



# Cardiogenesis with a focus on vasculogenesis and angiogenesis

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## Abstract

The initial intraembryonic vasculogenesis occurs in the cardiogenic mesoderm. Here, a cell population of proendocardial cells detaches from the mesoderm that subsequently generates the single endocardial tube by forming vascular plexuses. In the course of embryogenesis, the endocardium retains vasculogenic, angiogenic and haematopoietic potential. The coronary blood vessels that sustain the rapidly expanding myocardium develop in the course of the formation of the cardiac loop by vasculogenesis and angiogenesis from progenitor cells of the proepicardial serosa at the venous pole of the heart as well as from the endocardium and endothelial cells of the sinus venosus. Prospective coronary endothelial cells and progenitor cells of the coronary blood vessel walls (smooth muscle cells, perivascular cells) originate from different cell populations that are in close spatial as well as regulatory connection with each other. Vasculo- and angiogenesis of the coronary blood vessels are for a large part regulated by the epicardium and epicardium-derived cells. Vasculogenic and angiogenic signalling pathways include the vascular endothelial growth factors, the angiopoietins and the fibroblast growth factors and their receptors.

## KEYWORDS

angiogenesis, cardiogenesis, development, heart, vasculogenesis

## 1 | INTRODUCTION

The complex heart of birds and mammals developed from the primitive, linear “pumping organ” of primordial vertebrate ancestors, such as the lancelet in the order Amphioxiformes (Romer & Parsons, 1986). It is the first functioning organ in a vertebrate embryo. Its three layers, endocardium, myocardium and epicardium, mainly develop shortly after gastrulation from an area of the mesoderm located bilaterally to Hensen's node that is referred to as cardiogenic mesoderm (Garcia-Martinez & Schoenwolf, 1993; Linask & Lash,

1993). In addition, cells of the cephalic mesoderm, neural crest and prechordal endoderm are also involved in the formation of the heart (Chan et al., 2016; Hatzistergos et al., 2015; Kirby, Gale, & Stewart, 1983; Kirby et al., 2003; Noden, Poelmann, & Groot, 1995).

During the development of the heart, vasculogenesis, which is the in situ development of a vascular plexus from endothelial progenitor cells, and angiogenesis, referring to the sprouting of blood vessels from already existing ones, both play important roles. The establishment of the endocardium, the internal lining of the heart, marks the initial commencement of intraembryonic vasculogenesis

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(Drake & Fleming, 2000; Harris & Black, 2010; Patan, 2000). Apart from a few key transcription and growth factors, little is known about the regulatory networks orchestrating endocardial formation.

The outermost layer of the heart, the epicardial sheath, develops during the formation of the cardiac loop, starting from a zone of proliferation that is located at the venous pole of the heart. The epicardium and the subpopulation of epicardium-derived cells that originate from it ultimately migrate into the myocardium, where they function as essential signal transmitters for vasculogenetic and angiogenetic processes that occur in the subepicardium and myocardium and also form the coronary blood vessels. The diverse and complex regulatory mechanisms of coronary vasculogenesis and angiogenesis as well as the differentiation into venous and arterial endothelia have been studied relatively extensively (Chen, Poduri, et al., 2014; Chen, Sharma, et al., 2014; Lutun & Carmeliet, 2003). However, the complicated transcriptional interaction of the different cell types involved as well as the complexity of the morphogenetic events does not allow simple clarification.

### 1.1 | Origin and segregation of cardiogenic progenitor cells

The cardiogenic subpopulation of mesodermal progenitor cells is located in the E6.5 (embryonic day of development; for abbreviations, see Table 1) of the murine embryo (equals Hamburger Hamilton stage (HH) 3 in the avian embryo) in the anterior third of the primitive streak. Here, the cells are arranged anteroposteriorly in an order that corresponds to that identified in the subsequent heart tube [from anterior to posterior: cells of the future ventricular outflow tract (previously designated bulbus cordis), the ventricles, the arteries and the sinus venosus]. However, at this point in time, the cells have not settled into their final location (Camp, Dietrich, & Munsterberg, 2012; Garcia-Martinez & Schoenwolf, 1993; Redkar, Montgomery, & Litvin, 2001). Even so, it is already possible to classify cells into those of the first (posterior cell location) and second (anterior cells) heart fields as well as to identify future myocardial, endocardial and epicardial cells of the heart as well as smooth muscle cells of the cardiac blood vessels. A portion, <5% of the progenitor cells, predominately those of the second heart field, retain bipotent qualities (Devine, Wythe, George, Koshiba-Takeuchi, & Bruneau, 2014; Lescroart et al., 2014; Milgrom-Hoffman et al., 2011; Wei & Mikawa, 2000; see Figure 1).

