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Review

Cross-regulation of signaling pathways: An example of nuclear hormone receptors and the canonical Wnt pathway

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ABSTRACT

Predicting the potential physiological outcome(s) of any given molecular pathway is complex because of cross-talk with other pathways. This is particularly evident in the case of the nuclear hormone receptor and canonical Wnt pathways, which regulate cell growth and proliferation, differentiation, apoptosis, and metastatic potential in numerous tissues. These pathways are known to intersect at many levels: in the intracellular space, at the membrane, in the cytoplasm, and within the nucleus. The outcomes of these interactions are important in the control of stem cell differentiation and maintenance, feedback loops, and regulating oncogenic potential. The aim of this review is to demonstrate the importance of considering pathway cross-talk when predicting functional outcomes of signaling, using nuclear hormone receptor/canonical Wnt pathway cross-talk as an example.

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Introduction

Nuclear hormone receptors

There are 48 known members of the nuclear hormone receptor (NHR) family of transcription factors. They are generally divided into two subtypes: Type I and Type II (Type III and Type IV also exist but they are largely composed of orphan receptors, about which little is known). Type I NHRs include the sex steroid receptors such as estrogen receptor α and β (ER—*NR3A1* and *NR3A2*, respectively), progesterone receptor (PR—*NR3C3*), and androgen receptor (AR—*NR3C4*), as well as glucocorticoid receptor (GR—*NR3C1*), among others. These receptors are found in both the cytoplasm and the nucleus and generally bind as homodimers to their DNA recognition sequences. Type II NHRs include the vitamin D receptor (VDR—*NR1I1*), peroxisome proliferator-activated receptors α, β, and γ (PPARs—*NR1C1*, *NR1C2*, *NR1C3*, respectively), and retinoic acid receptors α, β, and γ (RARs—*NR1B1*, *NR1B2*, *NR1B3*, respectively), among others. These receptors are constitutively nuclear and generally bind as heterodimers, most frequently with the NHR retinoid x receptor (RXR—*NR2B1*, *NR2B2*, *NR2B3* for α, β, and γ, respectively), to their DNA-binding elements.

In the absence of ligand, the Type II receptors recruit a large co-repressor complex. On some occasions, ligand-dependent repression occurs on specific regulatory sequences such as negative VDR binding elements. Once ligand enters the cell, it traverses the nuclear membrane and binds to the receptor, inducing a conformational change that allows the sequential recruitment of histone modifying proteins, transcriptional mediator complexes, and, lastly, the basal transcription machinery to activating recognition sequences.

The Wnt pathway

The Wnt pathway is strongly associated with an oncogenic phenotype in many cancers including cancer of the liver, breast, and particularly, the colon. In the absence of canonical Wnts, the GSK3β/Axin/APC complex induces the phosphorylation of β-catenin, which targets it for degradation by the proteasome [1–3]. The presence of endocrine and paracrine Wnts induces binding of Frizzled (Fzd) receptor to low-density lipoprotein receptor-related protein 5 or 6 (LRP5/6), which ultimately leads to the inhibition of the GSK3β/Axin/APC phosphorylation complex and accumulation of unphosphorylated β-catenin.

β-Catenin is a multifunctional protein with important structural and signaling functions. β-Catenin plays a pivotal role in cell–cell adhesion, linking the cytoplasmic domain of the cadherin family of transmembrane proteins to α-catenin and thus connecting the adhesion complex to the actin cytoskeleton. β-Catenin is also an essential component of the Wnt/Wingless signaling pathway that plays important roles in development and pathogenesis. Through this dual role, β-catenin has the potential to allow changes in cell adhesion and junction formation to affect transmembrane signaling and gene expression. The many functions of β-catenin are derived from three cellular pools of the molecule under strict regulation: a membrane pool of cadherin-associated β-catenin, a cytoplasmic pool, and a nuclear pool [4]. β-Catenin that is not targeted to the proteasome by the GSK3β/Axin/APC complex can be found in the nucleus, as "activated" β-catenin. "Activated" β-catenin is a heterodimeric binding partner of LEF/TCF proteins that contain DNA-binding motifs [5]. Together these proteins form a transcription initiation complex and regulate the expression of many genes involved in cell growth [6,7].

Stabilization of β-catenin is likely the key event in the transduction of a Wnt signal and the cell has developed an elaborate system to regulate its steady-state levels. In addition to the GSK3β/Axin/APC destruction complex, the Wnt pathway is also controlled by extracellular antagonists. Secreted Frizzled-Related Protein (sFRP) and Wnt Inhibitory Factor 1 (WIF-1) are secreted factors that bind Wnts and prevent them from binding their cognate receptors. Dickkopf (DKK) family members and Wise, a context-dependent secreted protein [8], both antagonize the Wnt pathway by binding to LRP5/6 and preventing Wnts from binding. Dysregulation of any of these pathway components can lead to the production of over-abundant activated β-catenin and an oncogenic phenotype.

Cross-talk between these two pathways may have differing effects on oncogenic potential. Activation of β-catenin signaling is a key event in colorectal carcinogenesis where mutations in the tumor suppressor gene *APC* account for up to 80% of cancers [9]. In addition, activating β-catenin mutations have also been reported in melanomas, ovarian cancer, medulloblastomas, and endometrial cancer, underscoring the importance of β-catenin-mediated signaling in oncogenesis [10–12]. The transforming potential of *Wnt* genes correlates precisely with their ability to induce elevated β-catenin levels, suggesting that β-catenin is instrumental in Wnt-mediated transformation [13]. Although the aberrantly activated Wnt pathway is almost exclusively associated with a cancer phenotype, aberrantly activated NHR pathways have varied outcomes with respect to a cancer phenotype. The sex hormones, AR and ER, are thought to promote cancer, while others such as PPARγ and VDR are thought to prevent cancer. While methods of cross-talk are not likely to be exactly the same for each NHR, there are some commonalities. The mechanisms of cross-talk and the reported outcomes are reviewed presently in the context of both development and cancer.

Cross-talk between NHR and Wnt pathway components

Extracellular space

Many NHRs can regulate the transcription of Wnt antagonists. This becomes clear in the context of stem cell differentiation in certain tissues where Wnt expression can drive cell fate. One of the best-characterized processes involving Wnt and NHR signals in stem cell differentiation involves the driving of mesenchymal progenitor cells into an adipocyte or an osteoblast lineage. The commitment of mesenchymal stem cells to an adipogenic or osteogenic cell fate involves an intimate level of cross-regulation between the Wnt pathway and several NHRs (Fig. 1A). It is generally accepted that an osteogenic cell fate is induced by Wnt/Fzd activity, while an adipogenic cell fate is induced by PPARγ activity [14]. These two key regulators reciprocally inhibit each other on multiple levels. Wnt promotes osteogenesis by blocking the PPARγ and C/EBPα induction that would otherwise occur under adipogenic stimuli [15–17]. Orphan NHR, COUP-TFII, which is a direct target of β-catenin, and, thus, downstream of the Wnt pathway, also inhibits PPARγ expression. It binds to the PPARγ promoter and recruits

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