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Review

Receptor tyrosine kinase-like orphan receptor 1 (ROR-1): An emerging target for diagnosis and therapy of chronic lymphocytic leukemia

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is characterized by reposition of malignant B cells in the blood, bone marrow, spleen and lymph nodes. It remains the most common leukemia in the Western world. Within the recent years, major breakthroughs have been made to prolong the survival and improve the health of patients. Despite these advances, CLL is still recognized as a disease without definitive cure. New treatment approaches, based on unique targets and novel drugs, are highly desired for CLL therapy. The Identification and subsequent targeting of molecules that are overexpressed uniquely in malignant cells not normal ones play critical roles in the success of anticancer therapeutic strategies. In this regard, ROR family proteins are known as a subgroup of protein kinases which have gained huge popularity in the scientific community for the diagnosis and treatment of different cancer types. ROR1 as an antigen exclusively expressed on the surface of tumor cells can be a target for immunotherapy. ROR-1 targeting using different approaches such as siRNA, tyrosine kinase inhibitors, cell therapy and antibody induces tumor growth suppression in cancer cells. In the current review, we aim to present an overview of the efforts and scientific achievements in targeting ROR family, particularly ROR-1, for the diagnosis and treatment of chronic lymphocytic leukemia (CLL).

Contents

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1. Introduction

Identification and targeting molecules that are overexpressed uniquely in malignant but not normal cells are critical points for the success of cancer therapy. In recent years, growing interest has been towards the application of tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) as therapeutic, diagnostic and screening targets for cancers [1]. Such antigens have a vital role in the growth and survival of cancer cells and targeting them may lead to inhibiting the growth and survival of malignant cells. As Weinstein stated, tumor cells may be dependent on the activated oncogenic pathways for survival and accumulation, a phenomenon known as "oncogenic addiction" [2]. Phosphorylation of signaling proteins has a major role in regulating cellular activity and hence the protein kinases that are critical determinants of phosphorylation processes are of particular importance in tumorigenesis as well as natural evolution [3,4].

Protein kinases catalyze the transfer of a phosphate group from adenosine triphosphate (ATP) to specific amino acid residues in proteins involved in signaling pathways. These residues include tyrosine and serine/threonine. Tyrosine kinases (TKs) are considered a group of protein kinases and a class of TAAs which contribute to the most central cellular processes such as cell cycle, migration, metabolism, accumulation, survival and differentiation. Therefore, the activity of tyrosine kinases must be under strict control [5–8]. Among TKs, receptor tyrosine kinases (RTKs) are structurally transmembrane proteins with an intracellular kinase domain. The aberrant regulation of RTKs has been observed in a variety of cancer cells in the form of overexpression, abnormal expression, mutations and translocations which lead to constant kinase activity independent of ligand binding [9,10].

Receptor tyrosine kinase-like orphan receptor (ROR) as a member of RTK family has been recently brought into the focus of researchers in different fields of medical sciences due to its unique expression profile and other properties. Compatible with altered expression and activity of TKs in different cancers, overexpression of ROR protein has been observed in different malignancies such as chronic lymphocytic leukemia (CLL) [11].

CLL is one of the most common malignancies across the globe. CLL is histologically identified by the accumulation of small mature B lymphocytes in the blood, bone marrow, lymph nodes, and other lymphoid tissues. With an overview of cancer epidemiology in the Western societies, it can be concluded that CLL is the most frequent leukemia in these populations such that only in the United States of America this cancer is responsible for the death of about 5000 people yearly [12]. Unfortunately, there is no available efficient therapy for CLL patients and many research works are being conducted to find standard and effective therapeutic modalities for CLL. CLL diagnosis is performed based on clinical and laboratory findings, but there is major challenges for introducing a specific diagnostic marker that individually can be applied to diagnose CLL. Considering ROR1 expression profile in CLL, it can be used as a potential attractive target for CLL diagnosis, prognosis and treatment. In the current article, we try to review the efforts and scientific achievements on ROR family, particularly ROR-1 in the diagnosis and treatment of CLL.

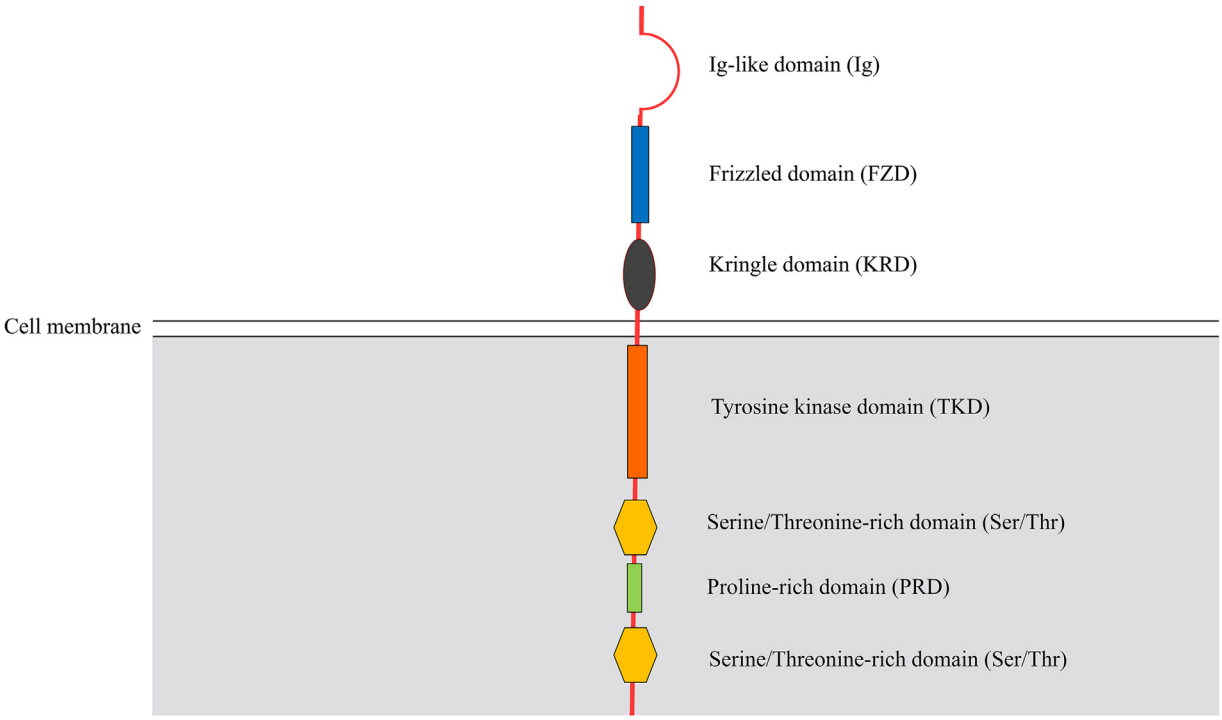

Fig. 1. Structure of the ROR-1 receptor tyrosine kinase.
Human ROR-1 consists of an immunoglobulin-like domain (IG), two cysteine-rich domain (CRD), frizzled (FZD) and kringle domain (KRD) at extracellular part. In the intracellular portion, ROR-1 possesses a tyrosine kinase domain (TKD), two serine/threonine-rich domains (Ser/Thr), and a proline-rich domain (PRD). Complete ROR-1 protein encompasses 937 amino acids.