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TCF/LEFs and Wnt Signaling in the Nucleus

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T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors are the major end point mediators of Wnt/Wingless signaling throughout metazoans. TCF/LEFs are multifunctional proteins that use their sequence-specific DNA-binding and context-dependent interactions to specify which genes will be regulated by Wnts. Much of the work to define their actions has focused on their ability to repress target gene expression when Wnt signals are absent and to recruit β-catenin to target genes for activation when Wnts are present. Recent advances have highlighted how these on/off actions are regulated by Wnt signals and stabilized β-catenin. In contrast to invertebrates, which typically contain one TCF/LEF protein that can both activate and repress Wnt targets, gene duplication and isoform complexity of the family in vertebrates have led to specialization, in which individual TCF/LEF isoforms have distinct activities.

Wnt signals play important roles during animal development (Logan and Nusse 2004), as well as in adult tissues that are refreshed and repaired by stem cells (Haegebarth and Clevers 2009). It is the essential function of Wnt signaling in stem cell self-renewal and cell proliferation that links this pathway to problems of aging and disease such as cancer and diabetes (Polakis 2007; Laudes 2011). The term "Wnt signaling" does not imply a single-purpose signal transduction system. Rather, it refers to a diverse collection of signals triggered by Wnt ligand–receptor interactions that direct cell behavior in multiple ways: cell polarity, movement, proliferation, differentiation, survival and self-renewal. Diversity in Wnt signaling derives from the diversity of its components, its set of 19 ligands, ten receptors, alternative receptors, its signal transduction components, as well as the cell's particular developmental history. Despite this complexity, many Wnt signals act through a single mediator, β-catenin, to regulate gene expression. Wnt ligand–receptor interactions at the plasma membrane are communicated to target genes by the translocation of β-catenin into the nucleus where it partners with DNA-binding proteins that recognize specific sequence motifs in promoters and enhancers of target genes. The central 12-armadillo repeat array of β-catenin is the main mediator of transcription factor interactions, whereas domains in the amino and carboxy termini carry potent transcription-activating functions (Orsulic and Peifer 1996; van de Wetering et al. 1997; Hsu

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et al. 1998). Thus, once β-catenin is recruited to target genes, transcription is activated via the actions of these domains and an array of transcriptional coactivators (Mosimann et al. 2009; Cadigan 2012).

Multiple transcription factors that recruit β-catenin to Wnt targets have been identified and this review will summarize those that are best characterized. However, the nuclear mediators most closely associated with Wnt/β-catenin action are the TCF/LEFs, high-mobility group (HMG) DNA-binding proteins with multiple domains for protein interaction and regulation. This review will focus attention on this family of factors and discuss recent advances that shed light on how Wnt signaling works in stem cell niches and differentiation.

TCF/LEF TRANSCRIPTION FACTOR FAMILY

Almost all invertebrate genomes carry a single TCF/LEF ortholog, whereas vertebrates have expanded to a family of four members (five in the Zebrafish) (Fig. 1) (Arce et al. 2006; Archbold et al. 2012). The first discoveries of TCF/LEFs came from searches for transcription regulators of cell-fate markers in human T lymphocytes. "T cell factor 1" (HUGO gene name *TCF7* [van de Wetering et al. 1991]) and "lymphoid enhancer factor 1" (HUGO gene name *LEF1* [Travis et al. 1991; Waterman et al. 1991]) were discovered in T and B cells. T cell factor 3 and T cell factor 4 were found later through low-stringency hybridization screens with *TCF7* cDNAs (HUGO gene names, *TCF7L1*, *TCF7L2* [Korinek et al. 1998b]). The immunology-connected nomenclature is thus historical, and as knockout studies and expression studies attest, these factors play important regulatory roles in almost all tissues of the body (Oosterwegel et al. 1993; Brunner et al. 1997; van de Wetering et al. 1997; Lin et al. 1998; Archbold et al. 2012).

DNA-Binding Domain

All TCF/LEFs contain a highly conserved HMG box and a small peptide motif of basic residues ("basic tail"); together the HMG box and basic tail comprise the HMG DNA-binding domain (HMG DBD) (Fig. 1). The HMG DBD can recognize specific DNA sequences with nanomolar affinity (Giese et al. 1991; van de Wetering and Clevers 1992; Love et al. 1995). In addition to DNA sequence specificity, the HMG box has a DNA bending function. It recognizes its specific nucleotide sequence in the minor groove of the DNA and enforces a bend in the helix between 90° and 127° (Giese et al. 1995; Love et al. 1995). Both directed and random screen studies have identified a consensus recognition sequence for the HMG DBD; 5′-SCTTTGATS-3′ (Fig. 2) (van de Wetering et al. 1997; van Beest et al. 2000; Hallikas and Taipale 2006; Atcha et al. 2007). Recent chromatin immunoprecipitation experiments to define TCF/LEF-β-catenin-binding patterns genome wide identify this consensus as the most frequently occurring sequence in TCF4 and β-catenin-binding peaks (Hatzis et al. 2008; Blahnik et al. 2010; Bottomly et al. 2010; Norton et al. 2011). The small basic tail motif is located nine residues carboxy terminal to the HMG box and serves two purposes: elevating DNA-binding affinity through contact with the positively charged DNA backbone and functioning as a strong nuclear localization signal for interactions with importins (Giese et al. 1991; Prieve et al. 1998).

β-Catenin-Binding Domain

The connection between TCF/LEFs and Wnt signaling came from yeast two-hybrid screens suggesting that β-catenin could bind tightly to LEF1 and TCF1, an interaction subsequently delimited to a conserved motif in the amino terminus of TCF/LEFs (Fig. 1) (Behrens et al. 1996; Huber et al. 1996; Molenaar et al. 1996; van de Wetering et al. 1997; Graham et al. 2000; Poy et al. 2001). Deletion of this domain was an important step in establishing TCF/LEFs as downstream mediators of Wnt and β-catenin. Truncated "dominant negatives" could no longer bind to β-catenin, they suppressed the ability of overexpressed Wnt or β-catenin to induce secondary axes in frog embryos, and they phenocopied the segment polarity defect *wingless* mutants in *Drosophila* (Behrens et al. 1996; Huber et al. 1996; Molenaar et al. 1996; van de

