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Review

Choose your destiny: Make a cell fate decision with COUP-TFII

San-Pin Wu[a,c], Cheng-Tai Yu[a], Sophia Y. Tsai[a,b,*], Ming-Jer Tsai[a,b,*]

[a] Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030, USA
[b] Program in Developmental Biology, Baylor College of Medicine, Houston, TX 77030, USA
[c] Adrienne Helis Malvin Medical Research Foundation, New Orleans, LA 70130, USA

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ABSTRACT

Cell fate specification is a critical process to generate cells with a wide range of characteristics from stem and progenitor cells. Emerging evidence demonstrates that the orphan nuclear receptor COUP-TFII serves as a key regulator in determining the cell identity during embryonic development. The present review summarizes our current knowledge on molecular mechanisms by which COUP-TFII employs to define the cell fates, with special emphasis on cardiovascular and renal systems. These novel insights pave the road for future studies of regenerative medicine.

Contents

1. Introduction

Chicken ovalbumin upstream promoter transcription factor II (COUP-TFII, also known as NR2F2) belongs to the steroid hormone receptor superfamily. COUP-TFII acts as a transcription factor to directly activate or repress transcriptional activities of target genes [1,2]. Alternatively, COUP-TFII can sequester other transcription regulators, such as Smad4, TR, RXR and RAR, to affect the expression of downstream targets [2–4]. At the cellular level, COUP-TFII promotes cell differentiation [5,6], proliferation [4,7,8], migration [7,8], survival [9] and intercellular communication [10–12]. Analyses of genetically engineered mouse models reveal regulatory functions of COUP-TFII in the development of many organs and tissues, including cerebellum [13], brain [14], eye [15], heart [16–18], stomach [19], diaphragm [20], limb [21], kidney [9], adipose [22], testis [23] and blood and lymphatic vessels [8,16,24,25]. In adult physiology, COUP-TFII modulates male and female fertility [12,23,26] as well as glucose and energy metabolism [22]. Pathologically, COUP-TFII facilitates tumor angiogenesis [10,27], promotes tumorigenesis [4] and suppresses endometriosis progression [28]. Upstream regulators of COUP-TFII include retinoic acid [29,30], Sonic hedgehog [31–33], Indian hedgehog [34,35], cyclic AMP [30], IL-1β [28], TNFα [28], TGFβ1 [28], Wnt/β-catenin [36], Sox7 [37], Sox18 [37], Notch [37,38] and microRNAs [28,39–41].

COUP-TFII's relevance in human embryonic development finds support from numerous genetic studies. The human COUP-TFII genomic locus locates at 15q26 on chromosome 15. Mutations in

* Corresponding authors at: Department of Molecular and Cellular Biology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA.
Fax: +1 713 798 8227.
E-mail addresses: stsai@bcm.edu (S.Y. Tsai), mtsai@bcm.edu (M.-J. Tsai).

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the 15q26 region are shown to associate with congenital diaphragmatic hernia [42–44], analogous to the phenotype observed in COUP-TFII conditional knockout mice [20]. In addition, patients with mutations in the COUP-TFII gene body and a subpopulation of patients with 15q26 mutations exhibit cardiac dysmorphogenesis [44–46]. Interestingly, kidney abnormalities are also seen in many patients of 15q26 mutations who also had congenital heart defects and/or congenital diaphragmatic hernia [47].

In developing embryos, cell fate specification occurs when progenitor cells proceed to derive various types of terminally differentiated cells. During this process, genomic profiles change drastically to produce designated cellular phenotypes, which require coordinated control by networks of transcription factors and other regulatory mechanisms. COUP-TFII has been shown to be essential for specifying cell fates of fat, bone, muscle and eye progenitors [6]. In the present article, we will summarize the role of COUP-TFII in cell fate decisions of cardiovascular and renal systems.

1.1. The atrial identity in hearts

The atrial and ventricular cardiomyocytes exhibit differences in contractile properties, electric patterns, excitation-contraction coupling and endocrine functions, despite both of them serving as the main contractile apparatus in hearts [48,49]. Morphologically, the atrial cardiomyocytes bear additional structural features as a hormone-producing cell with more extensively developed Golgi complexes, endoplasmic reticulum and storage granules [48,50]. Gene expression studies further reveal distinct profiles between atria and ventricles that reflect functional and structural differences between the two compartments [51–53]. These differences suggest unique regulatory programs may exist to confer chamber identities.