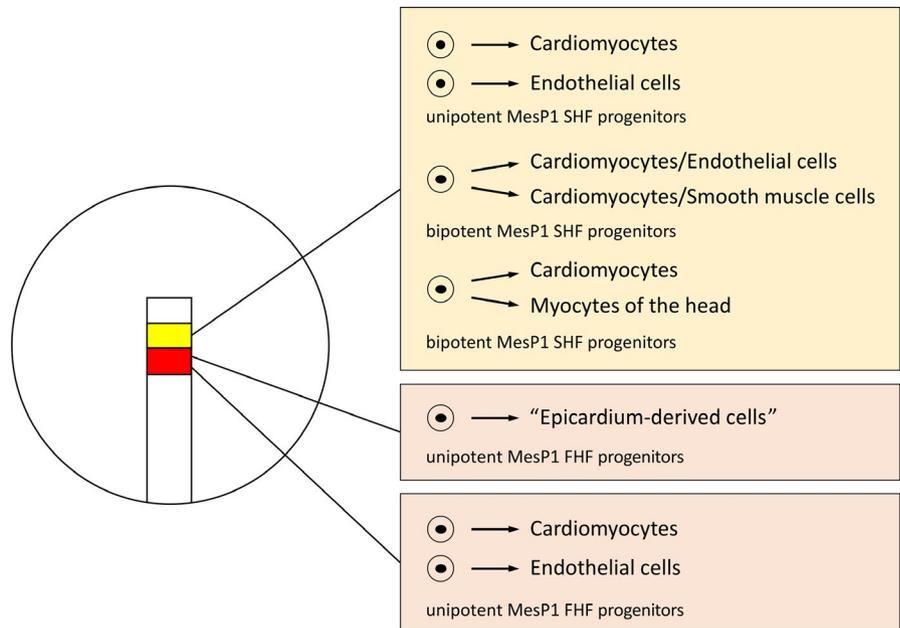
Transcription factor eomesodermin (Eomes), which is induced by canonical Wnt (Wingless-related integration site) signalling, activates from E6.5 transcription factor MesP1 (mesoderm posterior 1) in the multipotent cardiogenic progenitor cells of the primitive streak (Costello et al., 2011; Van den Aemele et al., 2012). MesP1 is regarded as the earliest marker (however not exclusively so) of the cardiovascular mesoderm and comprises progenitor cells of the myocardium, endocardium and epicardium as well as the vascular smooth muscle cells of the heart (Chan et al., 2013; Lescroart et al.,

**TABLE 1** Abbreviations and explanations

Abbreviation	Full name/explanation
Ang	Angiopoietin
BMP	Bone morphogenetic protein(s)
CD	Cluster of differentiation
COUPTFII	Chicken ovalbumin upstream promoter transcription factor II
Cxcl12	C-X-C motif chemokine 12, synonym stromal cell-derived factor 1
Cxcr	C-X-C chemokine receptor
E	Embryonic day of development
eNOS3	Endothelial nitric oxide synthase 3
Eomes	Eomesodermin
Eph	Erythropoietin-producing hepatocyte receptor
Ephrin	Ligand of Eph receptors
ETV2	Ets transcription factor variant 2
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
Flk1	Fetal liver kinase 1, synonym VEGFR2
Fog	Friends of GATA
GATA4	Gene encoding a member of the GATA family of zinc-finger transcription factors
HH	Hamburger Hamilton stage
HIF	Hypoxia-inducible factor
Isl, Islet	Insulin gene enhancer-binding protein
MesP	Mesoderm posterior
N	Neural
Nkx2.5	NK2 homeobox 5, a protein coding gene
NFATc	Nuclear factor of activated T cells
PECAM	Platelet endothelial cell adhesion molecule
RALDH	Retinaldehyde dehydrogenase
Shh	Sonic hedgehog
SMC	Smooth muscle cells
Tal1	T-cell acute leukaemia protein
Tbx18	T-box transcription factor gene
Tie2	TEK receptor tyrosine kinase
VE	Vascular endothelial
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
Wnt	Wingless-related integration site
WT	Wilms tumour transcription factor

2014; Milgrom-Hoffman et al., 2011; Saga, Kitajima, & Miyagawa-Tomita, 2000; Saga et al., 1999). As a fundamental prerequisite for the specification of these cells, it downregulates nodal expression and is involved in controlling several essential "key genes" of cardiogenesis, such as Nkx2.5 and GATA4 (Bondue et al., 2008; Costello et al., 2011; Lindsley et al., 2008). MesP1 expression irreversibly

**FIGURE 1** Illustration, where the outer circle indicates the blastodisc and the elongate rectangle is the primitive streak. Segregation of cardiogenic progenitor cells in the primitive streak; highlighted in red: progenitor cells of the first heart field (FHF), early *MesP1* (mesoderm posterior 1) expression; highlighted in yellow: progenitor cells of the second heart field (SHF), late *MesP1* expression; CMs, cardiomyocytes; ECs, endocardial cells; EPDCs, epicardium-derived cells; SMCs, smooth muscle cells. Modified from Lescroart et al. (2014)



indicates the restriction of the development potential of cardiovascular progenitor cells (Lescroart et al., 2014).

After gastrulation, cardiogenic progenitor cells are located anterolaterally on both sides of the primitive streak in the lateral plate mesoderm (Dehaan, 1964; Rosenquist, 1970). While forming the intraembryonic coelom that subsequently develops into the pericardial cavity, the lateral mesoderm splits into a somatic and a visceral layer, leaving the cardiogenic mesoderm in the visceral part (Linask, Knudsen, & Gui, 1997).

## 1.2 | Development of the endocardium

Endocardial progenitor cells originate from small groups of cells that detach between E7 and E7.5 in mice and between HH5 and 8 in chickens in a craniocaudal direction from the ventral side of the visceral (subsequently cardiogenic) mesoderm (De Ruiter, Poelmann, Vanderplasdevries, Mentink, & Gittenbergerdegroot, 1992; Sugi & Markwald, 1996; Viragh, Szabo, & Challice, 1989). These cells are extruded from the prospective myocardial compartment and develop into endocardial cells. They are continuously expelled and gather ventrally close to the endoderm (Drake & Fleming, 2000; Linask & Lash, 1993).

There are some markers, such as *Nkx2.5* or *gata5*, which are expressed in both endocardial and myocardial progenitors; however, most myocardial-specific markers are not expressed in endocardial progenitors.

