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ROR1 is an Intriguing Target for Cancer Therapy

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Abstract

Receptor Tyrosine Kinase-Like Orphan Receptor 1 (ROR1) is an oncofetal protein and has gained attention in cancer therapy since its initial discovery as a relatively specific surface antigen on B cell chronic lymphocytic leukemia (CLL) in 2008. The list of cancer types with ROR1 expression keeps growing, comprising, among others, malignant melanoma, breast cancer, and prostate cancer. It has been shown that ROR1 mediates several oncogenic pathways in a cancer type- and context-dependent manner. There are several ways to target ROR1 molecule, some of which have been in preclinical and clinical trials. We briefly summarize the oncogenic signaling pathways related to ROR1, as well as the update on ROR1-targeted therapies.

Background

ROR1 is transmembrane receptor tyrosine kinase-like protein that is mainly expressed in cells during embryogenesis; however, ROR1 has been shown to re-express in several cancer types [1]. At the amino terminus of ROR1 is an extracellular immunoglobulin-like domain, a cysteine-rich domain, also named the Frizzled domain, and a highly folded, cysteine-rich Kringle transmembrane domain [2]. WNT5A, the only known ligand for ROR1, binds to ROR1 via the Frizzled domain. The Kringle domain is responsible for the heterodimerization with another ROR family protein ROR2 in CLL cells, which leads to the activation of Rho family small GTPase, the subsequent cancer cell proliferation and migration [3]. The cytoplasmic segment of ROR1 contains a tyrosine kinase domain with debatable kinase activity, a Serine/Threonine-rich domain, a Proline-rich domain, and another Serine/Threonine-rich domain at the carboxyl terminus, presumably involved in protein-protein interactions [2].

ROR1-Mediated Oncogenic Signalling

The oncogenic function of ROR1 was first established in a screening for kinases involved in the inhibition of apoptosis [4]. ROR1 appears to promote oncogenic events in a cancer-type and context-dependent manner. In CLL cells, WNT5A induces several pro-survival pathways via ROR1, such as the activation of AKT and the above mentioned Rho GTPase activation via ROR2-heterodimers. In lung adenocarcinomas, ROR1 has been shown to potentiate EGFR/ErbB3 heterodimerization upon EGF treatment and further induce the phosphorylation/activation of c-Src [5]; and not surprisingly, ROR1 expression is correlated with shorter patient survival in non-small-cell lung cancer [6]. In malignant melanoma, there are mixed results from ROR1 in its oncogenic role. One report shows that it is also associated with poor survival rates, partially due to the up regulation of activated AKT [1]. A second study shows that ROR1 has a positive role in promoting proliferation, but inhibits cancer cell dissemination; whereas ROR2 has the exact opposite role [7]. In triple negative breast cancer strong expression of ROR1 is predictive of shorter overall survival [8]. The same group found that ROR1 can interact with casein kinase 1 epsilon (CK1ζ) to activate phosphoinositide 3-kinase/AKT which is associated with potentiated tumor growth and metastasis [9]. Under other pathophysiological conditions, ROR1 is known to mediate signalling pathways potentially involved in cancer. In colon stem cells, a paracrine WNT5A/ROR1/2 signalling has been identified by potentiating phosphorylation of SMAD3, which is involved in colon repairing process after injury [10]. Very recently, WNT5A/ROR1 axis has been shown to be involved in a feed-forward activation of TAZ/YAP1, which in turn leads to the expression of WNT5A and subsequent blockage of canonical WNT/-Catenin activation [11]. All these signalling pathways, along with others not mentioned here, are presumably involved in driving different oncogenic processes by ROR1.

ROR1-Based Targeted Therapies

ROR1 makes an intriguing and promising target for treating cancer for two key reasons. As discussed previously, ROR1 is expressed during embryogenesis but is absent in most adult tissues, and ROR1 is overexpressed on the cell surface of several types of cancer where it plays a role in promoting survival, proliferation and EMT [2]. Several approaches have been utilized to use ROR1 as a target for cancer therapy.

The first and most direct approach is the use of monoclonal antibodies (mAbs) targeting ROR1. Several groups have

developed mAbs targeting ROR1 for the treatment of CLL. The first mAbs targeting ROR1 were screened for their ability to bind ROR1 by phage display, however most of these antibodies bound the Ig-like domain of ROR1 and failed to directly induce significant cytotoxicity in human CLL cells [12]. Daneshmanesh et al. [13] generated mAbs against different regions of the extracellular domain of ROR1, and then tested the ability of these antibodies to induce apoptosis in human CLL cells. Antibodies that targeted the cysteine-rich domain or the kringle domain were the most effective, even more effective than Rituximab, an anti-CD20 mAb that is a currently approved treatment for advanced CLL. Dr. Kipps [14] group has generated a mAb designated UC-961 that has undergone preclinical specificity and safety studies and will begin clinical trials for the treatment of CLL patients. While these mAbs are being designed to treat CLL, they may be applicable for the treatment of solid tumors that express ROR1.

A second approach for targeting ROR1 for the treatment of cancer is the adoptive transfer of chimeric antigen receptor (CAR) T cells that target ROR1. CAR T-cells are engineered T cells that express a CAR that is comprised of a binding domain or a single chain antibody specific to a tumor antigen, such as ROR1 [15]. ROR1-specific CARs have been generated that show potent recognition of ROR1-expressing tumor cells, both in vitro and in vivo [12,16]. Adoptive transfer of these ROR1-specific CAR T cells has been shown to be safe and effective of eliminating ROR1+ B cells in primates [17]. CAR T cells are a very promising treatment for cancer, though the difficulty lies in identifying tumor specific antigens that make effective targets and controlling the sepsis-like cytokine storm. As ROR1 is not expressed in normal adult tissues, it makes a very promising target for generating tumor specific CAR T cells.

Other approaches targeting ROR1 include vaccine-based approaches and antibody-drug conjugates (ADC). Fooladi et al. [18] designed a ROR1 endotoxin B chimeric protein which was capable of stimulating ROR1-specific T and B cell mediated immune response. Such an approach may be used to generate a vaccine against ROR1-expressing cancers. Other applications of using ROR1 in treating cancer could be to use ROR1 antibodies to target drug delivery to cancer cells. Many ADCs are currently in clinical development and allow specific targeting of cytotoxic agents to tumor cells [19]. ROR1 may be a particularly good candidate ADC-based therapy as it is not expressed in adult tissues. A similar approach would be treating cancer with a ROR1-specific immunotoxin, which has shown promising result in vitro and in animal models of cancer [20].

Closing Remarks

Because ROR1 is only expressed during embryogenesis and not in normal adult tissues, it makes a very promising target for therapy. Several ROR1-specific therapies are currently in development and may prove to be good targeted therapies for several types of cancer. Some of these agents have already tested in preclinical models in several cancer types and showed some promising results. One emerging question related to ROR1-targeted therapies is to identify patient population who will benefit from these treatments. It is straightforward to use flow cytometry to determine ROR1 positivity in CLL or other lymphoma patients, but the clinical grade of immunohistochemistry for solid tumors is necessary for assessing the ROR1 positivity. It is also important to determine what the threshold is for ROR1-positivity on the surface of cancer cells for efficient killing by the above therapeutics. Clinical determination of HER2 positivity for Herceptin therapy can be adapted similarly for the determination of anti-ROR1 therapy in solid cancers.

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