Tumor Suppressor WT1

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The Wilms' tumor 1 (WT1) gene was originally identified based on its mutational inactivation in Wilms' tumor (nephroblastoma). This first discovery of WT1 as the responsible gene in an autosomal-recessive condition classified it as a tumor-suppressor gene. Mutations of WT1 were associated with the development of kidney tumors and urogenital defects.

Keywords: Wilms' tumor suppressor 1 (Wt1) ; heart ; cardiac development ; coronary vessel formation ; transcriptional regulation ; cardiac malformation ; epicardium ; epicardial derived cells (EPDCs) ; epithelial mesenchymal transition (EMT) ; cardiac cell fate ; regeneration

1. Introduction

WT1 encodes a zinc finger transcription factor and RNA-binding protein [1][2][3][4]. As a transcriptional regulator, it can either activate or repress various target genes. Thus, WT1 influences cellular differentiation, growth, apoptosis, and metabolism. WT1 exists in multiple isoforms. Alternative splicing of exon 5 and exon 9 gives rise to major isoforms. Splicing of exon 9 generates the KTS isoforms, which either include or exclude three amino acids lysin, threonine, and serin (KTS) between zinc fingers 3 and 4 of the protein [5]. Although the majority of WT1 proteins are in the nucleus, some are present in the cytoplasm, located on actively translating polysomes. WT1 isoforms shuttle between the nucleus and cytoplasm [6]. The complexity of WT1 is further enhanced by post-translational modifications and a plethora of binding partners. WT1 directs the development of several organs and tissues, among them the heart.

The heart develops mostly from embryonic mesodermal germ layer cells and to some extent from ectoderm-derived cardiac neuronal crest (cushions of the outflow tract). The cardiogenic mesoderm differentiates into proepicardial, endocardial, and myocardial cells. The epicardium is formed from a subset of the proepicardial cells. Proepicardial cells also contribute subepicardial cells, interstitial fibroblast, pericytes, and a subset of the endothelial cells of the coronary vessels. The inner lining of the heart tube is formed by endocardial cells. The vertebrate heart forms as two concentric epithelial cylinders of myocardium and endocardium separated by an extended basement membrane matrix commonly referred to as cardiac jelly. The primitive heart tube is formed at embryonic day 8.5 (E8.5) in the mouse [7]. The primitive tube elongates and undergoes rightward looping. Further remodeling of the heart involves formation and expansion of the chambers, and formation of valves and septa, resulting in a heart with two atria and two ventricles [8]. The heart is the first organ to develop and is already functional at an early stage of fetal development, in line with its essential role for the distribution of oxygen and nutrients and removal of waste products and carbon dioxide. Several excellent reviews have already described cardiac development in detail [9][10][11][12][13][14]. Thus, we focus here only on the role of Wt1. Wt1 expression was first observed in a transitory cluster of cells—the proepicardium and the coelomic epithelium at E9.5. Wt1-expressing proepicardial cells contact the dorsal wall of the heart from which the proepicardial cell migrate over the myocardium of the heart tube to form the epicardial layer by E12.5 [15][16]. This view has been challenged recently by the detection of a common progenitor cell population of epicardium and myocardium using single-cell RNA sequencing [17]. How these common progenitors might migrate during cardiac development is currently an open question.

A proportion of epicardial cells undergoes epithelial-to-mesenchymal transition (EMT), which induces the formation of epicardial-derived cells (EPDCs), a population of multipotent mesenchymal cardiac progenitor cells, which might differentiate into cardiomyocytes, fibroblasts, smooth muscle, and endothelial cells [18][19][20], which is discussed in detail later. First indications for the indispensable role of Wt1 in heart homeostasis came from the observations made in Wt1 knockout embryonic mice which died at mid-gestation due to cardiac malformations [21].

Here, we review the history of investigations characterizing the role of WT1 (i) in cardiac development, (ii) in cardiac disease and regeneration, and (iii) in different cardiac cell types and transcriptional regulatory mechanisms. We indicate emerging notions and point out problems and promises in the field of development of therapeutic strategies for cardiac repair.

2. WT1 in Heart Development

Wt1-expressing cell types during heart development in different species are summarized in **Table 1** and further described below. Of note, expression of Wt1 is limited to a subset of the identified cells. Functional differences between Wt1-expressing cells and the Wt1-negative counterparts remain mostly unknown at present.

