HHS Public Access

Author manuscript

J Steroid Biochem Mol Biol. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

J Steroid Biochem Mol Biol. 2016 March ; 157: 7–12. doi:10.1016/j.jsbmb.2015.11.011.

Choose Your Destiny: Make A Cell Fate Decision with COUP-TFII

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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.

Keywords

COUP-TFII; heart; blood vessels; lymphatic vessels; kidney; cell fate specification

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

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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 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.

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 (Figures 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 (Figures 1D-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 (Figures 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 Fgf1 and Fgf12, and cardiac transcription factors Lbh and Id2 [57]. Taken together, these findings support that specification of the atrial identity requires a COUP-TFII dependent regulatory network, in which COUP-TFII controls expression of a cascade of transcriptional and physiological regulators as well as cell type specific genes.

The COUP-TFII dependent specification of cardiomyocyte fate is also seen in fruit flies. The Drosophila COUP-TF homolog, seven-up, specifies a subpopulation of cardiac precursor cells fated for the future ostia, while tinman, homolog of vertebrate Nkx homeobox gene and a master cardiac transcription factor, marks the rest of the cardiac precursors that give rise to other segments of the heart [65,66]. Functionally, seven-up is essential and sufficient to repress the expression tinman for specification of tinman-negative cardiac precursors [65]. Interestingly, zebrafish require Nkx2.5 and Nkx2.7 to maintain their ventricular identity. Loss of Nkx2.5/Nkx2.7 results in adoption of atrial identity by ventricular cardiomyocytes [67]. Collectively, these findings implicate a potential role of Nkx homeobox transcription factors in the COUP-TFII dependent regulatory network for cardiac fate determination.

The Venous and Lymphatic Fate Specification in Vasculature

Arterial, venous and lymphatic vessels are the three types of major conduits to circulate body fluid. Blood pumped out from cardiac ventricles travels through arteries to reach micro vessels in peripheral tissue and returns via veins to atria. Meanwhile, lymphatic vessels collect and return interstitial fluid to the general circulation via connecting to subclavian veins. Fates of arteries and veins are determined during embryonic development [68]. We and others show that COUP-TFII and Notch signaling serve as key regulators in specification of venous and arterial fates, respectively [25,69-72]. Artery-fated angioblasts receive signals from vascular endothelial growth factor (VEGF) via the receptor VEGFR2 and the co-receptor neuropilin 1 (NRP1) to activate Notch signaling for further differentiation toward the arterial phenotype. Additionally, forkhead transcription factors Foxc1 and Foxc2 also promote arterial gene expression through increasing expression of Notch signaling genes Dll4 and Hey2 [73,74]. In contrast, vein-fated angioblasts express COUP-TFII, which suppresses notch signaling to confer vein identity. COUP-TFII directly suppresses expression of NRP1 and FOXC1, two upstream regulators of Notch signaling [7]. The resulting suppression of the Notch signaling is evidenced by reduced expression of Notch downstream effectors HES1, HES2 and HEY2, increased levels of venous marker gene EPHB4, and decreased expression of arterial marker EFNB2. Additionally, COUP-TFII also binds to the promoter of the HEY2 gene and directly represses its transcriptional activities [7]. Thus, COUP-TFII specifies the venous fate through suppression of the Notch signaling pathway at multiple points. Notably, Notch is shown to repress COUP-TFII expression in the dorsal aorta of zebrafish and cultured endothelial cells [37,38], suggesting a reciprocal repression mechanism of COUP-TFII and Notch during vascular development.

Recently, the chromatin remodeling enzyme Brg1 (also known as Smarca4) has been shown to positively regulate COUP-TFII expression, and is required for venous specification in mouse embryos [75]. Brg1 binds at the promoter and a −1.2-Kb upstream region of COUP-TFII gene. Brg1 depletion results in a reduced H3K9ac active enhancer mark and increased histone H3 binding at both Brg1 binding sites, leading to decreased RNA polymerase II recruitment at the COUP-TFII promoter region and reduced COUPTFII expression [75]. Veins of endothelial-specific Brg1 knockout mice exhibit decreased COUP-TFII expression and increased NRP1 and DLL4 levels, parallel to the COUP-TFII knockout phenotype [75]. Collectively, these findings indicate that Brg1 suppresses Notch signaling through epigenetically modifying COUP-TFII gene activities for venous fate specification.

