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Review article

Forkhead box transcription factors in embryonic heart development and congenital heart disease

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ABSTRACT

Embryonic heart development is a very complicated process regulated precisely by a network composed of many genes and signaling pathways in time and space. Forkhead box (Fox, FOX) proteins are a family of transcription factors characterized by the presence of an evolutionary conserved "forkhead"or "winged-helix" DNA-binding domain and able to organize temporal and spatial gene expression during development. They are involved in a wide variety of cellular processes, such as cell cycle progression, proliferation, differentiation, migration, metabolism and DNA damage response. An abundance of studies in model organisms and systems has established that Foxa2, Foxc1/c2, Foxh1 and Foxm1, Foxos and Foxps are important components of the signaling pathways that instruct cardiogenesis and embryonic heart development, playing paramount roles in heart development. The previous studies also have demonstrated that mutations in some of the forkhead box genes and the aberrant expression of forkhead box gene are heavily implicated in the congenital heart disease (CHD) of humans. This review primarily focuses on the current understanding of heart development regulated by forkhead box transcription factors and molecular genetic mechanisms by which forkhead box factors modulate heart development during embryogenesis and organogenesis. This review also summarizes human CHD related mutations in forkhead box genes as well as the abnormal expression of forkhead box gene, and discusses additional possible regulatory mechanisms of the forkhead box genes during embryonic heart development that warrant further investigation.

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1. Introduction

Human development begins with a unicellular zygote and progressively makes an organism composed of various tissues, organs and systems [1]. The developmental process of humans is regulated by genome of the zygote which expresses selectively in time and space, thereby determined by gene expression patterns during embryogenesis and organogenesis [1]. The heart is the first organ to form and function and its proper development is vitally important in human embryo. Cardiogenesis and heart development are very complicated processes controlled by genes and signaling pathways elaborately, which are coincident with the general rules of human development and definitely no exception. In addition, abnormalities in heart development have been recognized as the major causes of congenital heart disease (CHD) which commonly contribute to neonatal congenital defects, morbidity and mortality in humans [2,3]. Therefore, the developmental process of heart and the underlying molecular and genetic mechanisms have attracted much attention and been extensively studied. Because of the evolutionary conservation of the process, the major understandings and insights of heart inductive signals and transcriptional machinery during heart development have been acquired from an abundance of studies of the model organisms and the model systems, such as mouse, chick, amphibian, zebrafish, fly and stem cells. Among the model organisms and the model systems, mouse is the most valuable model because it has four-chambered heart like human in addition to its well-established genetics [4,5].

Forkhead box (Fox, FOX) proteins are a family of transcription factors characterized by the presence of an evolutionary conserved "forkhead" or "winged-helix"DNA-binding domain which are involved in chromatin remodeling and nuclear localization [6,7]. They have transcriptional effect domains that are totally different from each other in contrast to the evolutionary conserved forkhead domain [6]. So far, more than fifty five and fifty forkhead proteins have been discovered in mammals and humans respectively [7,8]. They are classified into 19 subgroups basing on sequence homology inside and outside the forkhead domain named Foxa (FOXA) to Foxs (FOXS) [7,8]. They exhibit notable functional diversity and participate in a wide spectrum of cellular processes, such as cell cycle progression, proliferation, differentiation, apoptosis, survival, migration, metabolism, DNA damage response and drug resistance [6,7]. They are transcriptional activators and repressors as well as pioneer factors, interacting with other transcription factors and epigenetic effectors [7]. Forkhead box proteins are important components of some signaling pathways which include transforming growth factor (TGF) β-Smad, mitogen-activated protein kinase (MAPK), Akt (PKB), Hedgehog and Wnt [6]. They play significant roles during development as well as maintain homeostasis of adult tissues due to their capabilities to organize temporal and spatial gene expression [6,7]. In cardiac tissue in the adult, forkhead box transcription factors regulate various cellular functions, such as cardiomyocyte metabolism, cell cycle progression, survival and Na+ channel activity [9–11]. Some Fox factors are critical for maintaining normal cardiac function and also correlated with cardiac diseases [9–11].Notably accumulating data have shown that Foxa2, Foxc1/c2, Foxh1 and Foxm1, Foxos and Foxps play crucial roles in different aspects of embryonic heart development. Mutations in some of the forkhead box genes lead to vascular and cardiac defects and embryonic lethality in mice, and are also commonly associated with the clinical processes of congenital heart defects in humans. This review summarizes the current understanding of heart development regulated by the forkhead box transcription factors and molecular genetic mechanisms by which these forkhead box factors modulate embryonic heart development. This review also summarizes human congenital heart defects linked mutations in forkhead box genes as well as the abnormal expression of forkhead box gene. Additionally, this review discusses the unexplored areas of molecular regulatory hierarchies by which forkhead box factors govern embryonic heart development.