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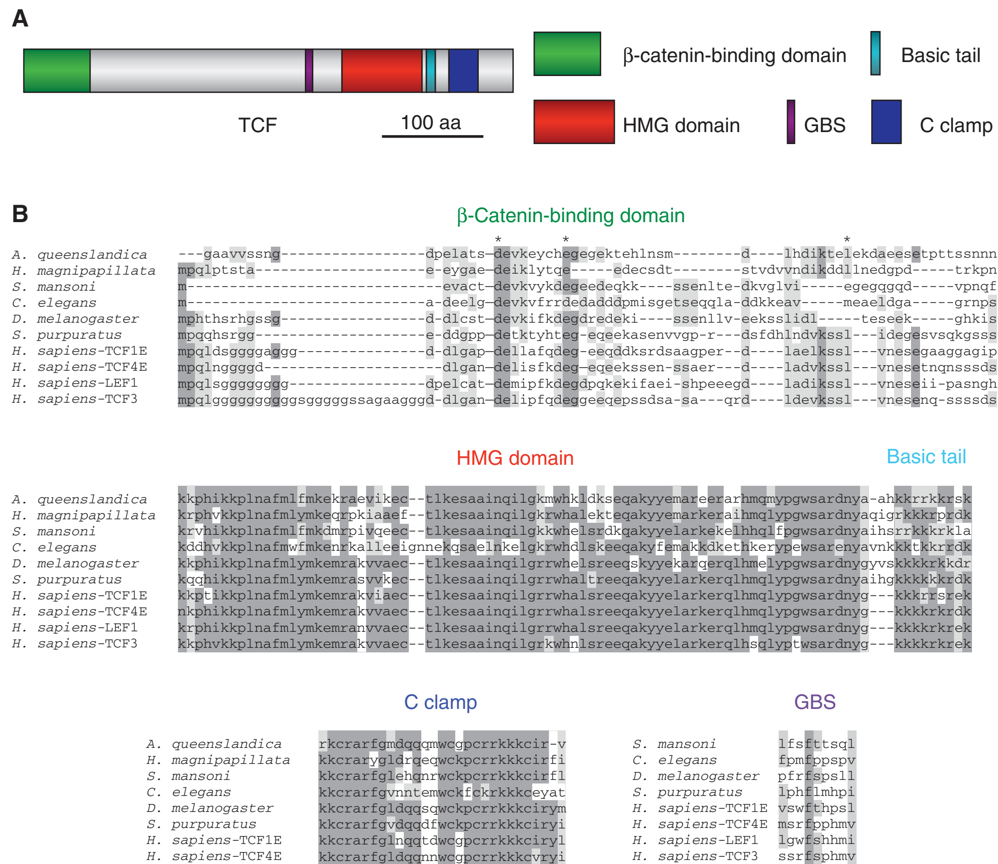

Figure 1. Hallmarks of the TCF/LEF family. (*A*) Schematic of TCF domains, showing the location of five conserved domains found in this family, the amino-terminal β-catenin-binding domain, the Groucho binding sequence (GBS), the high-mobility group (HMG) domain followed by a nuclear localization signal (basic tail), and the C clamp. The specific TCF shown is from the sea urchin *Strongylocentrotus purpuratus*. (*B*) Alignments of the five domains from six invertebrate TCFs and the four human family members. Consensus residues are highlighted in dark gray with conservative changes in light gray. The extent of conservation is far greater in the HMG, basic tail, and C-clamp domains compared with the β-catenin-binding domain and GBS. Three residues in the β-catenin-binding domain that contact β-catenin and are essential for interaction are marked with asterisks (Graham et al. 2000; Poy et al. 2001). A GBS could not be identified in TCF/LEFs from porifera and cnidarians and some flatworms, whereas a C clamp is found in nearly all invertebrate TCFs (it is not found in some flatworm TCF/LEFs) and in some vertebrate TCF1 and TCF4 isoforms. The sequences shown are from the sponge *Amphimedon queenslandica* (gene bank accession number ADO16566.1), the cnidarian *Hydra magnipapillata* (XP_002159974.1), the parasitic flatworm *Schistosoma mansoni* (XP_002572116.1), the nematode *Caenorhabditis elegans* (NP_491053.3), the dipteran *Drosophila melanogaster* (NP_726522), the sea urchin *Strongylocentrotus purpuratus* (NP_999640) and human TCF1E (EAW62279.1), TCF4E (CAB97213.1), and LEF1 (NP_001124185), and TCF3 (NP_112573.1).

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Wetering et al. 1997). These experiments showed how powerfully suppressive amino-terminally truncated TCF/LEFs can be. As we will discuss below, these forms occur naturally in the vertebrate family (see "TCF/LEF heterogeneity").

C Clamp

Alignment of TCF sequences reveals a third region as a highly conserved domain (Fig. 1B) (van de Wetering et al. 1997). This domain is

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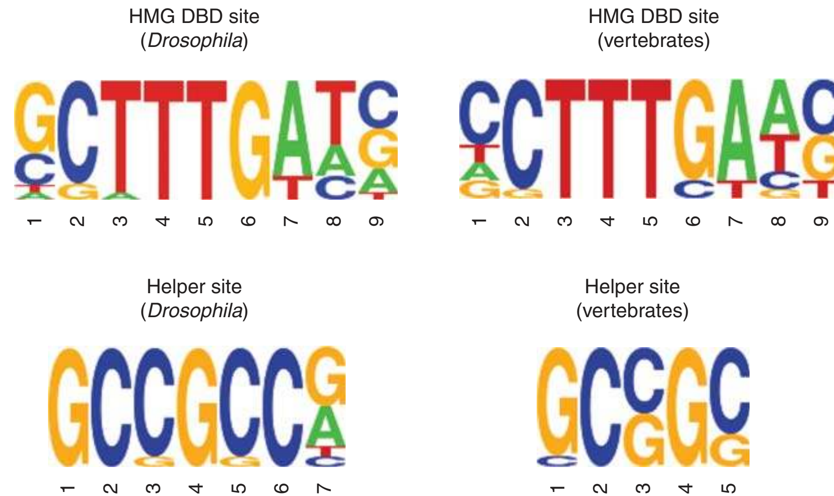

Figure 2. High-mobility group DNA-binding domain (HMG DBD) and Helper sites of *Drosophila* and vertebrate TCF/LEFs. Sequence logos were constructed from TCF/Pangolin sites described in Chang et al. (2008) and from a collection of vertebrate Wnt-regulated enhancers (N Hoverter, ML Waterman, and KM Cadigan, unpubl.).

small, enriched in basic, cysteine, and aromatic residues, and located carboxy terminal to the HMG DBD. The function of this domain was defined only recently when its requirement for gene regulation in human cancer cells (Atcha et al. 2007) and *Drosophila* (Chang et al. 2008) led to the discovery that it is a second DNA-binding domain. The domain is called the "C clamp" to highlight the absolute requirement for four cysteine residues in DNA binding (Atcha et al. 2007), and the first had been previously noted by the Clevers group as the "CRARF" domain (van de Wetering et al. 1997). Vertebrate TCF/LEFs containing the C clamp have been suggested to be important in regulating specific target genes (Wohrle et al. 2007; Weise et al. 2010). Although there is not yet an nuclear magnetic resonance (NMR) or crystal structure of the C clamp, experiments show that it has specific DNA-binding activities. The C clamp carries specificity for a secondary, GC-rich sequence called a "Helper site" (Fig. 2) that can occur with variable spacing and orientation relative to the Wnt response element (Atcha et al. 2007; Chang et al. 2008). It is unusual, but not unprecedented for transcription factors to carry two sequence-specific DNA-binding domains and, as will be discussed below, the C clamp is no longer present in every vertebrate TCF/LEF family member. However, one of the genome-wide chromatin immunoprecipitation studies for TCF4 binding noted enrichment of a Helper-like GC-rich sequence at a subset of targets (Hatzis et al. 2008). This suggests that despite the loss of the C clamp in a couple of family members, this domain is functionally relevant in vertebrates. Understanding the contribution of the C clamp to Wnt regulation in vertebrates and invertebrates requires further study.