Misfeldt et al. (2009) propose a working model of cardiac differentiation from multipotent progenitors where endocardial cells are a unique cardiac lineage. *Flk1*<sup>+</sup>, *Nkx2.5*<sup>+</sup> and *Isl1*<sup>+</sup> multipotent cardiovascular progenitors capable of generating cardiomyocytes, endothelium and smooth muscle have been described. Our findings, coupled with fate-mapping studies, indicate that endocardial cells are derived from these progenitors.

Early studies reported that the visceral mesoderm and cephalic mesoderm located peripherally to the heart fields are involved in the formation of the endocardium (Noden et al., 1995). In birds, cells of the endoderm also contribute to the formation of the endocardium (Li et al., 2014), probably upon signals from the endoderm, that lead to a downregulation of the cell adhesion molecule N(neural)-cadherin in the overlying heart mesoderm (Linask & Lash, 1993).

The proendocardial cells are initially irregularly dispersed in an area ventral to the prospective myocardium. Subsequently, they establish contact with each other by changing their shape, to form cords that form plexuses that eventually enclose the lumen.

Contrary to the long-held idea that the heart is derived from two tubular primordia, more recent information has furthered our knowledge to show that this is not the case; rather, it develops from a single endocardial tube (De Ruiter, Poelmann, Mentink, Vaniperen, & Gittenbergerdegroot, 1993; De Ruiter et al., 1992; Drake & Fleming, 2000; Hara et al., 2016). The large plexuses of both sides of the bilateral cardiogenic mesoderm merge under the ventral folding of the embryonic blastodisc and subsequently form the single endocardial tube (De Ruiter et al., 1992, 1993; Drake & Fleming, 2000; Hara et al., 2016). Previous studies in chickens and mice report that when the bilateral heart primordia merge, the endocardium is still largely plexiform as well as incomplete and "immature," even after the establishment of the primitive heart tube (De Ruiter et al., 1992, 1993; Drake & Fleming, 2000; Hara et al., 2016).

The transcription factor *MesP1* and the cell surface molecules *Flk1* (fetal liver kinase 1, synonym *VEGFR2*) are believed to be the earliest common markers of cardiovascular progenitor cells in the primitive streak (Bondue et al., 2008; Saga et al., 1999, 2000). The differentiation of cardiovascular progenitor cells to proendocardial cells, or more precisely cardiac haemangioblasts, occurs in the primitive streak before or during gastrulation (Cohen-Gould & Mikawa, 1996; Lescroart et al., 2014; Milgrom-Hoffman et al., 2011; Wei & Mikawa, 2000). Recently,

it has been confirmed that the endocardium itself is a place of transient haematopoiesis (Hu et al., 2017; Nakano, Nakano, Smith, & Palpant, 2016; Nakano et al., 2013). The expression of Tal1 (T-cell acute leukaemia protein 1) that is potentially involved in the migration of this cell population during plexus formation inhibits the differentiation of cardiomyocytes, as does transcription factor ETV2 (Ets transcription factor variant 2). Two different tissue-specific enhancers of Tal1 guide the development of the cell population to form either angioblasts or haemoblasts (Hu et al., 2017; Schumacher, Bloomekatz, Garavito-Aguilar, & Yelon, 2013; Van Handel et al., 2012). By modulating Wnt and BMP (bone morphogenetic protein(s)) interactions, the membrane glycoprotein endoglin seems to promote the haematopoietic development of cardiovascular progenitor cells in a way that is poorly understood (Baik et al., 2016). Potential haematopoietic cells are characterized by a loss of Flk1 expression (Bussmann, Bakkers, & Schulte-Merker, 2007; Drake & Fleming, 2000; Hu et al., 2017; Van Handel et al., 2012).

In the course of the proendocardium's maturation, the endothelial markers PECAM (platelet endothelial cell adhesion molecule), CD (cluster of differentiation) 34, VE (vascular endothelial)-cadherin and Tie2 (TEK receptor tyrosine kinase 2) are gradually expressed, and the Tal1 expression is downregulated (Drake & Fleming, 2000).

The transcriptional network of the proendocardial cells is similar to that of haemangioblast progenitors from which other subtypes of the endothelium develop. However, due to the close proximity of the myocardium and its associated molecular influence, it is under the control of cardiogenetic transcription factors such as Nkx2.5, Islet-1 (insulin gene enhancer-binding protein), GATA4 and GATA5 (Palencia-Desai et al., 2015). The endothelial and haematopoietic determination factor Etv2 is activated directly in the endocardium, for example, by the heart-specific transcription factor Nkx2.5 (Ferdous et al., 2009). In endothelial as well as endocardial cells, it inhibits the expression of myocardial genes (Palencia-Desai et al., 2011). In murine embryos from E7.5, the transcription factor NFATc1 (nuclear factor of activated T cells 1) specific to the endocardium is induced directly by Etv2 and, along with GATA5, synergistically activates endocardial gene expression (De la Pompa et al., 1998; Nemer & Nemer, 2002; Palencia-Desai et al., 2011).

Endothelial and endocardial cells share fundamental molecular and functional characteristics. However, the functional and physical contribution to valvulogenesis, the development of the electrical conduction system and the formation of the septa as well as the coronary blood vessels prove the endocardium to be a special subpopulation of endothelial cells (Bi, Drake, & Schwarz, 1999; Hu et al., 2017; Mickoleit et al., 2014; Milgrom-Hoffman et al., 2011; Misfeldt et al., 2009; reviewed in Haack & Abdelilah-Seyfried, 2016).

