1:LEF/TCF4 Complex

TCF4 is a component of the HMG family of transcription factors, which is the predominant partner of β-catenin in the canonical wnt pathway. TCF4 plays an essential role in normal development (91). However, the proto-oncoprotein c-Jun belongs to the AP-1 group of transcription factors and is a key regulator of cellular proliferation, apoptosis, and tumorigenesis (51, 92). It also plays pivotal roles in bone, liver, heart, skin, hematopoietic, and neuronal development (51, 93-95).

c-Jun heterodimerizes and forms functional transcription factors with a number of interacting partners including all members of the Fos and ATF families, via a leucine zipper interaction interface (51). AP-1 activity is strongly induced in response to numerous signals including growth factors, cytokines, and extracellular stresses. AP-1 stimulation is mediated, in part, by the c-Jun *N*-terminal phosphorylation (JNP) and by the JNKs within its transactivation domain. It is thought that JNP increases the transcription of target genes, including the *c-jun* gene itself (21), which is a well-characterized Wnt target gene (96, 97). This observation suggests that high JNK activity may not only stimulate the expression of AP-1 target genes, but also increase the expression of Wnt downstream target genes. Chromatin immunoprecipitation (ChIP) analysis indicates that c-Jun binds several Wnt promoters, which are misregulated by activated-FOS expression, confirming that members of the Wnt pathway can be primary targets of AP-1 transcriptional regulation (12). Similarly, the use of a genome-wide ChIP-on-chip analysis identified the *tcf4* promoter region as a target for phosphorylated c-Jun, which means that TCF4 is transcriptionally regulated through activated JNK signaling (11). In addition to TCF4, it has now been shown that JNK2, and to a much lesser extent JNK1, can phosphorylate and induce nuclear translocation of β-catenin (87). Moreover, molecular characterization of cultured keratinocytes and tumors indicates that c-Jun regulates the balance between the Wnt/β-catenin and Hedgehog signaling pathways through binding to several Wnt promoters (12). On the other hand, TCF/β-catenin strongly activates *c-jun* transcription in both hematopoietic and colon cancer cells (8, 96, 97). Moreover, GnRH stimulates the nuclear localization of β-catenin (98) and regulates, through a functional interaction between LEF/TCF and β-catenin, the expression of *jun* and c-Jun target genes in gonadotropes (99). Toualbi and colleagues (100) reported that c-Jun as well as c-Fos interact with β-catenin and activate the c-myc-luciferase reporter in a TCF-dependent manner.

Conditional ablation of c-Jun, for example deletion in the epidermis, causes an eye closure defect, affects keratinocyte proliferation *in vitro*, and delays skin tumor development

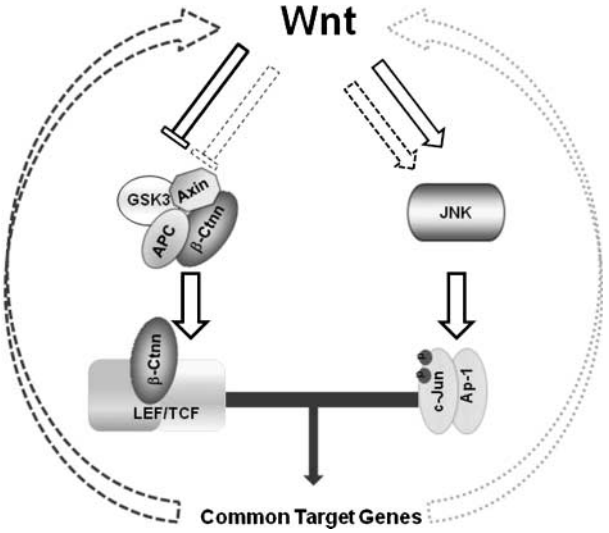

FIGURE 3. Two distinct β-catenin/TCF4 and JNK/c-Jun pathways are physiologically cooperating in tumorigenesis. These interactions cooperatively enhance transcriptional activities of promoters containing AP-1 and TCF-binding sites. The resultant proteins can promote a positive feedback loop for many of Wnt-target genes, which is consistent with their observed role in human colorectal tumors.

in vivo (101, 102). Moreover, genetic abrogation of JNP or gut-specific conditional *c-jun* inactivation reduced tumor number and size and prolonged lifespan in APC^{Min} mice (8), which develop multiple intestinal neoplasias because of excessive canonical Wnt signaling (8, 103). Therefore, the phosphorylation-dependent interaction between c-Jun and TCF4 regulates tumorigenesis by integrating JNK and β-catenin, two distinct pathways activated by Wnt signaling (Fig. 3). However, JNK inhibition impairs the function of both AP-1 and TCF4 transcription factors and may have potentially beneficial therapeutic effects on colon cancer progression (77).

