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Cardiac transcription factor Csx/Nkx2-5: Its role in cardiac development and diseases

Hiroshi Akazawa, Issei Komuro*

Division of Cardiovascular Pathophysiology and Department of Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

Abstract

During the past decade, an emerging body of evidence has accumulated that cardiac transcription factors control a cardiac gene program and play a critical role in transcriptional regulation during cardiogenesis and during the adaptive process in adult hearts. Especially, an evolutionally conserved homeobox transcription factor Csx/Nkx2-5 has been in the forefront in the field of cardiac biology, providing molecular insights into the mechanisms of cardiac development and diseases. Csx/Nkx2-5 is indispensable for normal cardiac development, and mutations of the gene are associated with human congenital heart diseases (CHD). In the present review, the regulation of a cardiac gene program by Csx/Nkx2-5 is summarized, with an emphasis on its role in the cardiac development and diseases.

Keywords: Homeobox; Transcriptional regulation; Cardiac development; Congenital heart disease; Cardiac hypertrophy; Cardioprotection

Abbreviations: ANP, atrial natriuretic peptide; ASD, atrial septal defect; AV, atrioventricular; BMP, bone morphogenic protein; BNP, brain natriuretic peptide; CARP, cardiac ankyrin repeat protein; CHD, congenital heart diseases; CKII, casein kinase II; Dpp, decapentaplegic; DMSO, dimethyl sulfoxide; DORV, double-outlet right ventricle; FGF, fibroblast growth factor; HOP, homeodomain-only protein; Irx4, Iroquois homeobox gene 4; MEF2, myocyte enhancer factor 2; MHC, myosin heavy chain; MLC2v, myosin light chain 2v; NES, nuclear export signal; NK2-SD, NK-2-specific domain; PI3-kinase, phosphatidylinositol 3-kinase; Sca-1, stem cell antigen-1; SRF, serum response factor; TAK1, TGF-β-kinase 1; TGF-β, transforming growth factor-β; TOF, tetratology of Fallot; VSD, ventricular septal defect; Wg, wingless.

Contents

* Corresponding author. Tel.: +81 43 222 2097; fax: +81 43 226 2557.
E-mail address: komuro-tky@umin.ac.jp (I. Komuro).

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1. Introduction

The heart is the first functional organ in the developing embryos, and the appropriate delivery of oxygen and nutrients through the circulatory system is prerequisite for embryonic growth and survival. The formation of the heart involves a precisely coordinated process of cellular differentiation and integrated multicellular morphogenesis, and even a minute perturbation of this process gives rise to congenital heart diseases (CHD). The susceptibility of the heart to malformation is reflected by the high incidence of congenital heart disease (nearly 1% of live births; American Heart Association, 2003).

Although the morphological events of heart formation have been described for centuries, it is not until a decade ago that the genetic explorations for cardiac development have started. Cardiogenic progenitors become committed to cardiac lineage in the anterior lateral mesoderm (primary heart filed) of the late gastrulation embryos in response to inducing signals secreted from adjacent endoderm (reviewed in Olson & Srivastava, 1996; Fishman & Olson, 1997; Srivastava & Olson, 2000). These cardiogenic cells, clustering in a form of bilaterally symmetrical crescent, migrate and fuse at the anterior midline to form a linear heart tube. The linear heart tube initiates autonomous contraction and undergoes rightward looping morphogenesis to form a mature four-chambered heart in association with atrioventricular (AV) septations. Maturation of the heart also requires coordinated proliferation and differentiation of myocardium to form functional trabeculated chambers. At the AV canal, mitral and tricuspid valves originate from endocardial cushions, regional swellings forming as a consequence of epithelial–mesenchymal transformation of endocardial cells. Endocardial cushions also participate in the formation of the aortic and pulmonary valves. Migrating neural crest cells populate the outflow tract as well as aortic and pharyngeal arches. Recently, it is proposed that a part of cardiomyocytes in the outflow tract and, possibly, right ventricle is generated from a "secondary (anterior) heart field" situated in splanchnic mesoderm medial and adjacent to the primary heart field (reviewed in Kelly & Buckingham, 2002).

A novel paradigm for heart development originated from the discovery of the *tinman* gene in the fruit fly *Drosophila melanogaster*, which is required for the primitive heart formation in this organism (Azpiazu & Frasch, 1993; Bodmer, 1993). The *tinman* encodes a homeobox-containing transcription factor, and the identification of the *tinman*-related gene *Csx/Nkx2-5* (Komuro & Izumo, 1993; Lints et al., 1993) in mammals attracted much attention to the key regulatory roles of cardiac transcription factors in the intricate program of heart development. Cardiac transcription factors are essential transcriptional activators that are expressed predominantly in hearts and that regulate the expression of the cardiac genes encoding structural proteins or regulatory proteins characteristic of cardiomyocytes (reviewed in Bruneau, 2002). In vertebrates, cardiac transcription factors are represented by the homeobox transcription factor Csx/Nkx2-5, the GATA family transcription factors, and myocyte enhancer factor 2 (MEF2) transcription factors.

Recent data have suggested the significant role of these transcription factors in postnatal hearts as well (reviewed in Akazawa & Komuro, 2003a). Cardiomyocytes are highly differentiated and lose their ability to proliferate soon after birth. Thereafter, cardiomyocytes grow in cell size without cell division to adapt to a demand for an increased workload. In a variety of pathological conditions (e.g., hypertension, valvular disease, myocardial infarction, and cardiomyopathy) that impose overwork on the heart, postnatal cardiomyocytes undergo hypertrophic cell growth. Although cardiac hypertrophy is initially compensatory for an increased workload, the prolongation of this process leads to deleterious outcomes such as congestive heart failure, arrhythmia, and sudden death (Levy et al., 1990; Lorell & Carabello, 2000). Cellular responses characteristic of cardiac hypertrophy include accelerated synthesis of sarcomeric and structural proteins and reprogramming of the fetal cardiac genes (reviewed in Komuro & Yazaki, 1993; Sadoshima & Izumo, 1997). With regard to the transcriptional adaptation induced by hypertrophic stimulation, it is reasonable to assume that cardiac transcription factors play the leading part because they directly regulate a number of cardiac genes that are up-regulated in hypertrophied myocardium. Indeed, the transcriptional activities of GATA and MEF2 transcription factors are enhanced in response to hypertrophic stimulations and they function as essential effectors of divergent intracellular signaling pathways mediating hypertrophic features (reviewed in Akazawa & Komuro, 2003a). However, the role of Csx/Nkx2-5 in the adult hearts remains elusive. Csx/Nkx2-5 is up-regulated in response to hypertrophic stimulations and may have implications in the transcriptional regulation of the cardiac gene program in hypertrophied hearts. In addition, the role of Csx/Nkx2-5 may extend to maintenance of homeostasis in highly differentiated cardiomyocytes.

In line with the involvement in transcriptional regulation of myriad cardiac genes, both during cardiogenesis and during the adaptive process in response to hemodynamic stresses, aberrant expressions of *Csx/Nkx2-5* directly give rise to heart diseases both in mice and humans. This review comprehensively summarizes recent advances in understanding the role of Csx/Nkx2-5 in transcriptional regulation in the heart, especially focusing on its role in cardiac development and diseases.

2. Cardiac homeobox transcription factor Csx/Nkx2-5

2.1. NK-2 class homeobox transcription factor Csx/Nkx2-5

Csx/Nkx2-5 is a member of the NK homeobox gene family that is conserved in evolution and acts as a DNA-