### 1.3 | The development of coronary blood vessels

During early embryonic development, passive diffusion of oxygen and nutrients becomes inadequate for the optimal growth of the developing myocardium of the atria and ventricles in avian and

mammalian hearts. Hence, the establishment of the heart's own blood vessel system is essential (reviewed in Sedmera, 2011).

This consists of an arterial part that originates in the aortic root and a venous part that drains via the coronary sinus into the right atrium, as well as into interjacent capillaries. These blood vessels consist of a layer of endothelial cells that line the basal lamina internally and perivascular pericytes. However, in larger coronary arteries and veins a middle layer consisting primarily of smooth muscle cells (tunica media) is also found. An outer layer (tunica adventitia) that consists mostly of connective tissue and fibroblasts is restricted to larger segments of coronary arteries (Olivey & Svensson, 2010; reviewed in Sharma, Chang, & Red-Horse, 2017).

The development of coronary blood vessels is closely related to that of the epicardium, which contributes progenitor cells to the formation of vessel walls (De Ruiter et al., 1993; Mikawa & Gourdie, 1996). The intense mutual signal exchanges between cells within the subepicardial space, that is the adjacent epicardium, the epicardium-derived cells and the myocardium induces vasculogenesis of progenitor cells. While epicardium-derived cells have been acknowledged as a source of smooth muscle cells and perivascular fibroblasts in coronary vessel walls (Dettman, Denetclaw, Ordahl, & Bristow, 1998; Mikawa & Gourdie, 1996), the origin of coronary endothelial cells is still unclear and is the subject of much intensive research (Katz et al., 2012; Perez-Pomares, Carmona, et al., 2002; Red-Horse, Ueno, Weissman, & Krasnow, 2010; Wu et al., 2012; reviewed in Sharma et al., 2017).

It is well documented that coronary endothelial cells do not develop from epicardium-derived cells but are an independent cell population (Cossette & Misra, 2011; Katz et al., 2012; Poelmann, GittenbergerdeGroot, Mentink, Bokenkamp, & Hogers, 1993). It appears that the sinus venosus endothelium and endocardium are important sources of haemangiopoietic cells for the formation of the coronary blood vessels' endothelium. The earlier notion that endothelial cells of the coronary blood vessels develop by angiogenic sprouting from the aortic endothelium is obsolete (Hirakow, 1983; Red-Horse et al., 2010; Tian, Hu, Zhang, et al., 2013; Voboril & Schiebler, 1969; Wu, Dong, Regan, Su, & Majesky, 2013).

### 1.4 | The origin of coronary endothelial cells

The proepicardial serosa originates in the proliferating coelomic epithelium and is a heterogeneous cell population that consists of proepicardial Tbx18 (T-box transcription factor gene 18) and WT1 (Wilms tumour transcription factor 1)-expressing cells and other subpopulations, with differing and overlapping transcriptional profiles and haemangiopoietic characteristics. Over the past two decades, the notion that a large number of coronary endothelial cells originate from this pool of progenitors has become accepted (Cossette & Misra, 2011; Katz et al., 2012; Männer, 1999; Perez-Pomares, Phelps, et al., 2002; Poelmann et al., 1993; Wang et al., 2015). The sinus venosus endothelium as well as the atrial and ventricular endocardium has been identified as additional sources of

coronary endothelial cells (Red-Horse et al., 2010; Tian, Hu, Zhang, et al., 2013; Wu et al., 2012).

However, recent studies using specific reporter genes to follow the fate of different cells from the three progenitor sources have shown that the largest portion of the coronary endothelium originates from the endothelium of the sinus venosus and secondly from the endocardium, whereas the proepicardial endothelial progenitor cells' contribution amounts to <20% (Chen, Sharma, et al., 2014; Zhang et al., 2016). It remains subject to further research whether these three presumed coronary endothelial progenitor cell populations are clearly distinguishable from each other and whether they are the starting points of their own vasculogenic and angiogenic events.

### 1.5 | Development and proliferation of vascular plexus

The first step in the development of coronary blood vessels is the formation of primitive endothelial plexuses. Initially, these highly branched networks of small blood vessels are formed primarily by angiogenic sprouting of specific ("dedifferentiated") sinus venosus endothelium through the myocardium to the epicardial surface of the heart at the dorsal side of the atrioventricular canal (Chen, Sharma, et al., 2014; Patan, 2000; Red-Horse et al., 2010).

According to recent findings, haemangiopoietic progenitor cells and endocardial cells that have sprouted into the myocardium only play a minor part (Chen, Sharma, et al., 2014; Zhang et al., 2016).

In embryonic mice at about day 11.5, blood islands develop both subepicardially and later intramyocardially from migrating haemangioblasts. Pre-endothelial cells differentiated from the haemangioblasts connect with each other and coalesce into a series of tubes that then form vascular networks (vasculogenesis). Subsequently, these plexuses keep branching out by the processes of angiogenesis and expand subepicardially from where they penetrate the myocardium (Chen, Sharma, et al., 2014; Lavine et al., 2006; Tian, Hu, Zhang, et al., 2013).

The subepicardial plexuses that are located closer to the outer surface are the origin of venous blood vessels, whereas the intramyocardial plexuses located further away from the surface differentiate into arteries and capillaries (Lavine, Long, Choi, Smith, & Ornitz, 2008; reviewed in Sharma et al., 2017). Plexus formation is particularly pronounced in the area of future large blood vessels in the atrioventricular and interventricular sulci as well as at the ventriculo-arterial junction (Gonzalez-Iriarte et al., 2003; Männer, 1992).