Table 1. WT1-target genes related to cardiac development and disease.

Gene	Reference
Insulin like growth factor 1 receptor (IGF-1-R)	[22]
Epidermal growth factor receptor (EGFR)	[23]
Retinoic acid receptor alpha (RAR- α)	[24]
Retinaldehyde-dehydrogenase (Raldh) 2	[25]
Insulin receptor (IR)	[26]
Paired box gene 2 (Pax2)	[27]
Platelet-derived growth factor A (PDGFA)	[28][29]
Early growth response protein 1 (EGR-1)	[30]
Insulin like growth factor 2 (IGF-2)	[31]
Transforming growth factor beta (TGF-β)	[32]
Colony-stimulating factor-1 (CSF-1)	[33]
Syndecan 1	[34]
Midkine	[35]
Vitamin D receptor (Vdr)	[36][37]
Podocalyxin	[38]
Nephrin (Nphs1)	[39]
Podocin (Nphs2)	[40]
Tyrosinkinase receptor (Trk)B	[41]
Nestin	[42]
Erythropoietin (EPO)	[43]
α4 Integrin	[44]
Vascular endothelial growth factor (VEGF)	[45][46]
Vascular endothelial growth factor receptor (Vegfr) 2	[47][48]
ETS proto-oncogene (ETS)-1	[47]
Snail (Snai1)	[49]
Slug (Snai2)	[50]
E-Cadherin	[49][51]
VE-Cadherin	[52]
Coronin1B	[53]
Cxcl10 (C-X-C Motif Chemokine Ligand 10)	[54]
Ccl5 (C-C Motif Chemokine Ligand 5)	[54]
Interferon regulatory factor (Irf)7	[54]
c-Kit (tyrosine-protein kinase KIT)	[55]
Pecam-1 (platelet and endothelial cell adhesion molecule 1)	[55]

Gene	Reference
Telomere repeat binding factor (Trf) 2	[56]
Bone morphogenetic protein (Bmp) 4	[57]

Studies in birds confirmed the expression of Wt1 in epicardium- and epicardial-derived cells (EPDCs) during embryonic development [58]. Using normal avian and quail-to-chick chimeric embryos, the origin and fate of Wt1-expressing EPDCs were later described and the effects of epicardial ablation on cardiac development investigated [20]. Wt1-expressing EPDCs were found to populate the subepicardial space and to invade the ventricular myocardium. Upon differentiation in smooth muscle and endothelial cells, Wt1 expression decreased in EPDCs. Undifferentiated EPDCs continued to express Wt1 and invaded the ventricular myocardium and the atrio-ventricular (AV) valves. Disruption of normal epicardial development either by proepicardial ablation or block reduced the number of invasive Wt1-positive EPDCs, and provoked anomalies in the coronary vessels, the ventricular myocardium, and the AV cushions. In addition to Wt1, EPDCs express retinaldehyde-dehydrogenase (Raldh) 2 [59][60]. It had been demonstrated that in humans WT1 transcriptionally regulates the retinoic acid receptor alpha (RAR-α) gene [24]. Transcriptional target genes of WT1 with relevance in the heart are summarized in **Table 2** and discussed below.

Table 2. WT1-target genes related to cardiac development and disease.

Gene	Reference
Insulin like growth factor 1 receptor (IGF-1-R)	[22]
Epidermal growth factor receptor (EGFR)	[23]
Retinoic acid receptor alpha (RAR- α)	[24]
Retinaldehyde-dehydrogenase (Raldh) 2	[25]
Insulin receptor (IR)	[26]
Paired box gene 2 (Pax2)	[27]
Platelet-derived growth factor A (PDGFA)	[28][29]
Early growth response protein 1 (EGR-1)	[30]
Insulin like growth factor 2 (IGF-2)	[31]
Transforming growth factor beta (TGF-β)	[32]
Colony-stimulating factor-1 (CSF-1)	[33]
Syndecan 1	[34]
Midkine	[35]
Vitamin D receptor (Vdr)	[36][37]
Podocalyxin	[38]
Nephrin (Nphs1)	[39]
Podocin (Nphs2)	[40]
Tyrosinkinase receptor (Trk)B	[41]
Nestin	[42]
Erythropoietin (EPO)	[43]
α4 Integrin	[44]
Vascular endothelial growth factor (VEGF)	[45][46]
Vascular endothelial growth factor receptor (Vegfr) 2	[47][48]
ETS proto-oncogene (ETS)-1	[47]
Snail (Snai1)	[49]
Slug (Snai2)	[50]