Gro/TLE-Binding Domain

TCF/LEFs repress gene transcription in the absence of available β-catenin. Several corepressors participate in this process, such as myeloid translocation gene related-1 (Mtgr1) (Moore et al. 2008), corepressor of Pan (Coop) (Song et al. 2010), and hydrogen peroxide-inducible clone (HIC5) (Ghogomu et al. 2006; Li et al. 2011). The most intensively studied TCF/LEF corepressors are the Groucho/transducin-like enhancer of split (Gro/TLE) repressor family. Genetic studies in *Drosophila* and *C. elegans* support a role for their Gro/TLE orthologs repressing Wnt targets (Cavallo et al. 1998; Calvo

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et al. 2001). Gro/TLEs contain a conserved glutamine-rich Q domain at their amino termini that binds to the central portion of TCF/LEFs as well as the portion containing the HMG DBD (Daniels and Weis 2005; Arce et al. 2009). A short motif in the central domain has been identified that is essential for binding of LEF1 to TLE1, and similar regions can be found in most other TCF/LEFs (Fig. 1) (Arce et al. 2009). Whether this small motif is the core site of bona fide Gro/TLE interactions in TCF/LEF-assembled complexes at endogenous target genes remains to be determined. Other small sequence motifs have been discovered between the β-catenin-binding and HMG domains and they appear to impart additional modes of repression (see "TCF/LEF heterogeneity").

EVOLUTION OF TCF/LEFs

Examination of the predicted protein sequences from sequenced genomes provides a picture of the evolution of the TCF/LEF family. Defining proteins solely by sequence similarity has an important caveat, nicely illustrated by the SYS-1 protein, which clearly functions as a β-catenin in *C. elegans* and is structurally similar to other β-catenins despite having almost no conservation at the primary sequence level (Kidd et al. 2005; Liu et al. 2008a). Leaving this consideration aside, examination of predicted proteomes suggests that Wnts, β-catenin, and TCF/LEFs are metazoan inventions, because they are absent in Choanoflagellates (a single-cell eukaryote) and present in Sponges (King et al. 2008; Adamska et al. 2010; Srivastava et al. 2010). Nearly all invertebrate genomes examined contain one recognizable TCF gene that codes for a TCF/LEF containing an amino-terminal β-catenin-binding domain, an HMG domain followed by a basic tail, and a C-clamp domain (Fig. 1). The one exception is found in *Platyhelminthes*, in which the parasitic flatworm *Schistosoma mansoni* genome (Berriman et al. 2009) contains three TCF/LEF genes and the genome of Planaria (*Schmidtea mediterranea*) has five (C Petersen, pers. comm.). These flatworm TCF/LEFs all have well conserved HMG and basic tail motifs, but C clamps are found in only one TCF/LEF from *S. mansoni* and two TCF/LEFs from *S. mediterranea* (C Peterson, pers. comm.). It is not yet clear which TCF/LEFs in these organisms mediate Wnt signaling, but it is interesting to note that a similar situation exists in amphibians and mammals, which contain four TCF genes that produce a large number of isoforms, but only the TCF1E and TCF4E isoforms contain a C clamp (Atcha et al. 2007). These findings are consistent with a rule in which TCFs from organisms containing a single TCF gene will have a C clamp, whereas this domain is lost from some TCFs in organisms possessing multiple TCF genes. Evolution to multiple-TCF genomes may enable organisms to refine Wnt signals to specific subsets of target genes.

TCF/LEF HETEROGENEITY

Refinement of Wnt signaling through TCF specialization is evident in vertebrates in which the TCF/LEF family has expanded to four loci with alternative promoters and alternative messenger RNA (mRNA) splicing. These capabilities create heterogeneous patterns of activity. Alternative promoters produce truncated dominant–negative forms of LEF1, TCF1, and TCF4, similar to the Wnt-interfering, amino-terminal deleted TCF/LEF forms created for epistasis analysis (van de Wetering et al. 1996; Hovanes et al. 2001; Vacik and Lemke 2011). Alternative mRNA splicing produces TCF/LEFs missing functional domains such as the C clamp and other small regions amino terminal of the HMG DBD domain (van de Wetering et al. 1996; Duval et al. 2000; Hovanes et al. 2000; Prokunina-Olsson et al. 2009b; Weise et al. 2010). With one exception for TCF4 (Kennell et al. 2003), nearly all variations retain the HMG DBD suggesting that TCF/LEF isoforms exert their spectrum of activities via specific DNA binding.

The functional outcome of all this heterogeneity is that TCF/LEF isoforms enable Wnt signals to be interpreted differently. For example, although Wnt can activate gene transcription by directing the formation of β-catenin-TCF/LEF complexes with transcription-activating complexes (Mosimann et al. 2009;

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Cadigan 2012), a recent example in *Xenopus* shows how it also uses β-catenin to disengage TCF3 and corepressors (Hikasa et al. 2010; Mahmoudi et al. 2010; Mohan et al. 2010). Heterogeneity also means that TCF/LEFs can specialize for unique gene targeting, or that they can engage distinct activating or repressing cofactors. To illustrate, TCF3 is generally known as a repressor of Wnt target genes (Kim et al. 2000; Merrill et al. 2004) and the full-length, β-catenin-binding form of TCF4 is also sometimes associated with target gene repression (Tang et al. 2008). In contrast, full-length TCF1 and LEF1 are more often linked to Wnt target gene activation (Reya et al. 2000; Kratochwil et al. 2002; Liu et al. 2005). The mechanistic basis for these differences is not completely known but they seem to track to small repressor-recruiting motifs in the central region and/or the carboxyl terminus of the proteins. For example, the five amino acid motifs LVPQ and SxxSS that are present obligatorily in TCF3 appear as alternatively spliced variations in TCF4 and not at all in TCF1 and LEF1 (Pukrop et al. 2001; Gradl et al. 2002; Liu et al. 2005). Original studies in *Xenopus* systems showed that forms with SxxSS behave like repressors, whereas forms missing this motif act like activators (Liu et al. 2005). This was recently confirmed in a study of human hepatocellular carcinoma in which of the 14 alternatively spliced TCF4 isoforms expressed in liver cancer cells, those that contained the SxxSS motif were growth suppressive, whereas those lacking the element were Wnt activating and growth promoting (Tsedensodnom et al. 2011). The fact that SxxSS forms of TCF4 are generated through alternative splicing means that the prevalence of these forms could differ among cell types and cell stages. Such variations could be one reason why TCF4 has been assigned either activating or repressing, oncogenic or tumor suppressor functions in intestine and colon cancer cells (Korinek et al. 1998a; Tang et al. 2008; Angus-Hill et al. 2011).

Other alternatively spliced regions of TCFs have been noted to increase or decrease target gene activation potential (Weise et al. 2010; Le Bacquer et al. 2011). Perhaps the most interesting of these are the CtBP motifs in the carboxyl terminus of invertebrate TCF/LEFs and mammalian TCF3 and TCF4 (PXDLS) (Brannon et al. 1999; Valenta et al. 2003). Direct CtBP:TCF-binding interactions are controversial and have been variously deemed irrelevant or functional depending on the study (Brannon et al. 1999; Valenta et al. 2003; Hamada and Bienz 2004; Fang et al. 2006). In *Drosophila* cells, CtBP represses Wnt targets in the absence of signaling, and CtBP associates with Wnt target gene chromatin independently of TCF/LEF (Fang et al. 2006). Interestingly, homo-oligomerization of CtBP is required for repression of some Wnt targets, but CtBP is also necessary for activation of other targets as a TCF/LEF-β-catenin-associated monomer (Bhambhani et al. 2011). These novel findings suggest that CtBP could be part of the heterogeneity and context-dependent actions of TCF/LEFs, including the activating/repressing functions of mammalian TCF3 and TCF4—a correlation that might refocus attention on the question of whether CtBP does or does not directly interact with the PXDLS motifs in the carboxyl terminus of these two TCF/LEFs.