In developing human and mouse hearts, COUP-TFII is prominently expressed in the atria while its levels in ventricles are at the baseline level [16,51]. At early stages of embryos, COUP-TFII expression is present in a subpopulation of Isl1^{+} progenitor cells at the posterior part of the second heart field near the venous pole of the heart tube (Fig. 1A–C). Later on, the Isl1^{+} progenitor cells in this region will migrate into the heart tube and form the atrial compartment of chamber hearts [54–56]. COUP-TFII continues to be present in cardiomyocytes of developing hearts and is co-localized with Myl7^{+} (MLC2a) atrial cardiomyocytes, but not with the Myl2^{+} (MLC2v) ventricular cells (Fig. 1D and E). This expression pattern supports the hypothesis that COUP-TFII may contribute to specification of the atrial identity. Indeed, atria of COUP-TFII null mice adopt a ventricular phenotype, as evidenced by the ectopic expression of ventricular marker Myl2 in atria (Fig. 1F–I). Further evidence indicates that maintaining the atrial identity requires COUP-TFII in immature cardiomyocytes [57]. Deletion of COUP-TFII specifically in nascent cardiomyocytes reprograms atrial cardiomyocytes to be structurally, functionally and molecularly similar to ventricular cardiomyocytes *in vivo* [57]. In contrast, ectopic COUP-TFII overexpression is also sufficient to confer the atrial phenotype to immature ventricular cardiomyocytes [57]. Notably, the COUP-TFII dependent plasticity of chamber identity is transient because such an identity switch is no longer seen when COUP-TFII is deleted at embryonic day 15 [57]. Collectively, these findings demonstrate that COUP-TFII serves as an important molecular regulator in specification of the atrial identity.

COUP-TFII employs a network of transcription factors, including Tbx5, Hey2, and Irx4 to specify the atrial identity. Tbx5 promotes atrial gene expression and is essential for atrial morphogenesis [58,59]. COUP-TFII binds at the Tbx5 genomic locus and positively modulates Tbx5 expression, suggesting that Tbx5 is a direct downstream target of COUP-TFII [57]. COUP-TFII may control Tbx5 transcription through interaction with Sp1 because a Sp1 binding site is required for COUP-TFII dependent promotion of Tbx5 expression [57]. The ventricular transcription factors Hey2 and Irx4 are necessary and sufficient to suppress expression of atrial genes [58,60–64]. It was further demonstrated that COUP-TFII silences the expression of Hey2 and Irx4 in atria through direct binding to imperfect direct repeat sequences of AGGTCA in Hey2 and Irx4 genomic loci and suppresses the expression of both genes [57]. Aside from controlling the expression of major transcription regulators, COUP-TFII also directly regulates a broad spectrum of genes that are important for atrial development and function. In embryonic atrial tissues, chromatin immunoprecipitation and sequencing assays (ChIP-seq) identified more than two thousand COUP-TFII binding sites that could be potential enhancers/repressors for a wide spectrum of cardiac genes. For example, COUP-TFII binds at and modulates expression of contractile genes Myl2, Myl7 and Myl4, ion channel genes Kcne1, Kcng2, Kcnj5, Kcnk2, Cacna1c and Cacna1d, growth factors

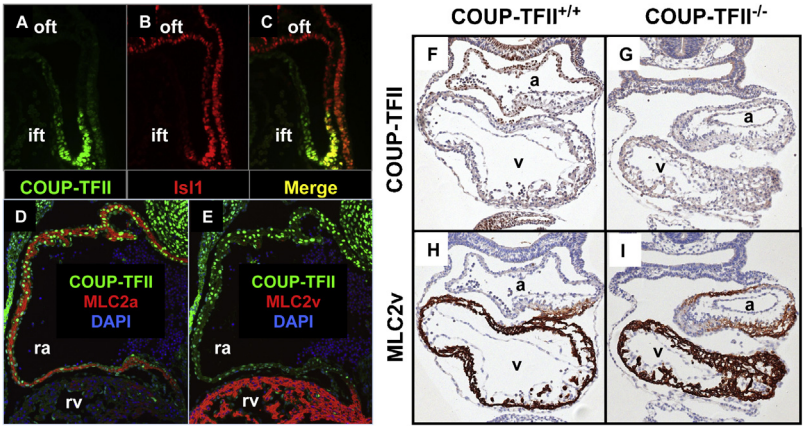

Fig. 1. COUP-TFII expression patterns in developing hearts and the cardiac phenotype in COUP-TFII null mice. (A–C) Cardiogenic area in sagittal sections of 27-somite wild type embryos stained for COUP-TFII (green) and cardiac progenitor marker Isl1 (red). (C) The merged image of (A) and (B). (D and E) Cross sections of E11.5 wild type embryos stained for denoted markers. DAPI marks nuclei. (F–I) Immunostaining of embryos at the 23-somite stage. Hematoxylin in blue serves as nuclear counterstaining. (F and H) Wild type mice, (G and I) COUP-TFII null mice, (F and G) COUP-TFII stained in brown and (H and I) Ventricular marker MLC2v stained in brown. Ift, inflow tract; oft, outflow tract; ra, right atrium; rv, right ventricle; a, primitive atrium; v, primitive ventricle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)