Gene	Reference
E-Cadherin	[49][51]
VE-Cadherin	[52]
Coronin1B	[53]
Cxcl10 (C-X-C Motif Chemokine Ligand 10)	[54]
Ccl5 (C-C Motif Chemokine Ligand 5)	[54]
Interferon regulatory factor (Irf)7	[54]
c-Kit (tyrosine-protein kinase KIT)	[55]
Pecam-1 (platelet and endothelial cell adhesion molecule 1)	[55]
Telomere repeat binding factor (Trf) 2	[56]
Bone morphogenetic protein (Bmp) 4	[57]

In addition, the relation between Wt1-expressing epicardial derivatives and the development of compact ventricular myocardium has been investigated. The differences in myocardial architecture specifically between the right ventricle (RV) and the left ventricle (LV) in association to epicardial formation and distribution of Wt1-expressing cells were studied. The authors demonstrated that the RV is less densely and later covered by the epicardium than the LV. They also observed that compact myocardial layer formation occurred in parallel with the presence of Wt1-expressing cells and was more pronounced in the LV than in the RV, and within the RV more accentuated in the postero-lateral wall than in the anterior wall, which might explain the lateralized differences in ventricular morphology of the heart [61]. The same group was able to identify a function of the epicardium in cardiac autonomic nervous system modulation, essential for proper cardiac activity by altering heart rate, conduction velocity, and force of contraction. They revealed expression of neuronal markers in the epicardium during early cardiac development, notably of tubulin beta-3 chain (Tubb3), which was colocalized with Wt1 in epicardium and the nervous system, neural cell adhesion molecule (Ncam), and the β2 adrenergic receptor (β2AR). Adrenaline (epinephrine), a catecholamine, is known to modulate heart rate, velocity of conduction, and contraction strength in the heart through its binding to β2AR. Inhibition of the outgrowth of the epicardium abolished the response to adrenaline administration, indicating that the epicardium is necessary for a normal response of the heart to adrenaline during early cardiac development [62]. This report further confirmed a role of Wt1 in neural function, as suggested by several studies [15][63][64][65][66][67][68].

WT1-target genes related to cardiac development and disease.

3. WT1 in the Adult Heart and Cardiac Pathologies

Already in 1994, Wt1 transcripts were detected by Northern blot in adult rat heart tissues [69]. Whether modifications in Wt1 expression occur under pathophysiological conditions and which cell types express the protein remained open questions. Our group was the first to demonstrate that Wt1 is a useful early marker of myocardial infarction [70], a finding later confirmed by others [71][72][73]. We focused on the de novo Wt1 expression in the coronary vasculature of the ischemic myocardium. As Wt1 is essential for normal growth of the heart during development, we originally reasoned that it might also play a role in adult cardiac hypertrophy. To test this hypothesis, we analyzed the expression of Wt1 in normal hearts and in the hypertrophied left ventricles of spontaneously hypertensive rats (SHRs), with activation of the renin–angiotensin system by transgenic (over) expression of human renin and angiotensinogen genes, and with postinfarct remodeling of the heart after ligation of the left coronary artery (LAD). Interestingly, we detected an over two-fold increase of cardiac Wt1 mRNA expression after LAD ligation, but no differences for the two hypertrophy models compared to controls. Further experiments using LAD ligation demonstrated a rapid increase of cardiac Wt1 levels already 24 h after LAD ligation, which remained elevated for nine weeks following the ischemic injury. Strikingly, in addition to its expression in the epicardium, we observed Wt1 localized to the coronary vessels in proximity to the infarcted tissue. Coronary vessels of non-infarcted animals did not express Wt1. Wt1 was expressed in endothelial as well as in vascular smooth muscle cells in the border zone of infarcted tissues. We confirmed this finding also in human cardiac ischemic tissues (unpublished results). Interestingly, WT1 expression could also be detected in healthy adult human myocardium by others [74]. Colocalization of Wt1 with proliferating cell nuclear antigen (PCNA) and vascular endothelial growth factor (VEGF) suggests a role of Wt1 in the proliferative response of the coronary vasculature to cardiac hypoxia [70]. In a following study, we were the first to demonstrate that Wt1 expression is indeed triggered by hypoxia, which involves transcriptional activation of the Wt1 promoter by the hypoxia inducible factor 1 (HIF-1) [75]. Later studies confirmed our finding that Wt1 is