THE TCF/LEF TRANSCRIPTIONAL SWITCH

For genes whose expression is induced by Wnt/β-catenin signaling, the standard model is that TCF/LEF represses transcription in the absence of signaling, and is converted to an activator by association with β-catenin. This model is well supported in *Drosophila* and *C. elegans*, organisms that contain a single TCF/LEF gene. However, the situation is more complex in vertebrates, in which individual TCF/LEF proteins have become more specialized in their ability to repress and/or activate Wnt target genes.

In *Drosophila* tissues and cell culture, loss or depletion of TCF/LEF (also known as Pangolin, or Pan) results in a strong reduction in activation of Wnt targets (Brunner et al. 1997; van de Wetering et al. 1997; Stadeli and Basler 2005; Fang et al. 2006; Parker et al. 2008). In addition, reduced TCF/Pan also causes derepression of several Wnt targets in the absence of signaling (Cavallo et al. 1998; Fang et al. 2006; Liu

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et al. 2008b). Studies with POP1, the nematode TCF/LEF, also support this dual role with both repression (Rocheleau et al. 1997; Thorpe et al. 1997; Maduro et al. 2002) and activation of Wnt targets being severely compromised in POP1 mutants (Herman 2001; Shetty et al. 2005; Lam et al. 2006). TCF/LEF loss-of-function studies are nicely complemented in both organisms by analysis of reporter genes whose expressions are driven by Wnt response elements (WREs). Mutation of the TCF/LEF binding sites in these WREs results in a reduction of activation by Wnt signaling, but also depression of reporter activity in cells where the WRE is normally not active (Yang et al. 2000; Knirr and Frasch 2001; Shetty et al. 2005). These results support the model depicted in Figure 3A,C, in which these invertebrate TCF/LEFs restrict WRE activity in cells receiving little or no Wnt signal, and activate the WRE in cells with sufficient Wnt signaling. It should be noted that the repression role for TCF/LEF is not observed at every WRE, presumably owing to the lack of elements that would activate gene expression in the absence of functional TCF/LEF sites (Lam et al. 2006; Chang et al. 2008).

In vertebrate systems, initial studies with simple reporters containing multimerized TCF/LEF sites indicated that all four TCFs can mediate activation of transcription by β-catenin (Molenaar et al. 1996; Korinek et al. 1997; van de Wetering et al. 1997; Hsu et al. 1998) and are bound by corepressors of the Gro/TLE family (Brantjes et al. 2001). However, loss-of-function analyses support the view that repression and activation capabilities of these factors have been divided among the family. In *Xenopus* ventral–lateral patterning, systematic knockdown of TCF/LEFs with morpholinos combined with a rescue by chimeric TCFs fused to repressor or activator domains, found that TCF3 and TCF4 acted as repressors, whereas LEF1 and TCF1

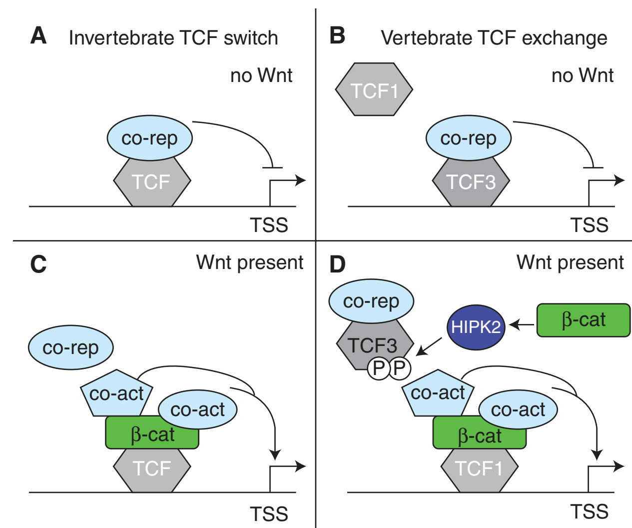

Figure 3. Regulation of TCF/LEFs in invertebrates and vertebrates. (*A*) Most invertebrates have one TCF/LEF gene producing a protein that can recruit corepressors to Wnt targets in the absence of signaling. (*B*) In vertebrates, TCF/LEFs are more specialized, with TCF3 often fulfilling this repressive role. (*C*) When high levels of β-catenin are found in the nucleus after Wnt signaling, it binds to invertebrate TCF, displacing (or inactivating) corepressors and recruiting coactivators through its amino- and carboxy-terminal transactivation domains. (*D*) For at least some vertebrate Wnt targets, a TCF/LEF exchange occurs, in which Wnt/β-catenin signaling promotes HIPK2-dependent phosphorylation of TCF3, causing it to leave Wnt target gene chromatin, allowing TCF1-β-catenin to occupy the WRE, facilitating transcriptional activation. See text for more information.

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acted as activators (Liu et al. 2005). A similar separation of roles was observed at a different developmental stage during Wnt-dependent induction of the Spemann organizer. Here, TCF3 and TCF1 provided repressor roles and TCF4 an activator function (Houston et al. 2002; Standley et al. 2006). TCF3 seems to act most often as a repressor as evident in genetic studies in other systems (Kim et al. 2000; Merrill et al. 2004; Cole et al. 2008; Yi et al. 2011), whereas LEF1 appears restricted to activation of Wnt targets (Reya et al. 2000; Kratochwil et al. 2002). TCF1 and TCF4 have both repressor and activator functions, depending on the cells or tissues examined (Korinek et al. 1998a; Galceran et al. 1999; Roose et al. 1999; Tang et al. 2008; Nguyen et al. 2009). An important limitation of these studies is the heterogeneity of TCF isoforms produced in cells. As described above, some TCF1 and TCF4 isoforms lack the β-catenin-binding domain and act as dominant negatives, so they would behave genetically as repressors of the pathway in a mouse knockout (Roose et al. 1999).

In addition to a Wnt-directed exchange of corepressors for the coactivator β-catenin, differential activities of vertebrate TCFs raise the possibility that the transcriptional switch promoted by Wnt could also involve an exchange of TCF family members. Direct evidence for this type of mechanism has been found in *Xenopus* for the *Vent2* gene, in which TCF/LEF repression and activation occurs through a single binding site (Hikasa et al. 2010). Wnt stimulation promotes the phosphorylation of repressor-acting TCF3 by homeodomain-interacting protein kinase (HIPK2), which results in its dissociation from the WRE (Hikasa et al. 2010). TCF1 is not phosphorylated by HIPK2 and replaces TCF3 on the *Vent2* WRE for gene activation (Fig. 3B) (Hikasa and Sokol 2011). Wnt-HIPK2 signaling also promotes the dissociation of LEF1 and TCF4 from the *Vent2* WRE (Hikasa et al. 2010), suggesting that the HIPK2 pathway could play a prominent role in regulating TCF/LEF chromatin occupancy in many contexts. One potential example is embryonic stem cells, in which it has recently been shown that Wnt signaling promotes an exchange of TCF3 and TCF1 at several Wnt targets (Yi et al. 2011). Whether HIPK2 is involved in the exchange in stem cells is not known.