The peritruncal circle of coronary blood vessels develops at the ventriculo-arterial junction and is a network of blood vessels from which, in 12.5-day-old embryonic mice, endothelial cells for the formation of the two proximal coronary artery trunks (*arteria coronaria dextra et sinistra*) are recruited. These endothelial strands penetrate through the largely undifferentiated progenitor cells of the tunica muscularis in the region of the opposing right and left sinus of the

aortic valves in order to ensure access to the systemic blood circulation (Chen, Poduri, et al., 2014; Poelmann et al., 1993; Tian, Hu, He, et al., 2013). From approximately E12.5, the coronary veins connect to the sinus venosus and later drain via the coronary sinus into the right atrium (Anderson, Brown, & Moorman, 2006; Katz et al., 2012).

### 1.6 | Regulation of vasculogenesis and angiogenesis

By the induction of vasculogenic and angiogenic signalling pathways, such as VEGF (vascular endothelial growth factor) A, angiopoietin (Ang) 1 and components of the sonic hedgehog signalling pathway, the epicardial transcription factor Tbx18 promotes subepicardial plexus formation (Wu et al., 2013). WT1, which is a transcription factor specific to the epicardium, activates the synthesis of retinoic acid in the epicardium by RALDH2 (retinaldehyde dehydrogenase 2) that in turn induces fibroblast growth factors (FGF) in the epi- and myocardium (Perez-Pomares, Phelps, et al., 2002).

The group of the vascular endothelial growth factors, especially VEGFA with its isoforms, are at the centre of vasculogenic and angiogenic regulation (Tammela, Enholm, Alitalo, & Paavonen, 2005; Tomanek, Holifield, Reiter, Sandra, & Lin, 2002; Tomanek et al., 2006). The induction of VEGFA in the myocardium takes place by epicardial retinoic acid-induced FGF9 secretion, whereby FGF receptors (FGFR) 1 and 2 are activated in the myocardium. In turn, these induce the expression of Shh (sonic hedgehog), a paracrine signalling protein that then activates myocardial VEGFA expression (Lavine et al., 2006).

For its part, VEGFA binds to the endothelial receptor VEGFR (vascular endothelial growth factor receptor) 2, which stimulates plexus formation. The soluble receptor VEGFR1 binds VEGFA and seems to be necessary to balance endocardial plexus formation (Zhang & Zhou, 2013).

VEGFC signals of the epicardium stimulate the sprouting of the sinus venosus endothelium into the subepicardial space (Chen, Sharma, et al., 2014). The same applies to myocardial Ang1 (Arita et al., 2014).

The interplay between VEGFs expressed in the myocardium that bind to receptors specific to the endothelium (VEGFR2) and FGFs (above all FGF2) is essential for the adequate growth of the endothelial plexuses, whereby VEGF primarily regulates tubulogenesis and FGF2 primarily regulates the proliferation of endothelial cells (Pennisi & Mikawa, 2005; Tomanek et al., 2001, 2010).

FGF2 and FGF18 seem to specifically stimulate the migratory capabilities of endothelial cells. Further FGFs (1, 4, 8, 9, 16, 20) expressed in the myocardium and epicardium only play a minor, possibly even redundant, role in the development of coronary heart vessels (Lavine et al., 2005; Tomanek et al., 2010). The growth factor Ang2 is also induced in the myocardium by Shh, along with VEGF (Lavine et al., 2006).

Myocardial expression of Ang1 seems to be regulated by the hormone erythropoietin. Erythropoietin is, like its receptor, expressed by endothelial cells and haematopoietic progenitor cells and is

essential for angiogenesis particularly in subepicardial blood vessels (Arita et al., 2014; Kertesz, Wu, Chen, Sucov, & Wu, 2004).

Ang1 and Ang2 are essential VEGF-independent parts of vasculogenic and angiogenic regulatory mechanisms that are mediated by their receptor Tie2, which is expressed on epicardial, endocardial and endothelial cells. Ang1 not only helps to maintain the integrity of epicardium, myocardium and endocardium, but also probably ensures the survival and migration of endothelial cells, as well as the stability of blood vessels (Augustin, Koh, Thurston, & Alitalo, 2009; Ward, Slyke, Sturk, Cruz, & Dumont, 2004). Ang2 is an Ang1 antagonist and functions mainly in regulating the Ang1 levels (Yuan, Khankin, Karumanchi, & Parikh, 2009; see Figure 2).

The myocardial transcription factor Fog (friend of GATA) 2 also plays an essential role during coronary angiogenesis by promoting proangiogenic factors and inhibiting anti-angiogenic factors (Zhou et al., 2009; reviewed in Sharma et al., 2017).

