Mechanisms of Development 143 (2017) 9–19

Contents lists available at ScienceDirect

Mechanisms of Development

journal homepage: www.elsevier.com/locate/mod

Mechanisms of retinoic acid signaling during cardiogenesis

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ARTICLE INFO

Article history:
Received 15 October 2016
Received in revised form 29 November 2016
Accepted 12 December 2016
Available online 19 December 2016

Keywords:
Heart development
Cell fate decisions
Retinoic acid
Retinoic acid receptors

ABSTRACT

Substantial experimental and epidemiological data have highlighted the interplay between nutritional and genetic factors in the development of congenital heart defects. Retinoic acid (RA), a derivative of vitamin A, plays a key role during vertebrate development including the formation of the heart. Retinoids bind to RA and retinoid X receptors (RARs and RXRs) which then regulate tissue-specific genes. Here, we will focus on the roles of RA signaling and receptors in gene regulation during cardiogenesis, and the consequence of deregulated retinoid signaling on heart formation and congenital heart defects.

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1. Introduction

The heart is the first organ to function and is essential for the distribution of nutrients and oxygen in the growing mammalian embryo. Normal cardiac morphogenesis is thus vital for embryonic survival. Heart development is a complex process that requires the precise and coordinate interactions between multiple cardiac and extra-cardiac cell types. Any perturbation in the cells that contribute to heart formation leads to cardiac defects. Congenital heart defects affect 1–2% of live births, and are found in up to one-tenth of spontaneously aborted fetuses (Bruneau, 2008; Fahed et al., 2013). Studies in the invertebrate *Drosophila melanogaster* have defined numerous regulators that determine cardiac cell specification and differentiation, revealing that the cardiac regulatory network is remarkably conserved during evolution.

Abbreviations: ALDH, aldehyde dehydrogenase; Coup-TfII, chicken ovalbumin upstream promoter-transcription factor II; DHRS3, dehydrogenase reductase 3; DRs, direct repeats; E, embryonic day; Fgf8, fibroblast growth factor; HAT, histone acetyl transferase; HDAC, histone deacetylase; Hoxa1, homeobox A1; Hoxa3, homeobox A3; Hoxb1, homeobox B1; Irx4, iroquois homeobox gene 4; Isl1, isl LIM homeobox 1; Nppa, atrial natriuretic factor; Nppb, atrial natriuretic factor; PRC2, polycomb repressive complex 2; PRC2, polycomb repressive complex 2; RA, retinoic acid; RALDH, retinaldehyde dehydrogenase; RAREs, retinoic acid response elements; RARs, retinoic acid receptors; RDH, retinol dehydrogenase; Tbx5, t-box5.

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http://dx.doi.org/10.1016/j.mod.2016.12.002
0925-4773/

More recently, genetic studies have identified mutations in genes encoding components of signaling pathways as well as proteins organizing chromatin structure that are responsible for congenital heart defects (Miyake et al., 2013; Vissers et al., 2004; Zaidi et al., 2013).

The specification of multipotent heart progenitor cells and their differentiation into different cell lineages is under tight spatial and temporal transcriptional control. Defining the transcriptional networks underlying normal heart development is a prerequisite for understanding the molecular basis of congenital heart malformation. Vitamin A (or provitamin A carotenoid) deficiency is a major public health problem in underdeveloped countries (Zile, 2010). Young children, pregnant and breast feeding women are the main groups affected because their requirements for Vitamin A are higher and the impact of deficiency more severe than the other population subgroups. Malformations following maternal vitamin A deficiency were first reported by Hale (1935) (F., 1935). The mammalian embryo is strongly dependent on the maternal delivery of retinol (carotenoids and retinyl esters) through transplacental transfer. The fetus needs vitamin A throughout pregnancy (Comptour et al., 2016). Consequently, both deficiency and excess of vitamin A cause severe damage during prenatal and postnatal development. Nutritional and clinical studies on animals and humans have shown that maternal vitamin A insufficiency can result in fetal death, or a broad range of abnormalities including cardiac malformations (D'Aniello and Waxman, 2015; Wilson et al., 1953). Moreover, it is suggested that the elevated incidence of heart malformations in developing countries could be partly explained by a low availability of retinol due to vitamin A deficiency in the diet (Sommer et al., 1986; Underwood, 2004). Conversely, a high level of retinol during pregnancy leads to toxicity of many organs including the heart. For example, maternal intake of isotretinoin has been shown to cause congenital cardiac defects in addition to other malformations (Guillonneau and Jacqz-Aigrain, 1997). Importantly, genetic alterations reducing retinol uptake (Golzio et al., 2007; Kawaguchi et al., 2007; Pasutto et al., 2007) or retinoic acid (RA) production (Pavan et al., 2009; Roberts et al., 2006) have been implicated in human congenital heart disease. Altered RA signaling either genetically or nutritionally could be a predominant risk factor, increasing the frequency of congenital heart diseases in humans (Huk et al., 2013; Jenkins et al., 2007; Underwood, 2004). In this review, we will discuss the role of retinoids in cardiac gene regulation and congenital heart defects.