TCF/LEF-β-CATENIN REGULATION OF HISTONE MODIFICATIONS

The transcriptional switch model for regulation of TCF/LEF activity by Wnt/β-catenin signaling proposes that in the absence of signaling, TCF/LEF recruits corepressors to target gene chromatin. Upon β-catenin association with TCF/LEF, these corepressors are displaced or inactivated, and a variety of coactivators are recruited via interactions with β-catenin. The list of transcriptional coregulators involved in this switch is large (Willert and Jones 2006; Parker et al. 2007; Cadigan and Peifer 2009; Mosimann et al. 2009; Cadigan 2012) and a comprehensive list will not be presented here. Rather, the connection between these factors and histone modifications of Wnt target gene chromatin will be discussed given the wealth of evidence that the state of chromatin has a profound influence on transcription (Berger 2007; Suganuma and Workman 2011).

The most extensive chromatin modification to be examined in the context of Wnt target gene regulation is histone acetylation. Addition of acetyl groups to several conserved lysine residues on the amino termini of histone H3 and H4 subunits is highly correlated with transcriptional activation. This reaction is catalyzed by histone acetyltransferases (HATs) and counteracted by histone deacetylases (HDACs). The role of HDACs in repression of Wnt targets in the absence of signaling was first proposed using an artificial Wnt reporter (Billin et al. 2000), but it has been extended to endogenous targets as well (Kioussi et al. 2002; Sierra et al. 2006; Lyu et al. 2011). In addition, TCF/LEF1-binding corepressors such as members of the Groucho/transducin-like enhancer of split (Gro/TLE) and myeloid translocation gene (MTG) families, which contribute to Wnt target gene repression (Cavallo et al. 1998; Roose et al. 1998; Moore et al. 2008), are known to act in part by binding to HDACs (Chen et al. 1999; Brantjes et al. 2001; Linggi et al. 2005).

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On the activation side of the transcriptional switch, there is abundant evidence that CREB-binding protein (CBP) and its close relative p300, both of which encode HATs, can bind to the carboxy-terminal transactivation domain of β-catenin and mediate activation of Wnt target gene expression (Mosimann et al. 2009; Teo and Kahn 2010). Recruitment of CBP/p300 to Wnt target gene chromatin has been correlated with an increase in H3 and H4 acetylation (Kioussi et al. 2002; Sierra et al. 2006; Parker et al. 2008; Badis et al. 2009; Lyu et al. 2011). In *Drosophila* cells, Wnt/β-catenin signaling causes a widespread increase in H3/H4 acetylation across the entire Wnt target locus (up to 40 kb), even though CBP recruitment is limited to the site of TCF binding (Parker et al. 2008). However, depletion of CBP resulted in loss of all the Wnt-dependent histone acetylation, supporting a model in which CBP directly or indirectly catalyzes the widespread modification. Although the evidence outlined above suggests a major role for histone acetylation in activation of some Wnt targets, other studies have found no evidence for a significant change in histone acetylation at other Wnt targets in response to pathway activation (Wohrle et al. 2007; Blythe et al. 2010).

Trimethylation of the fourth lysine of H3 (H3-K4me3) has also been linked to activation of Wnt targets and the function of the Wnt coactivator Pygopus. H3-K4me3 is a chromatin mark found at proximal promoters, a signature which is positively correlated with transcription (Berger 2007; Suganuma and Workman 2011). Wnt/β-catenin signaling causes an elevation of H3-K4me3 at various target promoters (Parker et al. 2008; Blythe et al. 2010; Chen et al. 2010) and the mixed-lineage-leukemia proteins (MLL1/2), the methyltransferases that catalyze this modification, are required for full activation of several Wnt targets (Sierra et al. 2006; Chen et al. 2010).

Pygopus proteins (Pygo in flies; Pygo1 and Pygo2 in mammals) contain PHD domains and are Wnt coactivators that bind to the amino-terminal transactivation domain of β-catenin indirectly through Legless (in flies) or BCL9 and BCL9-2 (in mammals) (Kramps et al. 2002; Jessen et al. 2008). The PHD domain of Pygo can bind H3-K4me3 (Fiedler et al. 2008; Gu et al. 2009; Kessler et al. 2009). Although the role of this interaction is controversial in *Drosophila* (Kessler et al. 2009), in mammalian systems Pygo2 also interacts with MLL2 (Chen et al. 2010), suggesting a model in which Pygopus proteins act to connect WREs bound by TCF and β-catenin with proximal promoters of Wnt targets (Cadigan and Peifer 2009). This idea is further strengthened by physical interactions between Pygo and Mediator subunits (Carrera et al. 2008) and TAF4 (a TFIID subunit) (Wright and Tjian 2009), both of which physically associate with the RNA polymerase II complex. Indeed, there is recent evidence that several WREs in the c-myc locus form loops with the proximal promoter to affect transcriptional activation (Wright et al. 2010; Yochum et al. 2010; Yochum 2011).

Other recent examples of histone modification complexes that participate in activation of Wnt targets are protein arginine methyltransferase 2 (PRMT2) in *Xenopus*, which promotes H3K8me signatures (Blythe et al. 2010), and the DOT-COM complex, responsible for H3K79me3, a chromatin mark associated with transcriptional elongation (Steger et al. 2008; Mahmoudi et al. 2010; Mohan et al. 2010). PRMT2 was biochemically associated with β-catenin in *Xenopus* embryonic extracts, and is required for Wnt/β-catenin signaling-dependent establishment of the dorsal (Spemann) organizer (Blythe et al. 2010). A more general role in the activation of other Wnt targets remains to be tested. Components of the DOT/COM complex, such as DOTL1 (the methyltransferase subunit; also called DOT1) are required for the pathway in *Drosophila* and mammalian cells (Mahmoudi et al. 2010; Mohan et al. 2010). In the latter system, transcription profiling suggested that DOTL1 functions predominately in the regulation of genes activated by Wnt/β-catenin signaling (Mohan et al. 2010). Further investigations will be needed to determine the role of the DOTL1 complex in general versus Wnt-specific gene activation, as well as exploring the mechanism by which DOT-COM and PRMT8 complexes are recruited to WRE chromatin.

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In addition to the chromatin marks discussed above, there are others (e.g., H4K20me via SET8 and H3R17me via CARM1) that have been linked to activation of Wnt targets (Li et al. 2011; Ou et al. 2011). Although still to be investigated, it seems likely that not all Wnt targets will require all the aforementioned chromatin marks, and a more genome-wide systematic analysis may reveal the existence of classes of chromatin signatures that define subsets of target genes. Adding to this complexity in vertebrate systems is the likelihood that different target genes will require different TCFs for regulation. For example, loss of TCF3 in a neuroblast stem cell results in global elevation of H3/H4ac levels (Lluis et al. 2011), a change consistent with its role in transcriptional repression. Perhaps targets that are more dependent on TCF3 will also show larger differences in histone acetylation in response to pathway activation.

TCF/LEF EXPRESSION AND REGULATION

Because TCF/LEFs are potent transcription regulators, it is important to control their activity. New insights into regulation of transcription and protein localization show how Wnt signaling and other signals control TCF/LEFs beyond just making β-catenin and its chromatin modifiers available.

