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Review

SOX family transcription factors involved in diverse cellular events during development

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ABSTRACT

In metazoa, SOX family transcription factors play many diverse roles. In vertebrate, they are well-known regulators of numerous developmental processes. Wide-ranging studies have demonstrated the co-expression of SOX proteins in various developing tissues and that they occur in an overlapping manner and show functional redundancy. In particular, studies focusing on the HMG box of SOX proteins have revealed that the HMG box regulates DNA-binding properties, and mediates both the nucleocytoplasmic shuttling of SOX proteins and their physical interactions with partner proteins. Posttranslational modifications are further implicated in the regulation of the transcriptional activities of SOX proteins. In this review, we discuss the underlying molecular mechanisms involved in the SOX-partner factor interactions and the functional modes of SOX-partner complexes during development. We particularly emphasize the representative roles of the SOX group proteins in major tissues during developmental and physiological processes.

Contents

Abbreviations: *Amh*, anti-Müllerian hormone; CBP, cAMP-response element-binding protein (CREB)-binding protein; CRM1, chromosome region maintenance 1; CNS, central nervous system; dpc, days post coitum; Fgf, fibroblast growth factor; HMG, high mobility group; NES, nuclear export signal; NLS, nuclear localization signal; PKA, protein kinase A; SOX, SRY-related HMG box; SF1, steroidogenic factor 1; SRY, sex-determining region on the chromosome Y; SUMO, small ubiquitin-like modifer; TES, testis-specific enhancer of *Sox9*.

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Introduction

In 1990, the *Sry* gene, the sex-determining region of the Y-chromosome, was first discovered in humans and mice as a testis-determining gene (Gubbay et al., 1990; Sinclair et al., 1990). The identification and homology-based analysis of the HMG (high mobility group) DNA-binding domain of SRY led to the discovery of the SOX transcription factor family. In vertebrates, this family comprises of more than 20 *Sox* genes which originate through a process of duplication and divergence (Koopman et al., 1991; Bowles et al., 2000). Evidence from gain-of/loss-of-function studies in *Sox* genes, relating to many diverse developmental processes in humans, mice and other vertebrates, reveal that *Sox* genes play important roles in tissue homeostasis, organogenesis, cell fate decision in many developmental processes from embryonic through to adult stages (Kamachi et al., 2000; Kamachi and Kondoh, 2013; Sarkar and Hochedlinger, 2013).

SOX proteins are characterized by the evolutionarily conserved HMG box which is a 79-amino-acid DNA-binding motif (Štros et al., 2007). The HMG box mediates the DNA-binding properties of SOX proteins on a common consensus site, (A/T)(A/T)CAA(A/T)G but with different levels of efficiency (Wegner, 2010). The HMG box of SOX proteins harbors two independent nuclear localization signals (NLSs) and one leucine-rich nuclear export signal (NES), which regulate the dynamic nucleocytoplasmic shuttling of SOX proteins and result in the diverse subcellular distribution of SOX proteins during development (Südbeck and Scherer, 1997; Gasca et al., 2002; Malki et al., 2010).

During development, the transcriptional activities of SOX proteins are regulated *via* multiple genetic pathways. The three major aspects of such regulation are as follows: (1) Regulation of the expression levels of SOX proteins in specific cell types and tissues and at precise timings within a series of major developmental stages (Kamachi and Kondoh, 2013); (2) Regulation of posttranslational modification of SOX proteins, altering their transactivation/transrepression properties to various extents (Bernard and Harley, 2010); (3) Regulation of recruited partner proteins which not only influence the specific recognition of the binding sites of SOX-partner complexes on the target genes, but also determine transcription activities and significantly enhance the activation/repression potential (Kamachi and Kondoh, 2013; Wilson and Koopman, 2002).

In this paper, we review the overlapping and diverse expression patterns of the *Sox* gene family in their representative organs and elucidate the functions of the HMG box in the dynamic nucleocytoplasmic shuttling of SOX proteins during diverse cellular events. Recent findings on the posttranslational modifications of SOX proteins, including phosphorylation, acetylation, SUMOylation and ubiquitination are described, all of which influence the transcriptional activities of SOX transcription factors at the protein level. The physical interactions of SOX-partner proteins and the underlying mechanisms of SOX-partner complexes during development are also particular focus. The crucial developmental roles of SOX proteins during central nervous system development, retinal development, chondrocyte differentiation, primary sex determination and cardio-vascular system development are also reviewed.

Groups and structures of SOX proteins

SRY was the founding member of the SOX protein family. It was discovered in the smallest region of the Y chromosome, a region associated with primary male sex determination and subsequent testis development (Gubbay et al., 1990; Sinclair et al., 1990; Koopman et al., 1991; Sekido and Lovell-Badge, 2008a,b). *Sry* encodes a transcription factor with an evolutionarily conserved high mobility group (HMG) domain of 79 amino acids, a domain found in all eutherian and marsupial mammals examined to date (Kashimada and Koopman, 2010; Sekido and Lovell-Badge, 2013). Several lines of phylogenetic analysis coincide with the evolutionary origin of *Sry* and suggest it diverged from the ancestral *Sox3* during the early evolution of mammals (Stevanović et al., 1993; Katoh and Miyata, 1999; Nagai, 2001). A recent study by Sato