In addition to colorectal cancer, this complex, alone or in combination with other transcription factors, may activate the transcription of different target genes; therefore, it could be involved in tumor formation in different organs.

AP-1:LEF/TCF Common Target Genes

A variety of Wnt target genes, including *c-myc, c-jun*, *cyclinD1, cd44, WNT*s, and *MMP*s are transcriptionally regulated through both TCF4 and c-Jun transcription factors (9-13, 51, 93, 104). It has been shown that *c-jun* expression is regulated by β-catenin/TCF4. ChIP analysis showed that binding of c-Jun and β-catenin/TCF4 to the *c-jun* promoter is dependent on JNK activity (8). Cyclin D1 is an important target gene through which c-Jun/AP-1 controls proliferation (105). Similarly, the expression of *cyclin D*1 is regulated by both JNK and Wnt signaling (104, 106) and AP-1/β-catenin/TCF4 cooperation is directly involved in the transcriptional induction of cyclin D1 (100). *CD44* is both c-Jun and TCF4 target gene (8, 107, 108).

On the other hand, Gan and colleagues showed that binding of c-Jun, TCF4, β-catenin, and Dishevelled is required for full c-*Myc* expression (109). Moreover, association of c-Jun, β-catenin, and TCF4, specifically with the downstream enhancer, triggers

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c-*Myc* transcription in HCT116 human colorectal carcinoma cells after mitogen stimulation (110). Most notably, the use of a genome-wide ChIP-on-chip analysis identified that TCF4 (*Tcf7l2*) is transcriptionally regulated through activated JNK signaling (11) with three of the AP-1/c-Jun binding sites, at position −996 to −833 base pairs (bp) relative to the TATA box, of the *tcf7l2* gene. In our current studies, we have shown TCF4/c-Jun colocalization in adenomas derived from APC^{Min} mice and microarray data suggest a significant similarity in TCF4 transactivation in response to mutations in APC and/or β-catenin genes (111). However, in mammary epithelia, the scenario seems to be different: El-Tanani and colleagues (112) described that β-catenin-Lef-1 and c-Jun cooperate with Ets transcription factors family in regulation of osteopontin transcription, which plays a key role in neoplastic transformation, metastasis (113), and the prognosis of breast cancer (114). It was concluded that the presence of these transcription factors in human breast cancer is responsible for the over-expression of osteopontin (112). Similarly, AP-1, the Ets transcription factor PEA3 synergizes with β-catenin/Lef-1 in the up-regulation of the *matrix metalloproteinase matrilysin* (*MMP7*) in intestinal tumors (115, 116), itself predominantly expressed in the cells of gastrointestinal, breast, and lung carcinomas (117). Furthermore, Rivat and colleagues (118) corroborated that Src-mediated activation of the human *MMP7* promoter requires the activation of AP-1 signaling and a cooperative interaction between c-Jun and LEF-1 transcription factors (118). Moreover, β-catenin, LEF/TCF, Ras, and c-Jun interact with, and synergistically activate, the *MMP-26* promoter (119). MMP-26 is involved in hyperplastic, and malignant endometrial (120), and is over-expressed in skin cancer (121). Immunohistochemical analysis of human colorectal tumors showed nuclear expression of c-Jun, TCF4, and β-catenin (122).

Concluding Remarks

Taken together, there is, therefore, significant crosstalk between JNK and the canonical Wnt pathways. The connection between these two pathways may result in co-expression of both c-Jun and TCF4 target genes. These genes, in turn, form a positive feedback loop increasing the strength of Wnt signaling (Fig. 3) and thereby maintaining tissue homeostasis and cancer development. However, the mechanisms through which β-catenin:TCF4/JNK:AP-1 cooperate to maintain a mechanistic basis for the stem cell phenotype in cancer remains to be elucidated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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