2. Early heart development

The mammalian heart has four chambers and is composed of a variety of cell types. Distinct sets of cardiac progenitors differentiate to form the different parts of the heart. It develops from cardiac progenitors that can be traced back to the early gastrulating embryo (embryonic day (E) 6.5 in the mouse). The earliest progenitors originate from the primitive streak and migrate toward the anterior lateral region to form the cardiac crescent, defined as the first heart field (E7–7.5). By E7.5–8.0, during folding of the embryo and formation of the foregut, the two sides of the cardiac crescent are brought together to form the primary heart tube (Fig. 1). The embryonic myocardium of the tube is characterized by a primitive phenotype, i.e. lower proliferation, a poorly developed contractile apparatus and slow conduction (Christoffels et al., 2010; Moorman and Christoffels, 2003). Growth of the heart tube depends on the addition of progenitor cells from adjacent pharyngeal mesoderm to the arterial and venous poles. This cell population, named the second

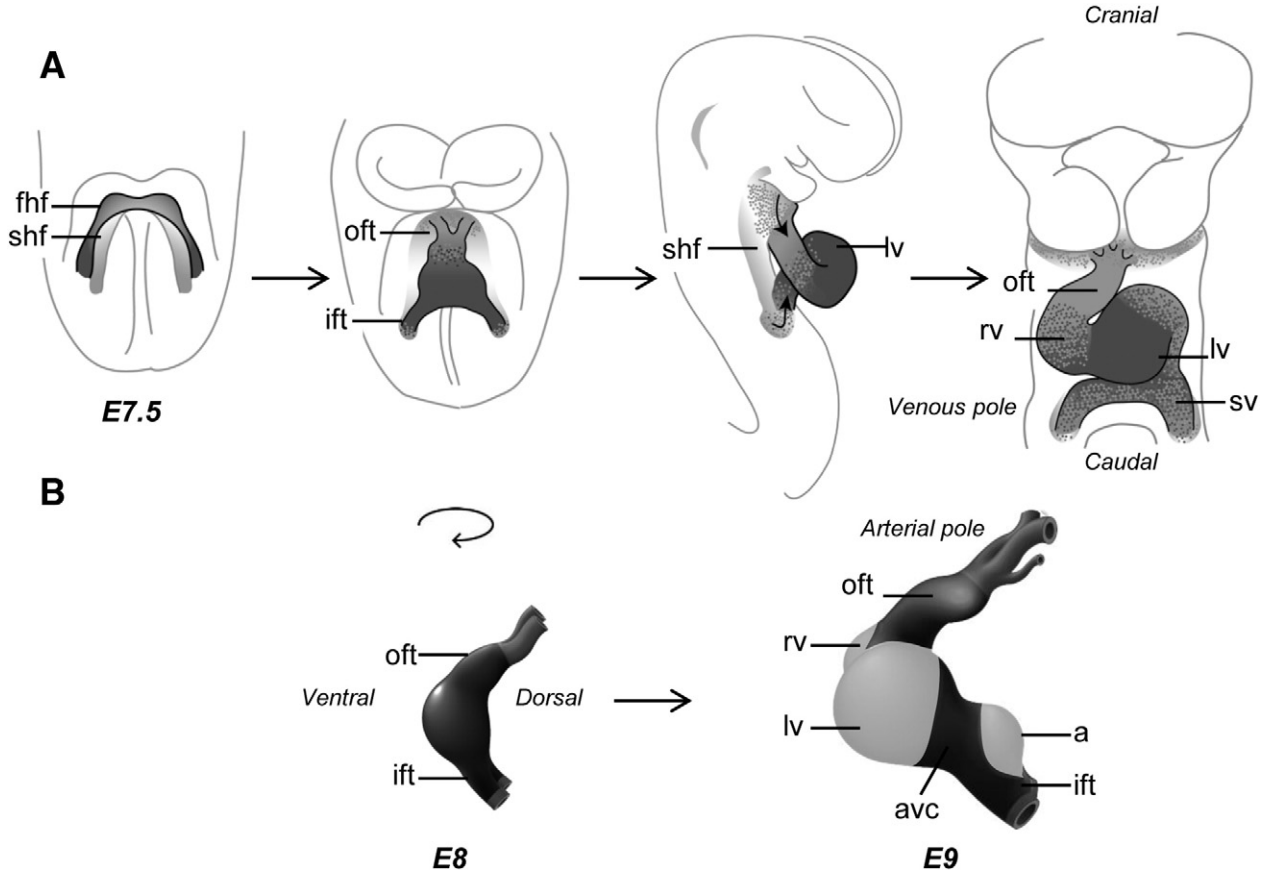

Fig. 1. Heart fields and their contributions to the developing heart. (A) The second heart field (light grey) is located dorsally from the forming heart derived from the first heart field (dark grey). The second heart field is added at the venous and arterial poles of the definitive heart. Ballooning model of cardiac chamber formation (B). The early heart tube has an embryonic phenotype (dark grey). Chamber myocardium (light grey) expands from the outer curvature, whereas non-chamber myocardium (grey) of the inflow tract, atrioventricular canal, outflow tract and inner curvature does not expand. a indicates atrium; ift, inflow tract; la, left atrium; lv, left ventricle; ra, right atrium; rv, right ventricle; sv, sinus venosus.