The lymphatic vessels arise from the anterior cardinal veins and intersomitic vessels [76,77]. In mid-gestation embryos, a subset of endothelial cells fated as lymphatic precursors migrate out of blood vessels to form lymphatic sac and subsequent lymphatic vasculature[76-78]. Specification of lymphatic precursors requires COUP-TFII and Sox18 to promote expression of the lymphatic master regulator Prox1, in which direct transcriptional regulation serves as the underlying mechanism of action [24,79]. In addition, ERK signaling also stimulates Sox18 and Prox1 expression for lymphatic specification [80]. The ERK signaling may work in parallel or downstream of COUP-TFII because constitutive activation of ERK does not affect COUP-TFII expression [80]. After fate specification, the Prox1-positive lymphatic precursors bud out and leave blood vessels to undergo further

differentiation and sprouting in response to mesenchyme-derived vascular endothelial growth factor C (VEGFC) [77]. In lymphatic precursors, expression of the VEGFC receptor, VEGFR3, requires physical interaction between COUP-TFII and Prox1 to jointly promote its transcription [81]. Regulation of VEGFR3 by COUP-TFII continues to be essential during the process of lymphangiogenesis. Loss of COUP-TFII results in decreased VEGFR3 expression and impairs proliferation and migration of lymphatic endothelial cells [8]. In summary, COUP-TFII controls lymphatic system development by regulating cell fate specification, migration, proliferation and differentiation.

Fate Determination of Renal Progenitor Cells

During embryogenesis, kidneys derive from renal progenitor cells in the metanephric mesenchyme. The metanephric mesenchyme arises from a subpopulation of intermediate mesodermal cells that are specified to adopt the renal progenitor fate [82]. The intermediate mesodermal cells express high levels of COUP-TFII and COUP-TFII deficient mice fail to develop metanephric mesenchyme [9]. These findings together indicate that specification of renal progenitors requires COUP-TFII. After formation of metanephric mesenchyme, COUP-TFII remains prominently expressed in these renal progenitors. At this stage, COUP-TFII works in parallel with Osr1, another master renal development gene, to regulate the Eya1-Pax2-Six2 axis that promotes expression of Gdnf for subsequent induction of nephron formation [83]. At the same time, COUP-TFII also promotes expression of the Wt1 gene that is essential for survival of renal progenitors cells in the metanephric mesenchyme. Mechanistically, COUP-TFII modulates these two pathways by Sp1-dependent binding at the Eya1 and Wt1 promoters to induce their transcriptional activities [9]. Taken together, COUP-TFII is central to a network of renal transcriptional regulators that control fate specification, cell survival and intercellular communication of renal progenitors.

The nephron is the working unit of a kidney. Each nephron is segmented into four functional domains – glomerulus, proximal tubule, loop of Henle and distal tubule. During the process of nephron segmentation, Notch2 specifies the identity of proximal tubules. Deletion of Notch2 results in kidney hypoplasia where glomeruli and proximal tubules are absent but the distal tubules remain in place [84]. On the other hand, COUPTFII is expressed in distal tubules but not in proximal tubules of developing kidneys [85,86]. Interestingly, deletion of COUP-TFII in renal progenitor cells ($CKO^{six2\text{-}cre}$) also produces kidney hypoplasia with an opposite phenotype in which proximal tubules form with much less corresponding distal tubules (Yu et al., unpublished observations). Further analysis found that the COUP-TFII deficient tubule cells acquire the capacity to bind *Lotus tetragonolobus* lectin (LTL) that marks the proximal tubules [86], suggesting that cells alter characters subsequent to loss of COUP-TFII, possibly through adaptation of the proximal tubule fate. These findings collectively implicate that, in contrast to Notch2 dependent specification of proximal tubule fate, COUP-TFII may play a critical role in specifying cells that are fated for distal tubules during nephron segmentation.

In adult kidney, COUP-TFII is required to maintain expression of renin [87], the enzyme that activates the renin-angiotensin system to regulate blood pressure. COUPTFII and renin are both expressed in the juxtaglomerular cells that are the primary renin-expression cells [87].

Deletion of COUP-TFII, after the kidney is fully matured, reduces the basal levels of renin expression in renin-expressing cells. At the molecular level, COUPTFII binds to a direct repeat at the proximal renin promoter and works with another transcription factor cAMP-binding protein to promote renin expression [87]. It is worthy to note that genome-wide association studies have linked COUP-TFII to hypertension in human [88,89], supporting the clinical relevance of COUP-TFII in regulation of the reninangiotensin system. Intriguingly, the renin expressing cells also arise from progenitors in the metanephric mesenchyme where COUP-TFII is highly expressed [9], while emerging evidence suggests that Notch signaling regulates the expansion of renin-expressing cell population under pathological conditions through cellular reprogramming [90-92]. Owing to the close relation between COUP-TFII and Notch signaling in cell fate determination, it is tempting to speculate that COUP-TFII might also participate in this reprogramming event at the adult stage.