a hypoxia-regulated gene [46][76]. Interestingly, it had been demonstrated that ischemia in vivo (through myocardial infarction in mice) or in vitro (hypoxia exposition of epicardial human explants) induced an embryonic reprogramming of the epicardial compartment, involving migration of epicardial-derived stem cell marker c-Kit expressing Wt1-positive cells which contributed to re-vascularization and cardiac remodeling [77]. As we identified c-Kit as a transcriptional target of Wt1 in the context of vascular formation [55], it seems conceivable that mobilization of c-Kit precursor cells represents one mechanism of Wt1-mediated cardiac neovascularization after ischemia. We further identified the telomere repeat-binding factor (Trf) 2 to be regulated by Wt1 [56]. Down-regulation of Trf2 has been demonstrated to provoke cardiomyocyte telomere erosion and apoptosis, linking telomere dysfunction to heart failure [78].

Thymosin β4 (Tβ4), a 43-amino-acid G-actin-sequestering peptide which is expressed in the embryonic heart and implicated in coronary vessel development in mice [79], has been shown to activate cardiac regeneration through stimulation of the expression of embryonic developmental genes in the adult epicardium, leading to de novo coronary vessel formation after myocardial infarction. However, a significant increase could only be reported for Vegf, Vegfr2, and TGFβ levels, whereas Wt1 levels were not significantly altered 24 h after MI compared to vehicle-treated animals [80]. A later study additionally revealed that adult Wt1 + GFP + EPDCs cells obtained through Tβ4 priming and myocardial infarction are a heterogeneous population expressing cardiac progenitor and mesenchymal stem markers that can restore an embryonic gene program, but do not revert entirely to adopt an embryonic phenotype [81].

First suspicions for a role of Wt1 in human cardiac pathologies originated in 2004, with a case report from an adult XY karyotype patient with a N-terminal WT1 missense mutation presenting a very unusual phenotype: ambiguous genitalia, but normal testosterone levels, absence of kidney disease, and an associated congenital heart defect [82]. Later, a role for WT1 in some cases of congenital diaphragmatic hernia associated with the Meacham syndrome phenotype had been suggested [83]. Meacham syndrome is a rare sporadically occurring multiple malformation syndrome characterized by male pseudo-hermaphroditism with abnormal internal female genitalia, complex congenital heart defects, including hypoplastic left hearts, and diaphragmatic abnormalities [84]. In a number of Meacham syndrome patients, heterozygous missense mutations in the C–terminal zinc finger domains of WT1 could be identified, suggesting that at least some cases displaying phenotypes of Meacham syndrome are caused by mutations at the WT1 locus [83]. We reported the case of a 4-month-old girl, who presented with end-stage renal disease, nephroblastomatosis, thrombopenia, anemia, pericarditis, and cardiac hypertrophy accompanied by severe hypertension. Sequence analysis identified a heterozygous nonsense mutation in exon 9 of WT1 , which leads to a truncation of the WT1 protein at the beginning of zinc finger 3 [85]. WT1 is a transcriptional regulator of erythropoietin, which might explain the persistent anemia in this patient [43]. Evolution over time showed severe and resistant high blood pressure, despite multi-drug therapy and bilateral nephrectomy, which did not result in the normalization of the blood pressure values. Acute episodes of high blood pressure were associated with cardiogenic shock and anemia. The little patient showed a severe concentric myocardial hypertrophy, with moderate signs of heart failure and intermittent pericarditis [85]. Still awaiting kidney transplantation, the child died due to myocardial infarction at the age of five years. Later, another case of cardiac pathology in a patient with a WT1 mutation was reported: A 46, XY phenotypic male patient with isolated nephrotic syndrome, end-stage renal disease, and hypertension, presented at the age of 6.3 years. A mutation in exon 8 of the WT1 gene was identified. After starting hemodialysis, manifestations of hypertension and renal failure improved, but he died at 6.8 years of age as a result of heart and respiratory failure [86]. Monozygotic twins with congenital nephrotic syndrome caused by a WT1 mutation have been reported to have died due to sepsis and extensive thrombosis of central venous system and sepsis and sudden heart failure at ages 23 weeks/13.5 months, respectively [87]. WT1 misexpression has been reported in autopsy findings from two human fetuses, displaying congenital pulmonary airway malformation, bilateral renal agenesis, and congenital heart defects [88]. Shortly after, re-evaluation of autopsy data from fourteen additional fetuses with combined renal agenesis and cardiac anomalies revealed abnormalities of Wt1 expression, mostly in liver mesenchymal cells. As WT1 is widely expressed in mesothelium, it had been suggested that the defects could be caused by abnormal function of mesenchyme derived from mesothelial cells [89]. WT1 is further expressed in cardiac angiosarcomas, which is the most common malignant neoplasm of the heart in adults. As other primary cardiac malignancies such as synovial sarcoma, leiomyosarcoma, and unclassified sarcomas are frequently negative for WT1, this finding might be helpful for differential diagnosis. It further confirms the implication of WT1 in vascular formation [90].