TCF/LEFs are expressed in distinct but broadly overlapping patterns such that it is common for more than one TCF/LEF to be coexpressed in any one cell. Double knockout studies in mice show that functional redundancy is common, as mice missing more than one TCF/LEF develop early and severe embryonic lethal phenotypes, much more than single knockouts (Galceran et al. 1999; Gregorieff et al. 2004). TCF3 is unique in that its knockout leads to an early embryonic lethal phenotype (Houston et al. 2002; Merrill et al. 2004; Liu et al. 2005). Given that TCF3 is the most abundant family member in embryonic stem cells, this phenotype makes sense. However, single knockout experiments also show that TCF/LEFs have specialized in their function and expression patterns. What are the pathways that control expression, and do these pathways regulate all TCF/LEFs or specific members?

First, TCF/LEF gene transcription can be regulated by the Wnt pathway. With the exception of *TCF3* (*TCF7L1*), all of the TCF/LEF promoters (including the promoters for dominant–negative isoforms) contain predicted WREs (Fig. 4) (K Pate and ML Waterman, unpubl.). These WREs have been experimentally validated in the *LEF1* and *TCF7* promoters and both genes often appear as Wnt-regulated transcripts in microarray studies (Roose et al. 1999; Hovanes et al. 2001; Li et al. 2006). In addition, genome-wide ChIP-ChIP experiments show that the promoters for full-length *LEF1*, *TCF7*, and *TCF7L2* are occupied by TCF4 (Hatzis et al. 2008; Bottomly et al. 2010). The *TC7L1* promoter (for TCF3) is the lone exception; it is not occupied by TCF4 and its promoter does not have identifiable TCF/LEF binding sites.

Second, regulation of the internal promoters for dominant–negative TCF/LEFs is equally important and could vary during development or disease progression. For example, dominant–negative forms of TCF1/*TCF7* are detected in normal colon crypt epithelial cells but they are absent in colon cancer cells (Najdi et al. 2009). A switch in isoform expression from a Wnt-opposing dominant negative in normal cells, to a Wnt-promoting full-length isoform in cancer cells could explain why knockout of *TCF7* in mice produces adenomas in the intestine, whereas knockout of *TCF7* in colon cancer cell lines slows their growth (Tang et al. 2008). Likewise, the *LEF1* locus is aberrantly activated in colon cancer, but only the promoter for full-length LEF1. The promoter for dnLEF1 is silent (Hovanes et al. 2001). Reexpression of dnTCF1 or dnTCF4 in colon cancer cells can shut down Wnt signaling and force a stall in the G1 phase of the cell cycle (van de Wetering et al. 2002). How is it that dnTCF/dnLEF promoters are silent in cancer? A partial explanation is available for the dnLEF1 promoter: Its promoter is silenced through active repression by an upstream distal repressor element that makes WREs in the promoter inaccessible (Li et al. 2006; Yokoyama et al. 2009). The YY1 transcription factor

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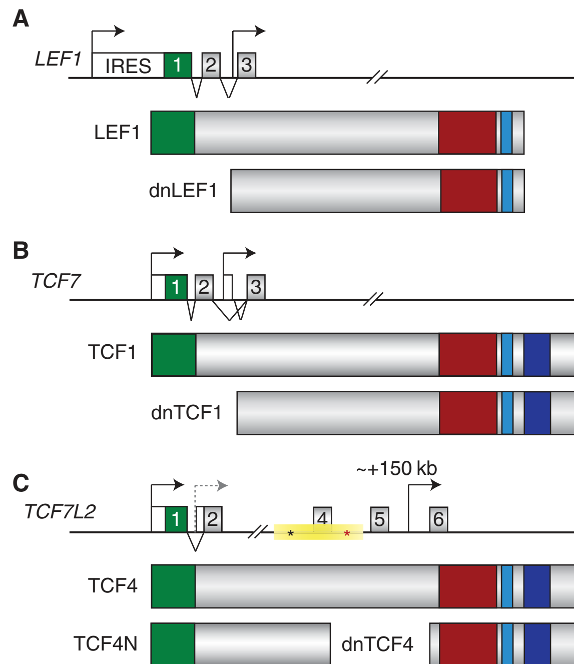

Figure 4. TCF/LEF isoform diversity. (*A*) Schematic of the *LEF1* locus with two promoters. The first promoter produces an mRNA with an internal ribosome entry site in the 5′ UTR (encoded by exon1) (Jimenez et al. 2005; Tsai et al. 2011). A second promoter in intron2 produces a truncated, dominant–negative form of LEF1 missing the β-catenin-binding domain (green rectangle) (Hovanes et al. 2001; Li et al. 2006). Red and blue domains are the HMG and basic domains for DNA binding (refer to Fig. 1). (*B*) Schematic of the *TCF7* locus (which codes for TCF1). Similar to *LEF1*, the *TCF7* locus codes for full-length and dominant–negative forms through the use of two promoters (van de Wetering et al. 1996). (*C*) The *TCF7L2* locus (codes for TCF4) produces multiple truncated isoforms in addition to the full-length form. A putative intron1 promoter has been proposed that produces a dnTCF4 similar to dnLEF1 and dnTCF1 (Duval et al. 2000). A third promoter in intron5 has been defined (Vacik and Lemke 2011). This promoter produces a dnTCF4 isoform because it is missing the β-catenin-binding domain. The promoter lies immediately downstream from a 92-kb genomic interval (yellow rectangle) that contains the strongest known risk alleles for type 2 diabetes (black asterisk; rs7903146 and rs12255372 [Grant et al. 2006]) as well as an alternative polyadenylation signal that might produce the previously discovered inhibitory form referred to as TCF4N (red asterisk) (Kennell et al. 2003; Locke et al. 2011).

is necessary for this repression as it binds to the core promoter and communicates with the distal repressor (Yokoyama et al. 2009).

Another example comes from the recent discovery of a promoter for dominant–negative TCF4 and an intronic enhancer connected to risk of diabetes. The strongest diabetes-associated polymorphism identified to date occurs in an intervening sequence of the *TCF4/TCF7L2* gene (Grant et al. 2006; Lyssenko et al. 2007; and reviewed in Doria et al. 2008). Single-nucleotide polymorphisms (SNP) in introns can change splicing efficiencies and influence the relative expression of spliced isoforms (Prokunina-Olsson et al. 2009a,b), but the most significant diabetes-associated SNP lies within a 92-kb genomic interval that has additional activities. A recent bacterial artificial chromosome (BAC) survey in transgenic mice determined that this region contains a strong regulatory enhancer (Savic et al. 2011). This region also contains a signal for alternative polyadenylation for production of a truncated, inhibitory TCF4 isoform missing the HMG DNA-binding domain (Fig. 4) (Kennell et al. 2003; Locke et al. 2011). The SNP-containing interval is clearly an important regulator of the levels of *TCF7L2* gene expression. But there is an even deeper

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consideration. A recent study of TCF4 expression during development showed that the fifth intron of the *TCF7L2* locus harbors a highly conserved promoter for a dominant–negative isoform of TCF4—a form missing the β-catenin-binding domain but retaining the HMG DNA-binding domain. This promoter is activated during embryogenesis by VAX1/VAX2, a homeobox regulator essential for negative feedback of Wnt signaling. Although the VAX-induced dnTCF4 form is most prevalent in the brain, it might be important to reassess how the diabetes-associated SNPs located upstream affect the production of full-length versus dominant–negative TCF4 in tissues such as the pancreas. Such changes would be mostly invisible in microarray and RNA-seq data unless one was specifically looking for it. Sorting out the connection between expression and activity of TCF4 isoforms is important because out of all the vertebrate TCF/LEFs, this family member shows the most polymorphisms and mutations in cancer and diabetes (Grant et al. 2006; Sjoblom et al. 2006; Cauchi et al. 2007; Bass et al. 2011; Mullighan et al. 2011).

