TRANSCRIPTION FACTOR 21

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Article History: Received: 10.05.2023 **Revised:** 25.06.2023 **Accepted:** 01.07.2023

Abstract

Transcription factor 21 (TCF21) is one of the essential transcription factors in kidney development. Urinary TCF21 showed a positive correlation with its podocyte expression level and is considered a useful marker of kidney injury.

Keywords: TCF21**;** HLH**;** DNA

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DOI: 10.48047/ecb/2023.12.8.625

Introduction

The helix-loop-helix (HLH) family of transcription factors possesses highly conserved bipartite domains for DNA binding and protein-protein interactions, which is pivotal in various developmental processes, covering myogenesis, neurogenesis, and hematopoiesis (1). The HLH family members are divided into seven families according to tissue distribution, dimerization ability, and DNA binding specificity (2). Transcription factor 21 (TCF21, 6417bp)—also known as Pod1, bHLHa23, or Capsulin—encodes a transcription factor belonging to the cell-type-specific class II basic helix-loop-helix (bHLH) family at chromosome 6q23.2 (3). Moreover, TCF21 is specific for mesoderm and is expressed in the embryos' mesenchymal derived tissues, such as the epicardium, lung, intestine, gonad, and kidney (4). It regulates the cell differentiation during embryonic development, such as coronary vasculature (5). The ChIP-Seq studies in primary cultured human coronary vascular smooth muscle cells (VSMCs) have identified several TCF21 target genes, such as smooth muscle contraction, growth factor binding and matrix interaction, which are involved in the processes associated with coronary heart disease (CHD) pathophysiology (6). A wealth of evidence confirms that TCF21 takes an active role in VSMC phenotypic modulation in CHD. In this review, we endeavor to provide a detailed introduction of the biological roles of TCF21 in epicardial fate determination and the development of CHD.

The Origin of Epicardial Cells

The proepicardial cells, a mesoderm-derived cell cluster, are highly conserved in vertebrates including Xenopus, zebrafish, mice and even human (7), which could migrate to the myocardial surface, adhere and form the epicardium during embryogenesis (8). Once the original epicardium forms, a portion of the epicardial cells could enter the subepicardial domain and produce epicardium-derived cells (EPDCs) by undergoing epithelial-mesenchymal transition (EMT) (9). During the EMT, epithelial cells downregulate their epithelial gene expression, lose their unique characteristics, and activate the mesenchymal genes to increase cell viability and motility, including aggressiveness (Li et al., 2018). Recent studies have confirmed that EMT could be affected by several signaling pathways in epicardial cells, including but not limited to transforming growth factorβ (TGF-β), retinoic acid (RA), platelet-derived growth factor (PDGF), and extra-cellular matrix (ECM) components (10). EPDCs are highly plastic and have been reported to differentiate into myocardial fibroblasts, VSMCs, and pericytes (11). Lineage tracing studies also confirmed that the VSMCs originated from the epicardial cells (12).

TCF21 and Epicardial Cells

The Role of TCF21 in Epicardial Cells During Heart Development

Studies in different animal models have delivered several molecular signatures of proepicardial cells, including the conserved transcription factors [TCF21, Wilms tumor 1(WT1), and T-box factor 18 (Tb×18)] (13). The study of Xenopus embryos showed that proepicardial cells could migrate to the heart, retain their precursor cell characteristics and impair maturity in the absence of TCF21 (14). It suggested that the morphological defect in epicardial

integrity might be caused by the absence of TCF21 through regulating the specification and maturation of the proepicardial cells at earlier stages of epicardial development **(Figure 1).**

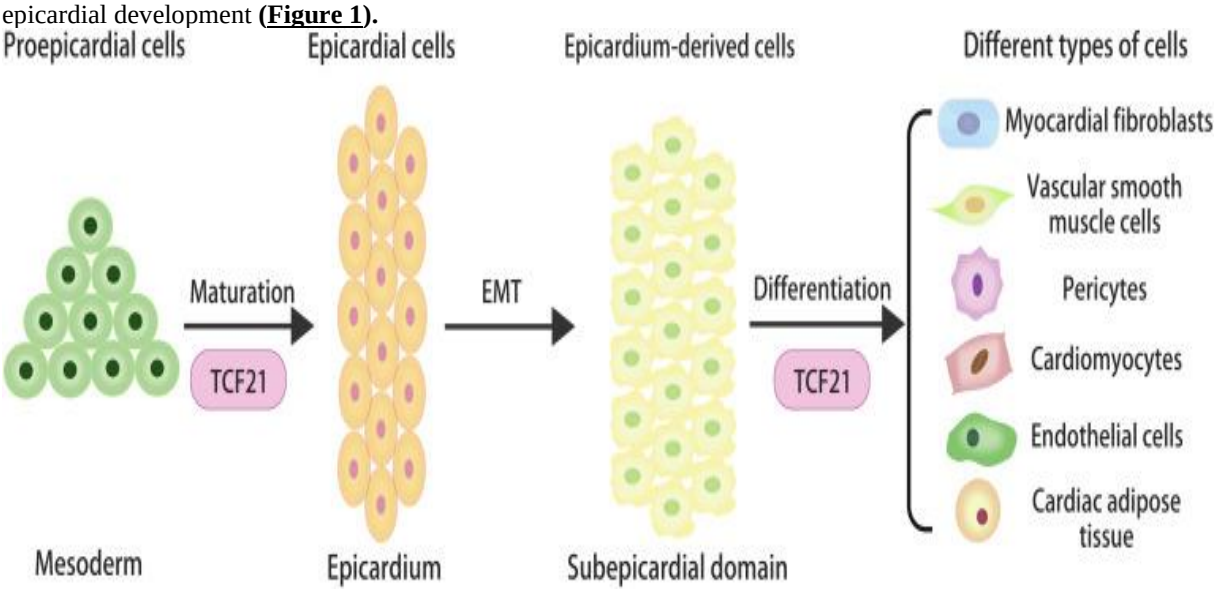

FIGURE 1: The origin and cellular contributions of epicardial cells during heart development, and the regulatory role of TCF21 in the specification and maturation of proepicardial cells and the determination of epicardial cell fate.

Previously, we recognized that TCF21 could promote cardiac fibroblast development and inhibit VSMC differentiation of EPDCs. Asha et al. found most epicardial cells expressing TCF21 were lumped in the myocardial fibroblast lineage before the initiation of EMT (12). It was concluded from the study that a TCF21-deficient heart could not undergo EMT and form cardiac fibroblasts, which confirmed the unique role of TCF21 in epicardial EMT and differentiation (15). The *in vivo* experiment showed that loss of TCF21 in mice resulted in a decrease of myocardial fibroblasts due to the premature differentiation of EPDCs into VSMCs through RA signals (16). Together, these data support the thesis that TCF21 plays an indispensable role in the development of

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