Hypoxia is an important stimulus during coronary development, particularly in the arterial outflow tract. In the myocardium of the outflow tract, local hypoxia induces the expression of transcription factors HIF (hypoxia-inducible factor) 1 $\alpha$  and HIF2. HIF1 $\alpha$  intensifies VEGF and VEGFR2 expression at the base of the aorta (Sugishita, Leifer, Agani, Watanabe, & Fisher, 2004; Wikenheiser et al., 2009). When the coronary artery stems are established in the area of the outflow tract, the production of VEGFC and the chemokine Cxcl12 (C-X-C motif chemokine 12) in particular is increased. These are essential for connecting the coronary plexuses, which bind these molecules by receptors VEGFR2/3 and Cxcr4 (C-X-C chemokine receptor type 4), respectively, to the aorta (Chen, Poduri, et al., 2014; Ivins et al., 2015). VEGFC and Cxcl12 are also both expressed by the stem of the pulmonary artery. However, the fact that the two coronary trunks establish at stereotypical places of the aortic trunk (right and left coronary sinuses of the aortic valves) and anastomose there with the aorta instead of the pulmonary artery is probably due to the specific occurrence of cardiomyocytes in the vicinity of the future entry points of the coronary arteries at the aorta (Chen, Poduri, et al., 2014). These cardiomyocytes probably produce a signalling molecule, still to be identified, that regulates/guides coronary endothelial cells. It is also possible that the BMP-signalling pathway,

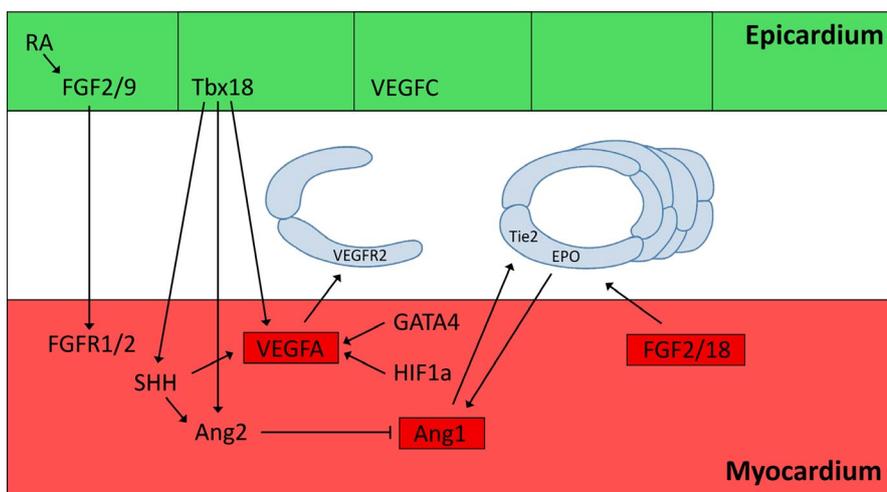
which is involved locally in these processes, plays a role in the cardiomyocyte-dependent determination of the entry points of the coronary trunks (Cavallero et al., 2015; Dyer, Wu, Moser, & Patterson, 2014; Ivins et al., 2015).

After anastomosing with the aortic endothelium and consequent supply with an arterial blood flow, remodelling of the entire coronary vascular plexus occurs, with expansion of the proximal blood vessels probably due to mechanisms such as fusion of smaller blood vessels and retrograde migration of endothelial cells (Lavine et al., 2008; Sato et al., 2010; Udan, Vadakkan, & Dickinson, 2013; Waldo, Willner, & Kirby, 1990).

## 1.7 | Establishment of arterial and venous identity of coronary vessels

From E12.5 (in mice) and HH31 (in chickens), the coronary artery trunks anastomose with the aorta. The resulting blood flow is the main trigger for the genotypical and phenotypical remodelling of coronary blood vessels, as is also the case for other vascular beds emerging during embryonic development (Chen, Poduri, et al., 2014; Ivins et al., 2015; Le Noble et al., 2004; Lucitti et al., 2007; Lucitti, Visconti, Novak, & Keller, 2006; Volz et al., 2015).

During the development of the coronary plexuses, the segregation of arterial (intramyocardial) and venous (subepicardial) blood vessels appears to take place, at least at a molecular level. This segregation manifests by the expression of ligand ephrin B2 in arterial endothelial cells and of its receptor EphB4 (erythropoietin-producing human hepatocellular receptor 4) in venous endothelial cells. This emphasizes the importance of a mutual exchange of signals between both endothelial types for the formation of arteriovenous branches and their connection patterns (Lavine et al., 2008; Wang, Chen, & Anderson, 1998). Ephrin B2 expression is probably induced by Notch ligands that are expressed only in the arterial endothelium, such as delta-like 4 and Jagged1. The activation of the Notch-signalling pathway, which is in turn activated by a VEGFA-VEGFR interaction (VEGFA from the myocardium, VEGFR of the endothelium), inhibits the venous differentiation of the endothelium and stabilizes the



**FIGURE 2** Transcriptional regulation of vasculogenesis and angiogenesis in the heart. RA, retinoic acid; Tbx18, Tbx18; VEGFA/C, vascular endothelial growth factor A/C; VEGFR2, vascular endothelial growth factor receptor 2; SHH, sonic hedgehog; Tie2, angiopoietin receptor/tyrosine kinase; EPO, erythropoietin; HIF1 $\alpha$ , hypoxia-inducible factor 1 alpha; GATA4, transcription factor GATA4; FGF2/9/18, fibroblast growth factor 2/9/18; FGFR1/2, fibroblast growth factor receptor 1/2; Ang1/2, angiopoietin 1/2

arterial identity (Fischer, Schumacher, Maier, Sendtner, & Gessler, 2004; Grieskamp, Rudat, Ludtke, Norden, & Kispert, 2011; Lawson et al., 2001; Lawson, Vogel, & Weinstein, 2002; Van den Akker et al., 2008; Wu et al., 2012).

Epicardium-derived cells that initially surround arterial coronary endothelial cells as pericytes express Notch3 upon the onset of blood flow, which activates receptor *Jagged1* on endothelial cells. *Jagged1* activity is essential for arteriogenesis (Del Monte et al., 2011; Domenga et al., 2004; Hofmann et al., 2012; Liu, Zhang, Kennard, Caldwell, & Lilly, 2010; Volz et al., 2015).