2. Synopsis of the embryonic heart development in human and mouse

Human embryonic heart development can be described as 4 major stages: (1) from zygote to around day 15 of the human embryo (embryonic day(E) 7.5 of the mouse), during which cardiac progenitor cells are specified in the anterior lateral plate mesoderm and then condense to form two lateral heart primordia composed of myocardial and endocardial precursors [2]. The two lateral heart primordia join at their anterior margins to form "cardiac crescent" [2,4] (Fig. 1). The key transcription factors contributing to this stage include NKX2-5, GATA4, MEF2 family proteins and SRF, which play critical roles in cardiomyocyte specification, proliferation and differentiation [1,2,12] (Fig. 1). Bone morphogenetic protein (BMP), WNT and fibroblast growth factor (FGF) signals are inductive for all aspects of cardiogenesis at this period [1,2,4,12] (Fig. 1). Of note, non-canonical Wnt/Ca^{+} and Wnt/polarity signals are positive mediators of cardiogenesis, whereas canonical Wnt/β-catenin signaling inhibits cardiogenesis [1,4,5]. (2) After formation of the cardiac crescent, the bilateral heart primordial move medially and fuse at the midline to form a heart tube including an external myocardial and an internal endocardial layer by day 20 of the human development (E8.5 of the mouse) [2,4] (Fig. 1). GATA4/5/6, MESP1/2, TBX5 and miles-apart are required for proper heart development at this period [1,2,4] (Fig. 1). In addition, the terminal differentiation of cardiomyocyte is controlled by BMP and FGF signals [1,4] (Fig. 1). (3) Following formation of the heart tube, the linear heart tube undergoes rightward looping by day 30 of the human embryo (E10-12 of the mouse) [2,4] (Fig. 1). At this time, cells from the second heart field join to generate the right ventricle (RV) and outflow tract (OFT) [2]. NKX2-5, SNAI1, PITX2, HAND1/2, XIRP1 and LEFTY1/2 are the important regulators of heart looping [1,5, 12] (Fig. 1). Furthermore, NODAL and Hedgehog signals are required for setting the left–right axis and left–right asymmetry during this period [1,5] (Fig. 1). LEFTY1 and LEFTY2 are NODAL antagonists [1,5]. (4) At the later stage of development (day 40 or so of the human embryo-birth, E14-18 of the mouse), the heart undergoes a diversity of remodeling processes, such as growth, merging, shrinkage, leading to formation of the mature four chambered heart with septa, valves, functional conduction system and separate inflow (venous) and outflow (arterial) structures [1,2,4] (Fig. 1). The endocardial cushions, which septate the heart into the four chambers and the OFT into the aorta and pulmonary artery, begin to appear at the sixth and seventh week of human embryo [2]. There are many well characterized regulatory genes and signaling pathways at this period. NKX2-5, GATA4, MEF2C and HAND1/2 are required for cardiac chamber maturation. TBX5 is involved in the development of cardiac conduction system. PAX3 is essential for the development of OFT. Notch signaling is involved in endocardial cushion formation, heart valve formation, ventricular septation and OFT development. BMP, WNT, FGF, TGFβ as well as retinoic acid signals are required for endocardial cushion formation and OFT development [1–3, 5] (Fig. 1). The OFT of heart includes the aorta, pulmonary arteries, aortic arch and ductus arteriosus. Of note, FGF signals mainly transduce through MAPK, AKT (PKB) and phospholipase Cγ1 (PLCγ1)-Ca^{2+} signaling pathways [1,5].

3. The regulation of embryonic heart development by forkhead box transcription factors

3.1. Foxa2

Accumulating data from model organisms, mice in particular, have established that Foxa2 plays critical roles in embryonic patterning and endoderm formation, and regulates normal development of heart as well. Foxa2 and Gsc are co-expressed in mouse embryos from E6.5 to E8.75, and double-mutant mouse embryos of the genotype $Gsc^{-/-}$; $Foxa2^{+/-}$ have abnormal forebrain, branchial arches and foregut, and anomalies in heart looping at E8.75 [13]. Histological analyses of the