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The role of SOX11 in mantle cell lymphoma

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ABSTRACT

The mechanism of SOX11 function has been widely published recently mainly focused on histone modifications. Besides diagnostic value in mantle cell lymphoma (MCL), SOX11 has also prognostic significance. Although it can also be observed in a fraction of other T and B-cell lymphomas, a monoclonal antibody, called SOX11-C1, may improve the function of SOX11 in both diagnosis and prognosis evaluation. In addition, detection of modified SOX11 cDNA by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) has a higher sensitivity than traditional CCND1 examination in minimal residual disease (MRD) detection, which is an appealing option for predicting disease outcome and status.

Contents

1. Introduction

The Sry-related high-mobility-group (HMG) box (SOX) is a group of developmentally regulated transcription factors. There are approximately 20 SOX genes which can be further subdivided into eight groups (groups A to H), according to the degree of Sry, sharing both within and outside the HMG domain [1]. SOX C group is comprised of SOX4, SOX11, and SOX12 [2]. They share two functional domains: a Sry-related SOX DNA-binding domain, located in the N-terminal, and a transactivation domain (TAD) at the C-terminal [3]. SOX11, a member of the SOX gene family, had been cloned and characterized by the partial cloning of both human and mouse SOX11 genes and mapped it to chromosome 2p25 [4]. Many of the SOX genes, including SOX11, are widely expressed in the developing nervous system and may have a role in neurogenesis, neural cell survival and neurite outgrowth [5]. In contrast, it has been shown that many adult tissues are absent for SOX11 [6]. In addition, SOX11 plays an important role in tissue remodeling and SOX11-deficient mice presented with various craniofacial and skeletal malformations, asplenia and hypoplasia of the lung and stomach, and SOX11 mutation is corresponding human malformation syndromes [1]. SOX11, which is expressed in virtually all aggressive mantle cell lymphoma (MCL), has recently been recognized as a diagnostic and prognostic antigen in MCL [7]. The

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mechanism of SOX11 function has been published recently [8–10]. DNA hypermethylation of SOX11 seems to be functionally inserted to SOX11 expression whereas histone modifications are much more important [11,12]. In addition, SOX11 could target a lot of genes resulting in blocking of mature B-cell differentiation, modulations of cell fate, apoptosis and stem cell development [13]. Silence of SOX11 expression reduces tumor growth both in vitro and in vivo [13]. MCL is characterized by overexpression of CCND1 as the result of the translocation t(11;14) (q13;q32), and shows an aggressive clinical course with a frequent relapse pattern and a median survival of only 3–5 years [14]. However, approximately 10% of MCL lacked this specific translocation and did not express CCND1 [7]. SOX11 is specifically expressed in almost all of MCL regardless of CCND1 status [15–18]. Meanwhile, there is a subgroup of MCL does not express SOX11 and presents with an indolent behavior, which might not need therapy at diagnosis [12,19–21]. All of these make SOX11 a differentiation biomarker of great importance. However, batch-to-batch variations of commercially available polyclonal antibody make the result of immunohistochemistry (IHC) controversial, which have hampered its routine clinical use [22]. At the same time, a fraction of other T and B-cell lymphomas were also reported expressing SOX11 [15,18]. Recently, a monoclonal mouse antibody, called SOX11-C1, plays robust activities in both IHC and flow cytometry (FCM) [22], which may improve the performance of SOX11. A quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) assay, designed by Hamborg et al. [23], using SOX11 cDNA with higher sensitivity than CCND1, seems to be an appealing option for minimal residual disease (MRD) detection.

2. SOX11 and tumors

The transcription factor SOX11, which is a member of the SOX family and plays a critical role in the regulation of cell cycle and differentiation in major developmental processes [24], has recently been recognized as a diagnostic, prognostic and/or functional antigen in a variety of tumors including MCL [7,12,15–17,25,26], epithelial ovarian cancer (EOC) [27,28] and gliomas [26]. Of major clinical interest, the expression of SOX11 in non-malignant tissues is limited to immature neurons [29] and tissue remodeling [1,30,31]. It is initially expressed throughout the central nervous system (CNS) and then down-regulated in the spinal cord [31,32], and expressed outside of the CNS [1,30–32]. In contrast to its extensive occurrence during embryogenesis, there is little SOX11 expression in the adult [30]. The malformations showed by Sock et al. [1] in the SOX11-deficient mice indicated that an original function for SOX11 in tissue remodeling. In addition, SOX11 plays important roles in tumorigenesis. Sernbo et al. [28] reported that SOX11 is a functionally related protein in EOC with prognostic value for high-grade tumors. SOX11 is also highly expressed in malignant gliomas whereas normal in adult brain and other organs [26]. Human glioma-initiating cells (GICs) lost expression of SOX11, and overexpression SOX11 prevented their oncogenesis in vivo [33]. SOX4, the SOX family member with the highest homology to SOX11, is a prominent transcription factor in B and T cells [34] and is crucial for B-cell lymphopoiesis. In contrast, SOX11 has no known lymphopoietic function and it is not expressed in lymphoid progenitors or mature normal B-cells. However, it is expressed in virtually all aggressive MCL and at lower levels in some Burkitt lymphomas (BL) and acute lymphoblastic leukemia (ALL) but not in other lymphoid neoplasms [15,16,18].