The Shh-signalling pathway is also, at least indirectly, involved in the determination of the arterial versus venous fate of the endothelium by promoting VEGF (Lavine et al., 2008). Specific Shh signals received by the myocardium are essential for the development of (subepicardial) coronary veins, whereas intramyocardial, arterial endothelial cells rely on Shh signals to the perivascular cells that surround them. In the case of the subepicardial plexuses, this probably involves a scattered production of VEGF, while in the case of intramyocardial plexuses the production of VEGF is more likely locally concentrated. Furthermore, this research points to the differentiation of arterial as opposed to venous blood vessels that take place earlier and is possibly dependent on VEGF concentration, which could also play a role in determining the endothelial identity (Lavine et al., 2008).

In addition, VEGF induces the expression of the enzyme endothelial nitric oxide synthase 3 (eNOS3), a local producer of nitric oxide. This substance has proven to be necessary for coronary arteriogenesis (Liu et al., 2014).

Little is known on the mechanisms of establishing the venous identity of specific coronary blood vessels. Along with exclusive expression of receptor EphB4, another feature of venous endothelium is the expression of transcription factor COUPTFII (chicken ovalbumin upstream promoter transcription factor II), which suppresses the Notch-signalling pathway (Lin, Tsai, & Tsai, 2007; You et al., 2005).

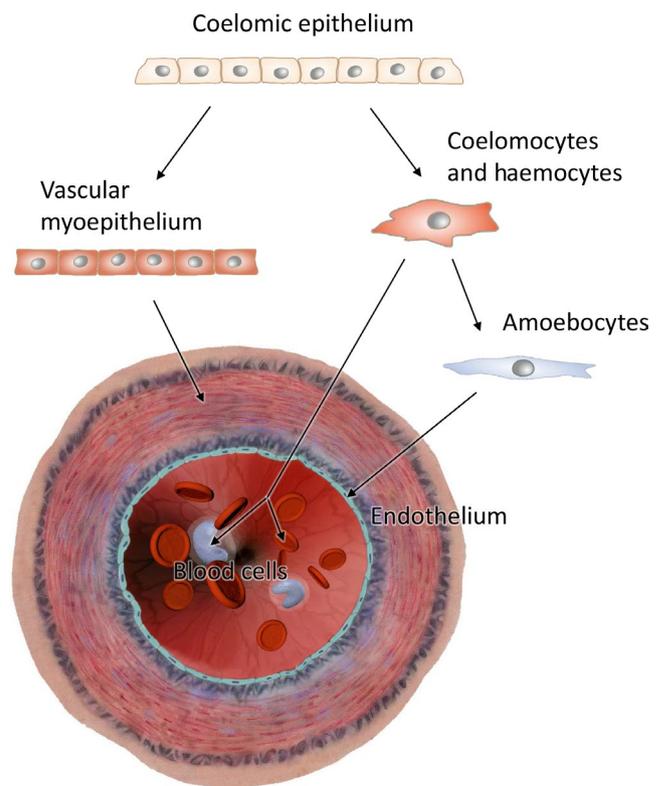
## 1.8 | Origin of cardiovascular cells

The coelom of primitive invertebrates, which serves to transport liquid nutrients, is lined with (myo-) epithelium and often divided by internal septa, was probably a precursor to the actual blood vessels of vertebrates. The latter developed dorsally and ventrally in the coelomic extracellular matrix (Ruppert & Carle, 1983). It is well established that the vascular smooth musculature and pericytes as well as the endothelial cells and blood cells were recruited initially from the coelomic epithelium (Hartenstein & Mandal, 2006; Munoz-Chapuli, Carmona, Guadix, Macias, & Perez-Pomares, 2005; Munoz-Chapuli et al., 1999; Rosenthal & Harvey, 2010; Ruppert, 2005; Xavier et al., 2007). In the living lancelet, the primitive blood vessels consist of smooth muscle cells only. It is assumed that endothelial cells originally evolved from ancestral blood cells, that is motile amoebocyte-like cells that originated in the coelomic epithelium and developed

intercellular junctions along the blood vessel walls (Munoz-Chapuli et al., 1999, 2005).

Crucial evolutionary advantages in the acquisition of an endothelium were probably an improved immune defence by local co-operation and communication with the blood cells, fine-tuning of blood flow and the ability to perform angiogenesis that facilitated the expansion of the blood vessel system to body regions far distant from the coelom (Rosenthal & Harvey, 2010). According to this hypothesis, cardiovascular cells originate in the embryonic coelomic serosa, where muscle progenitor cells (vascular smooth muscle cells and cardiomyocytes) developed along separate lines from haemangioblasts (Hu et al., 2017; Lescroart et al., 2014; Rosenthal & Harvey, 2010). Thus, the common archetype of the vertebrate heart may be traced back to the organization of a layer of contractile myocytes that originated in the embryonic coelomic epithelium and was secondarily lined by endothelium/endocardium (Xavier et al., 2007; see Figure 3).

Beyond the initial events of intraembryonic vasculogenesis that result in the formation of a primitive heart tube, primitive aortae and vitelline veins, the embryonic coelomic epithelium retains its ability to proliferate locally and produce pre-vascular cells. This primarily occurs in the vicinity of developing internal organs such as the liver primordium or in the aorta-gonad-mesonephros region that



**FIGURE 3** Hypothesis of the phylogenetic development of the immediate ancestor of the vascular progenitor that according to Rosenthal and Harvey (2010) is the coelomic epithelium. This gives rise to the vascular smooth muscle cells, endothelium and blood cells. Modified from Rosenthal and Harvey (2010)

probably send signals inducing vasculogenesis (Arima et al., 2012; Rosenthal & Harvey, 2010).