Interestingly, it has been shown recently using patient biopsies that the thickening of the epicardium and migration of Wt1-positive EPDCs contributes to atrial fibro-fatty infiltration, a source of atrial fibrillation. Employing Wt1 genetic lineage mouse lines, the authors showed that adult EPDCs maintain an adipogenic potential in the epicardial layer and can shift to a fibrotic phenotype in response to distinct stimuli, identifying the epicardium as a central regulator of the balance between fat and fibrosis accumulation [91]. Additionally, the expression of TGFβ1 and FGFs (fibroblast growth factors) by EPDCs has been suggested to contribute to the pathogenesis of myocardial fibrosis, apoptosis, arrhythmias, and cardiac dysfunction in a mouse model of arrhythmogenic cardiomyopathy (ACM) [92].

4. WT1 in the Heart–Focus on Different Cell Types and Regulatory Mechanisms

Table 3 summarizes WT1-expressing cell types in the adult heart. Reported functions and regulatory mechanisms are discussed below.

Table 3. Wt1-expressing cell types in adult heart.

Cell Type	Species	Reference
epicardial cells	rat, mouse, human	[70][77]
endothelial cells	rat (MI, ischemia), mouse (MI, ischemia)	[70][93]
vascular smooth muscle cells	rat (MI, ischemia)	[70]
cardiomyocytes	mouse (priming with Tβ4, followed by MI, ischemia)	[94]
	mouse	[95]
fibroblasts	mouse (MI, ischemia)	[93]
adipocytes	mouse (MI, ischemia)	[96]
macrophages	zebrafish (cardiac injury)	[97]

Regarding a possible implication of epicardial-derived Wt1-expressing progenitor cells for cardiac repair, the opinions are diverging. Some studies suggest an important role after myocardial infarction [93][94][98][99][100], while others did not confirm these results [101]. These controversial results derive from the different experimental approaches, staining procedures, and limitations of the Wt1-Cre mouse models used [102][103]. Re-activated epicardium is heterogenous and different from developmental epicardial cells [81], only a few cells in adult epicardium express Wt1 and are reliable targeted by the Wt1Cre lines [102][104].

Not much is known how Wt1 is regulated in the heart. Apart from hypoxia and direct transcriptional activation by HIF-1 [75], which are likely to be involved in cardiac development and repair, Hippo signaling components have been proposed to regulate Wt1 expression, epicardial EMT and epicardial cell proliferation and differentiation into coronary endothelial cells [105]. Vieira and colleagues identified an epigenetic mechanism implicating chromatin remodeling of the Wt1 locus as a critical event in epicardial activity in the developing and adult heart after cardiac injury. They suggested that Wt1 is dynamically controlled by SWItch/sucrose nonfermentable (SWI/SNF) chromatin-remodeling complexes containing Brahma-related gene 1 (BRG1) and Tβ4 [106].

Identification of WT1-modulating factors is of great interest regarding a potential role for cardiac repair in vivo, which is limited due to the lack of techniques to isolate, expand, differentiate, and transfer Wt1+ progenitor cells. However, Wt1 upregulation to enhance cardiac repair might promote tumor growth in patients at risk and should be cautiously monitored. Further research is necessary to delineate the intricacies of modulating WT1 for an optimized therapeutic benefit.

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