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Ror2 as a Therapeutic Target in Cancer

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ABSTRACT

Ror2 is a signaling receptor for Wnt ligands that is known to play important roles in limb development, but having no essential roles known in adult tissues. Recent evidence has implicated Ror2 in mediating both canonical and non-canonical signaling pathways. Ror2 was initially found to be highly expressed in osteosarcoma and renal cell carcinomas, and has recently been found in an increasingly long list of cancers currently including melanoma, colon cancer, melanoma, squamous cell carcinoma of the head and neck, and breast cancer. In the majority of these cancer types, Ror2 expression is associated with more aggressive disease states, consistent with a role mediating Wnt signaling regardless of the canonical or noncanonical signal. Because of the pattern of tissue distribution, the association with high-risk diseases, and the cell surface localization of this receptor, Ror2 has been identified as a potential high value target for therapeutic development. However, the recent discovery that Ror2 may function through non-kinase activities challenges this strategy and opens up opportunities to target this important molecule through alternative means.

Contents

1. Introduction

Ror2 is a member of the receptor tyrosine kinase orphan receptor (ROR) family, which belongs to the receptor tyrosine kinase (RTK) superfamily. RTKs are a large family of glycoproteins that regulate cell proliferation, polarity, differentiation, migration, metabolism and survival (Ullrich & Schlessinger, 1990; Blume-Jensen & Hunter, 2001). Aberrant RTK activation due to deregulated receptor expression and/or constitutive activation are major mechanisms by which tumor cells contribute

Abbreviations: RTK, receptor tyrosine kinase; Ror1 and Ror2, receptor tyrosine kinase like orphan receptor; CRD, cysteine rich domain; Wnt, wingless family gene; SH2, src homology domain 2; MMP, matrix metaloprotease; EMT, epithelial to mesenchymal transition; ATP, adenosine triphosphate.

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to the development of various forms of cancer in humans (Forbes et al., 2001; Lemmon & Schlessinger, 2010).

Ror2 is a developmentally regulated protein that has significant expression and roles in a wide variety of tissues during early embryonic development. Expression is downregulated during midgestation and the protein is absent in adult tissues except for residual compartments of expression in the uterus and osteoblasts ((Saldanha et al., 1998; Yoda, Oishi, & Minami, 2003; Billiard et al., 2005; Cha et al., 2014). Roles in normal adult tissues are not understood. However, it is now established that Ror2 is upregulated in a large number of human tumors including osteosarcoma (Morioka et al., 2009), melanoma (O'Connell et al., 2010), renal cell carcinoma (Wright et al., 2009), prostate carcinoma (Yamamoto et al., 2010), colorectal cancer (Mei et al., 2014), squamous cell carcinomas of the head and neck (Kobayashi et al., 2009), and stromal tumors (Edris et al., 2012), and recently was identified as a feature of breast cancers (Henry et al., 2015). Ror2 has become a focus of attention in the cancer community due to its expression in cancers, its frequent association with higher risk disease, and competing roles as a tumor progressor, or some studies that suggest that it may act as a negative disease modifier in certain tissue specific scenarios (Ford et al., 2013).

Previously an orphan receptor, Ror2 is now known to interact with several of the Wnt ligands, which makes the name inapt (Green et al., 2008). Wnt5a and Wnt3a are now well known to act as ligands for Ror2 to activate a combination of noncanonical and canonical Wnt signaling activity, respectively (Yamamoto et al., 2007; Green et al., 2008; Rasmussen et al., 2013). Through these signaling cascades, Ror2 mediates polarized cell migration, invasion, and tumor growth. However, the mechanism by which Ror2 functions to promote cancer remains incompletely understood. Long taken as a kinase, the kinase activity of Ror2 is now also controversial (Artim et al., 2012; Mendrola et al., 2013).

Due to these interesting features and its association with cancer signaling, Ror2 has recently become a central focus for developing therapeutic intervention. Here, we review what is known about Ror2, its roles in cancer and the potential as a therapeutic target in cancer.