As illustrated with the HIPK2-directed "TCF exchange," TCF/LEF localization appears to be dynamic on target gene chromatin. As mentioned above, Wnt signals direct a swap of TCF3 for TCF1 in a β-catenin- and HIPK2-dependent manner in *Xenopus* embryos and mouse embryonic stem cells (mESCs) (Hikasa et al. 2010; Hikasa and Sokol 2011; Yi et al. 2011). The swap results in activation of Wnt target genes because TCF3 is repressive, whereas TCF1 is activating. Multiple sites of phosphorylation in the central portion of xTCF3 are essential target residues for the switch, and these sites are also phosphorylated in the corresponding region of xTCF4 and mLEF1 (Fig. 5) (Hikasa and Sokol 2011). It is worth noting that these residues are conserved in human orthologs of TCF3, TCF4, and LEF1, but they are not present in any TCF1 homolog (Fig. 5). This suggests that Wnt-triggered HIPK2 signals may be especially effective at promoting TCF1 occupancy of WREs. It is also worth emphasizing that HIPK2 activation and the TCF3/TCF1 swap is β-catenin dependent.

The Wnt- and β-catenin-dependent feature of HIPK2 action has intriguing parallels to regulation of the *C. elegans* ortholog POP1. In this case, a Wnt signal that is delivered asymmetrically to dividing daughters of the EMS progenitor cell directs the alternative catenin WRM1 and a Nemo-like kinase (NLK) called LIT1, to bind the carboxyl terminus of POP1 and phosphorylate its context-dependent regulatory domain (CRD) (Lo et al. 2004; Yang et al. 2011). NLK phosphorylates CRD residues that are similar to those targeted by Wnt/β-catenin/HIPK2 (Fig. 5). Phosphorylated POP1 is recognized by 14-3-3 proteins for rapid nuclear export, an action that lowers

```
HIPK2
     LEF1  SLSPPIPRT-SNKVPVVQPSHAVHPLTPLITYSDEHFSPGSHPSHIPSDV  178
     TCF3  TRSPSPAHL-SNKVPVVQHPHHMHPLTPLITYSNDHFSPGSPPTHLSPEI  215
     TCF4  ARSPSPAHIVSNKVPVVQHPHHVHPLTPLITYSNEHFTPGNPPPHLPADV  201

LIT1/NLK
     LEF1  SLSPPIPRT-SNKVPVVQPSHAVHPLTPLITYSDEHFSPGSHPSHIPSDV  178
     TCF4  ARSPSPAHIVSNKVPVVQHPHHVHPLTPLITYSNEHFTPGNPPPHLPADV  201
     POP1                   ..PPYAAALRSPSLMFPMGAMSPTFPMFPPSPVY  130

TNIK
     TCF3  TRSPSPAHL-SNKVPVVQHPHHMHPLTPLITYSNDHFSPGSPPTHLSPEI  215
     TCF4  ARSPSPAHIVSNKVPVVQHPHHVHPLTPLITYSNEHFTPGNPPPHLPADV  201
```

Figure 5. TCF/LEF phosphorylation sites for HIPK2, LIT1/NLK, and TNIK. Amino acid alignment of human LEF1, TCF3, and TCF4 and the *C. elegans* ortholog POP1. The indicated regions are amino terminal of the HMG domain. Residues in red are validated, mapped phosphorylation sites by the kinase HIPK2 (Hikasa and Sokol 2011), the kinase NLK and its *C. elegans* ortholog LIT1 (Ishitani et al. 2003; Lo et al. 2004), and TNIK (Mahmoudi et al. 2009).

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nuclear concentrations of POP1 and results in an increase in target gene activation (Thorpe et al. 1997; Maduro et al. 2002; Shetty et al. 2005). Activation of mammalian NLK also has negative actions on TCF/LEFs. In this case, NLK is activated by Wnt ligands such as Wnt5a to phosphorylate TCF4 and LEF1 and trigger their dissociation from DNA (Ishitani et al. 1999, 2003). Similar to LIT1 and HIPK2, Wnt directs the formation of a complex between NLK, β-catenin, and the TCF/LEF protein, and once again, the residues phosphorylated by NLK are a subset of the LIT1- and HIPK2-dependent phosphorylations (Fig. 5) (Sokol 2011).

There is one other kinase that phosphorylates TCFs in a Wnt- and β-catenin-dependent manner. TNIK (for Traf2- and Nck-interacting kinase) was discovered through proteomic analysis of TCF4 complexes in mouse intestine and human colon cancer (Mahmoudi et al. 2009). This kinase is recruited by β-catenin to WRE-bound TCFs for phosphorylation. TNIK is a Germinal Center/Ste20-type kinase, very different from NLK and HIPK2, yet it targets a residue in the CRD region of TCF3 and TCF4 that is identical to a HIPK2 site (Fig. 5) (Shitashige et al. 2010). TNIK actions enhance Wnt target gene activation much like the outcomes of HIPK2 and LIT1 action but how it does this is unknown (Mahmoudi et al. 2009; Satow et al. 2010; Shitashige et al. 2010). TNIK could certainly function in a manner that is completely different from HIPK2, but it is also possible that it triggers a transcriptional switch between TCF/LEFs. In fact, TCF4 has been recently proposed to function as a growth suppressor in colon cancer cells, whereas TCF1 has been observed to promote Wnt signals and proliferation (at least in colon cancer) (Tang et al. 2008; Angus-Hill et al. 2011). Because TCF1 is expressed as a full-length activating form in colon cancer, and because it is not targeted by any of these kinases, it would be interesting to know whether TNIK can activate Wnt target gene transcription by directing a transcription switch between TCF4 and TCF1.

TCF1 appears as a stand-alone in that it is not phosphorylated by HIPK2, NLK, or TNIK, but its TCF1 actions are controlled in other ways. First, normal colon crypts express a dominant–negative form of TCF1 that can oppose its full-length counterpart (Najdi et al. 2009). As mentioned above, this Wnt-suppressing form is missing in colon cancer. A second tier of negative regulation uses specific Wnt signals (Wnt1, Wnt5a) to trigger nuclear export of TCF1 (Najdi et al. 2009; R Najdi, unpubl.). This action shares similarities with the Wnt-directed inhibition of other TCF/LEFs because β-catenin appears to be involved, but whether TCF1 is phosphorylated by a different kinase for export is not known.

The heterogeneity inherent in the TCF/LEF family means that linking the molecular effects of β-catenin-dependent kinases (HIPK2, NLK, and TNIK) to their overall effect on Wnt signaling in any one cell type or tissue may not be straightforward because multiple TCF/LEFs with different activities are often coexpressed. For example, can we conclude that Wnt-HIPK2 always results in Wnt target gene activation and that Wnt-NLK-nuclear export of TCF1 always leads to Wnt target gene repression? The answer is clearly no. Because the vertebrate family has expanded and specialized, the functional outcome of HIPK2 or NLK kinases on Wnt signaling depends on how they alter the relative concentrations of activating and repressing TCF/LEFs versus the available pool of β-catenin (Sokol 2011). In fact, Wnt-NLK-TCF1 export predicts a very different outcome for normal colon epithelia in which dnTCF1 is expressed (export would lead to Wnt target gene activation), versus colon cancer cells that express full-length TCF1 (export would reduce Wnt target expression) (Najdi et al. 2009). Another important case in point is the observation in *C. elegans* that exporting the single TCF ortholog POP1 from the nucleus leads to overall Wnt target gene activation. It may seem paradoxical that reduction of TCF/POP1 concentrations in the nucleus leads to target gene activation, but a recently proposed model suggests that nuclear concentrations of TCFs are as important as nuclear β-catenin concentrations for establishing an optimal β-catenin:TCF ratio (Phillips and Kimble 2009). Too much TCF might translate into target gene repression rather than activation.