Conclusions and Remarks

COUP-TFII serves as a master regulator for cell fate specification in multiple tissues. Numerous studies indicate that COUP-TFII establishes specific cell identities in conjunction with or working through various key transcriptional regulators (Figure 2). Although compositions of COUP-TFII dependent regulatory networks may be context-dependent, control of common important cell fate determinants by COUP-TFII are conserved among tissues. For example, in hearts and blood vessels, COUP-TFII directly suppresses transcription of the Hey2 gene, which is a common regulator for ventricular and arterial fate specification [7,57]. Furthermore, COUP-TFs repress Pax2 gene expression in both renal and ocular progenitors, despite going through different effectors[9,15]. On the other hand, collaborations between COUP-TFII and other transcription regulators may increase COUP-TFII's functional diversity. This mechanism has been shown to result in distinct genomic profiles that underlie individual cell fates [93]. Therefore, genome-wide motif analyses in COUP-TFII binding regions and unbiased proteomic analyses of COUP-TFII interacting proteins should facilitate the discovery of COUP-TFII dependent genetic codes that are utilized to determine cell fates. Interestingly, deletion of COUPTFII at the adult stage does not produce overt phenotypes, which suggests that COUPTFII may mainly operate at a permissive window of plasticity for cell fate specification [57]. This notion finds further support in previous studies that fate plasticity is time-sensitive in hearts and blood vessels [94,95]. With the emerging cell-based therapeutic strategies in sight, learning from COUP-TFII dependent regulatory mechanisms would help to better understand the time and molecular circuits that define cell fates.

Acknowledgments

This work was supported by grants from NIH DK59820 and HL114539 (S.Y.T. and M.J.T.) and DK45641 (M.J.T.). We thank Mrs. Jodie R. Hebert for manuscript editing. The authors acknowledge the joint participation by Adrienne Helis Malvin Medical Research Foundation through its direct engagement in the continuous active conduct of medical research in conjunction with Baylor College of Medicine and the Cancer Program.

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Highlights

1. COUP-TFII is expressed in progenitor cells of multiple lineages.
2. COUP-TFII controls major regulators of cell fate specification.
3. This review focuses on the role of COUP-TFII in cardiovascular and renal systems.

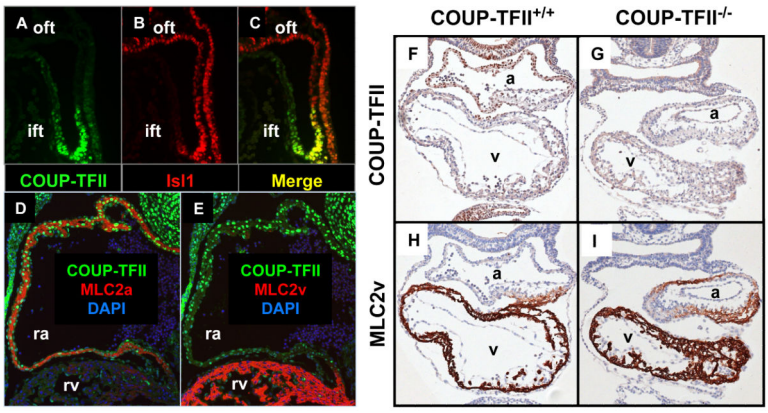

Figure 1. COUP-TFII expression patterns in developing hearts and the cardiac phenotype in COUP-TFII null mice

(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.

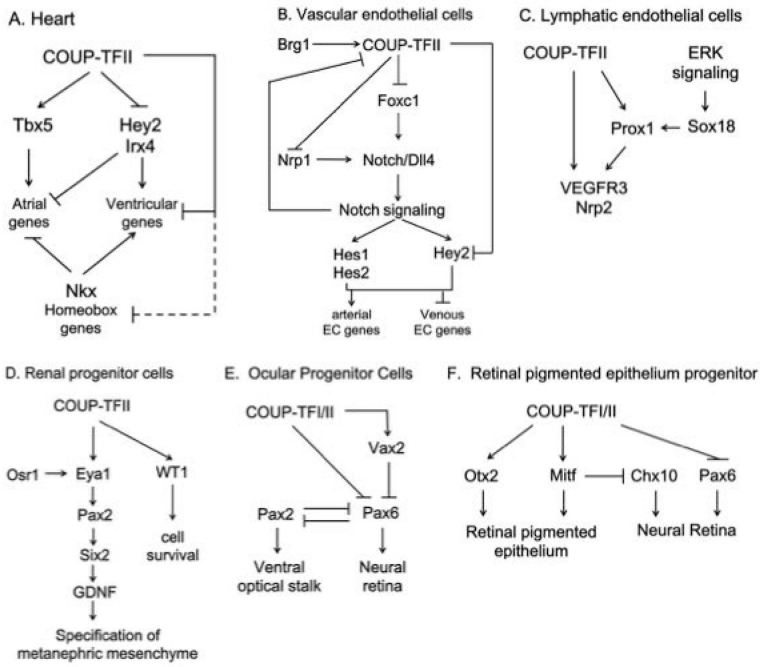

Figure 2.

Summary of COUP-TFII dependent regulatory networks in cardiovascular and renal systems.