2. The Ror receptors

There are two Ror receptors in the Ror family, Ror1 and Ror2, and were first identified in a human neuroblastoma cell line by screens for tyrosine kinase-encoding genes (Masiakowski & Carroll, 1992). The Ror-encoding genes, Ror1 and Ror2, are located on chromosome 1 and 9, respectively, both encoding 104-kDa proteins (Reddy et al., 1997; Forrester, 2002). These receptors are highly homologous to one another, and structurally are very similar to Trk and Musk families of RTKs (Forrester, 2002). Similar to the other RTKs, the molecular architecture and key intracellular signaling pathways of Ror1 and Ror2 are highly conserved in evolution from the nematode *Caenorhabditis elegans* to humans (Yoda et al., 2003).

3. Ror2 structure and function

Ror2 is a Frizzled family protein which belongs to the 7 transmembrane class of receptors. As a member of the RTK family, the structure of Ror2 consists of three main parts (Fig. 1): extracellular, transmembrane and intracellular regions (Hojjat-Farsangi, 2014). The extracellular regions of Ror2 are divided into several domains, the immunoglobulin (Ig)-like domain, the cysteine rich domain (CRD), and the Kringle domain (Hojjat-Farsangi, 2014). Ror2 possesses a single CRD within the extracellular region that is defined by the presence of 10 conserved cysteines and by several additional conserved amino acids (Forrester, 2002). The CRDs are composed mainly of α-helices and act as the binding site for the Wnt ligand (Bhanot et al., 1996; Green et al., 2008). The Ig-like domains consist of ~100 amino acids residues, including a conserved disulfide bridge, and are thought to mediate protein–protein interactions and also modify the function of CRD and Kringle domains (Minami et al., 2010). The Kringle domain is a triple-disulfide-linked domain and is reported to function as the recognition module for binding to other proteins (Oishi et al., 1997).

The cytoplasmic regions of Ror2 contain the putative tyrosine kinase (TK) domain. Both Ror family members contain the predominant RTK YXXDYY sequence (Feike et al., 2010). And the kinase domain contains

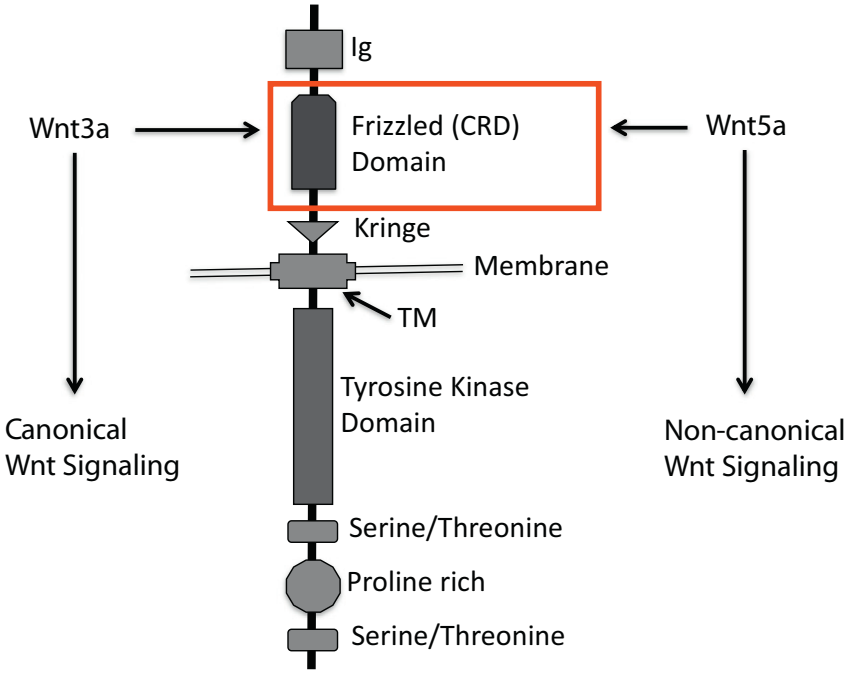

Fig. 1. Depiction of Ror2 domains and Wnt signaling: Extracellular part of Ror2 contains an Ig-like domain (Ig), a frizzled or cysteine-rich (CRD) domain and a kringle domain. The extracellular and intracellular domains are separated by a transmembrane (TM) domain across the cell membrane. Intracellularly, ROR2 contains a tyrosine kinase (TK) domain and a proline-rich domain (PR) flanked by serine/threonine (ST) rich domains. The CRD domain acts as a binding site for Wnt3a and Wnt5a to mediate canonical and non-canonical Wnt signaling respectively.