A large proportion of the progenitor cells of the coronary heart vessels that secondarily colonize the heart, originate in the highly proliferating coelomic epithelium as well. The proepicardial serosa in the caudal pericardial cavity differs from the original cardiogenic mesoderm *sensu stricto* by its prominent, “cauliflower-like” shape and in its transcriptional profile (Männer, 1992; Mommersteeg et al., 2010; Van Wijk et al., 2009). It is assumed that this cardiogenic cell population is an evolutionary derivative of the primordium of a primeval external renal glomerulus (Cano, Carmona, Velecela, Martinez-Estrada, & Munoz-Chapuli, 2015; Pombal et al., 2008).

There is clear and uncontentious evidence that proepicardial cells give rise to vascular smooth muscle cells as well as pericytes of coronary heart vessels (Christoffels et al., 2009; Perez-Pomares, Phelps, et al., 2002; Schlueter, Manner, & Brand, 2006). However, the origin of coronary angioblasts has not been ascertained beyond doubt. Some experiments show evidence in favour of a common origin along with coronary smooth muscle cells and pericytes in the proepicardial serosa with a similar or differing transcriptional profile (Cossette & Misra, 2011; Guadix, Carmona, Munoz-Chapuli, & Perez-Pomares, 2006; Katz et al., 2012; Perez-Pomares, Phelps, et al., 2002). Others negate this connection and refer to the endocardium and sinus venosus endothelium as the source of coronary endothelial progenitor cells (Grieskamp et al., 2011; Red-Horse et al., 2010; Tian, Hu, Zhang, et al., 2013; Wu et al., 2013). According to this view, sinus venosus endothelium and endocardium sprout by angiogenesis in order to penetrate the myocardium to finally reach the subepicardial surface of the heart and expand further by forming coronary plexuses (Grieskamp et al., 2011; Red-Horse et al., 2010; Tian, Hu, Zhang, et al., 2013; Wu et al., 2013). More recent research proves that the predominant part of coronary endothelial cells originates in the sinus venosus endothelium, closely followed by the endocardium, whereas fewer than 20% of cells originate in the proepicardial serosa (Chen, Sharma, et al., 2014; Zhang et al., 2016).

It is remarkable that of the three WT1-negative endothelial progenitor cell populations in the murine proepicardial serosa discovered by Cossette and Misra (2011), one is associated with the liver bud and another with the sinus venosus endothelium. The third progenitor population does not seem to bear any relation to adjacent tissue. Derivatives of the two coronary endothelial progenitor populations in the proepicardium identified by Katz et al. (2012) were discovered in the endothelium of the sinus venosus and in parts of the endocardium. If these links are combined with the fact that the sinus venosus endothelium originates in the proliferation zone of the proepicardial serosa, it can be speculated that proepicardial coronary endothelial progenitors are identical to the prospective coronary endothelial cells, discovered by Red-Horse et al. (2010), Tian, Hu, Zhang, et al. (2013), Wu et al. (2013), Chen, Sharma, et al. (2014) and Zhang et al. (2016) in the sinus venosus endothelium and the endocardium. The different expression of tissue-specific markers in these three presumed progenitor populations can possibly be explained by the molecular influence of their environments. Hence,

it would no longer be necessary to distinguish between different sources of coronary endothelial progenitor cells, but between alternative migration routes of the cells that originate in the proepicardial serosa (a) from the proepicardial serosa via the pericardial cavity to the surface of the heart and (b) from the proepicardial serosa via the sinus venosus endothelium and endocardium of the primitive heart tube to the myocardium and subepicardial space. On the other hand, there is clear evidence that the endocardium has the ability to generate haemangiopoietic progenitor cells, which is why it could well be a source of endothelial progenitor cells, independent of the proepicardium (Nakano et al., 2013).

Studies of the fins of zebrafish and of the retinae of mice showed that in newly developing vascular beds, the arterial endothelium arises mostly from venous endothelium (Xu et al., 2014). This also seems to be true for the coronary vascular bed, since both sinus venosus endothelium and the subepicardial plexus, from which arterial intramyocardial plexuses develop, display a venous phenotype. Furthermore, this contradicts the assumption that the arterial and venous parts of coronary blood vessels originate from different sources (endothelium/endocardium vs. proepicardial serosa; Wu et al., 2012). However, a compartmentalization of the coronary endothelium in terms of the migration route of its progenitor cells and its immediate place of origin is very likely (heart endothelium vs. epicardium; sZhang et al., 2016; reviewed in Sharma et al., 2017).

## 2 | CONCLUSION

This review summarizes recent advances in research on vasculogenesis and angiogenesis in the context of avian and mammalian cardiogenesis. Obsolete concepts are critically commented upon, and relevant morphogenetic events in association with the underlying molecular regulatory mechanisms are briefly recapitulated. However, due to the complexity of the subject, several aspects, such as the field of epithelial- and endothelial-to-mesenchymal transition during cardiovascular development, have not been mentioned. We are only starting to understand these events in cardiogenesis—and this is only one organ system. In the light of the tremendous increase in knowledge, it will be a huge challenge for anatomists, histologists and embryologists to teach coming generations of students the overview necessary to navigate through their professional life and at the same time give them an idea on the enormous complexity of these subjects (Borasch, 2019).

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## CONFLICT OF INTEREST

The authors declare they have no conflict of interest with respect to publication of this review.

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