3. SOX11 and MCL

Non-Hodgkin lymphomas (NHL) can be divided into several subgroups according to their morphological and phenotypic properties refer to WHO classification [14]. MCL represents 5–10% of all NHL and predominates in males with advanced age. The clinical evolution is usually very aggressive with short responses to treatment, continuous relapses and a median survival of 3–5 years [14], and patients cannot be cured with current therapies. The diagnosis of MCL is characterized by overexpression of CCND1 because of the translocation t(11;14) (q13;q32), and examination of CCND1 protein by IHC or evidence of CCND1/immunoglobulin heavy chain (IGH) fusion by fluorescence in situ hybridization (FISH). However, genomic expression profiling (GEP) studies have shown that approximately 10% of MCLs with an otherwise similar GEP lacked this specific translocation and did not express CCND1, which makes diagnosis of MCL difficult in these cases [7]. Since the clinical behavior of CCND1 negative MCL is also aggressive, it is important to find biomarkers that reliably identify this entity and separate them from the other B-cell NHLs (B-NHLs) in the routine clinical laboratory setting. Some cases of CCND1-negative MCL demonstrate CCND2 or CCND3 mRNA overexpression [35]; however, GEP and performance of CCND2 or CCND3 qRT-PCR assays are not extensively feasible in clinical diagnostic laboratories and also prevented by the fact that both are also expressed in other B-NHL. The transcription factor SOX11, a neural transcription factor whose function in normal and neoplastic B-cell development is unknown, is specifically expressed in the nucleus of MCL compared with other lymphomas and benign lymphoid tissues. Whether SOX11 expression is correlated to CCND1 expression or CCND1 translocation is controversial. Recent studies show both SOX11 mRNA up-regulation and SOX11 protein overexpression in MCL regardless of CCND1 expression and CCND1 translocation status [15–18]. Similar report showed no general co-regulation was found between CCND1 and SOX11 mRNA.

4. How does SOX11 work in tumorigenesis

SOX11 has a synergistic effect with WT1, a regulator of Wnt4 promoter, in the regulation of Wnt4-promoted nephrogenesis [8]. Knockdown of SOX11 in neuroblastoma cells increased the expression of the pro-apoptotic gene BNIP3 (BCL2 interacting protein-1 NIP3) and decreased the expression of the anti-apoptotic gene TANK (TNF receptor-associated factor family member-associated NF-κB activator) [9]. Therefore, it is hypothesized that SOX11 may contribute to the pathogenesis and progression of MCL by regulating genes involved in cell proliferation and apoptosis [10]. SOX11 up-regulation has been detected in various types of solid tumors including medulloblastomas, gliomas and epithelial ovarian tumors [26,27,36]. On the other side, Hide et al. [33] revealed that overexpression of SOX11 prevented tumorigenesis of in mouse glioma cell line (NSCL61s) by inducing their neuronal differentiation accompanied with decreased levels of plagl1, which was originally shown to regulate both cell cycle arrest and apoptosis. Plagl1 plays an important role in tumorigenesis of GICs, which has been shown to regulate the expression of several imprinted genes those are involved in tumorigenesis and embryonic growth [37]. Experiments in the induced NSCL61 cell line have disclosed that overexpression of SOX11 blocked their tumourigenicity and recurrent glioblastomas. In addition, downregulation of SOX11 mRNA resulted in diminished patient survival [33]. Using global gene expression analysis, Gustavsson et al. [38] showed that the CCND1-related Rb-E2F pathway [39,40] was affected by the increased level of SOX11. Besides, a significant positive relationship was documented between SOX11 and p-STAT-3 expression, which is a promoter of neurite growth [7] and induces astrocytic differentiation during CNS development [8]. Similarly, silencing of SOX11 in MCL cell lines caused a deregulation of STAT-1 transcription [9]. However, whether a similar interaction may exist between SOX11 and STAT-3 is presently unknown.

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