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Consistent with this, quantitative modeling of Wnt signaling in *Xenopus* shows that sensing fold changes in Wnt signals works best by monitoring the relative amounts of two interacting factors (i.e., β-catenin and TCF) than by trying to measure absolute levels of stabilized β-catenin (Goentoro and Kirschner 2009). Thus, it could be that Wnt signals regulate gene expression by dynamically controlling the concentrations of TCF/LEFs in the nucleus as much as they do β-catenin.

NON-TCF RELAYS: WNT/β-CATENIN SIGNALING THROUGH NON-TCF/LEF PROTEINS

As outlined thus far in this review, TCFs are major nuclear recipients of Wnt/β-catenin signaling. However, there are other transcription factors that can bind β-catenin and activate transcription. These include type I and type II nuclear receptors (Mulholland et al. 2005; Beildeck et al. 2010), several members of the SOX family (Kormish et al. 2010), FOXO proteins (Essers et al. 2005; Almeida et al. 2007), the homeodomain proteins Prop1 and PitX2 (Kioussi et al. 2002; Olson et al. 2006), hypoxia-inducible factor 1α (HIF1α) (Kaidi et al. 2007), and the bHLH protein MyoD (Kim et al. 2008). Here we summarize some of this work, to highlight general questions regarding non-TCF proteins and their role in Wnt/β-catenin transcription and biology.

One well-studied example of β-catenin interacting with a nuclear receptor is the androgen receptor (AR). The ligand-binding domain of AR binds directly to the Arm repeats of β-catenin (Mulholland et al. 2002; Yang et al. 2002; Song et al. 2003). Androgen increases the strength of the AR-β-catenin interaction (Truica et al. 2000; Song et al. 2003) and promotes nuclear accumulation of the complex (Mulholland et al. 2002; Pawlowski et al. 2002; Song et al. 2003). Consistent with these studies, Wnt/β-catenin signaling promotes transcriptional activation by AR at the level of simple reporter constructs (Truica et al. 2000; Mulholland et al. 2002; Verras et al. 2004) and AR target genes (Masiello et al. 2004; Cronauer et al. 2005; Read et al. 2007). Both AR and β-catenin can bind to TIF2/GRIP1, a p160 steroid receptor coactivator and the three proteins may act together in a complex to activate transcription (Song and Gelmann 2005).

The AR-β-catenin interaction likely plays a crucial role in prostate cancer, in which AR is required for progress of this cancer at all stages (Culig et al. 2002; Niu et al. 2010). Mutations stabilizing β-catenin are found in 5%–7% of prostate cancers (Voeller et al. 1998; Chesire et al. 2000) and other proteins that elevate nuclear β-catenin levels are also found at high frequency in tumors (Rios-Doria et al. 2004; Chen et al. 2006). Most prostate cancers initially respond to a reduction in androgen levels, but eventually convert to an androgen-independent state (Culig et al. 2002; Niu et al. 2010). In the mouse, expression of a stabilized form of β-catenin can promote prostate hyperplasia pre- or post-castration (Bierie et al. 2003; Yu et al. 2009) and the physical association of AR and β-catenin is stronger post-castration (Wang et al. 2008) or with an AR mutant that is hormone insensitive (Masiello et al. 2004). Thus, β-catenin may play an essential role in enabling AR to operate independently in low androgen environments (Schweizer et al. 2008).

β-catenin-binding proteins have the potential to compete with TCF/LEF for limiting amounts of β-catenin. For example, overexpression of AR inhibits activation of the TCF/LEF reporter TOPFLASH by β-catenin (Chesire and Isaacs 2002; Pawlowski et al. 2002). The significance of this competition is not clear for AR, but has been proposed to be significant in the case of HIF-1α (Kaidi et al. 2007). Hypoxia (which increases HIF1α levels) reduces TCF/LEF-β-catenin transcriptional activity, which is correlated with cell-cycle exit of colorectal cancer cells (Kaidi et al. 2007), and it also regulates gene expression in a β-catenin-dependent manner (Kaidi et al. 2007; Zhao et al. 2011). However in some hypoxic stem cells, there appears to be sufficient β-catenin to interact with both TCFs and HIF1α (Mazumdar et al. 2010). In colorectal cancer cell lines, a positive-feedback loop occurs, in which HIF1α represses APC transcription, elevating β-catenin protein

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levels, which promotes high levels of HIF1α transcript and protein (Newton et al. 2010). These data indicate a complex interaction between HIF1α, TCF/LEFs, and β-catenin, which may differ between cell types.

Given the large number of transcription factors that can bind and recruit β-catenin to regulatory sequences, how much of Wnt/β-catenin is mediated through TCFs in vertebrate systems? To answer this question, mutations that specifically abolish β-catenin binding will have to be examined in vivo. For example, the vitamin D receptor (VDR) a type II nuclear receptor, can bind β-catenin independent of vitamin D to promote transcription (Palmer et al. 2001; Malloy et al. 2002; Shah et al. 2006). Recessive mutations of the human VDR gene result in hereditary vitamin D-dependent rickets (HVDDR) and are usually accompanied by epidermal defects such as alopecia, i.e., hair loss (Malloy and Feldman 2011). However, some VDR alleles display HVDDR without alopecia (Malloy et al. 2002; Malloy and Feldman 2011). Characterization of one such mutation showed that it lacked the ability to respond to vitamin D (Malloy et al. 2002) but still retained the ability to be activated by β-catenin (Shah et al. 2006; Palmer et al. 2008). Given recent data that β-catenin and VDR act together to promote hair follicle development (Palmer et al. 2008; Baker et al. 2010), these data suggest that VDR acts in bones primarily through vitamin D and through β-catenin in hair formation. Although this model requires further testing, it provides a blueprint for dissecting the importance of β-catenin interactions for other transcription factors.

CONCLUDING REMARKS

The transcription regulatory actions of β-catenin are much more varied and complex than originally assumed when TCF/LEFs were first identified as a β-catenin partner. This review has highlighted how β-catenin participates in the switch-in/switch-out of different TCFs at target genes, how it recruits varied and multiple histone modifying complexes, and how it interacts with other types of transcription factors. Likewise, we have reviewed how the transcription regulatory actions of TCF/LEFs are equally complex and powerful. Genomes with multiple TCF/LEFs have evolved individual family members with specialized functions, a feature that might explain how some TCFs can act as growth suppressors or tumor suppressors and how some TCFs access selective subsets of target genes. Multiple isoforms from alternative promoters and alternative splicing create many of these specialized functions. Defining the regulatory networks that control isoform expression is not only important for understanding how each TCF/LEF gene functions in stem cells and their differentiating progeny, but it is important for understanding how these isoforms participate (or oppose) disease states such as diabetes or cancer. Tools that detect specific TCF/LEF forms, and mutations that selectively remove one form or another will be critical for this understanding.

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