Development of the cardiovascular system in vertebrate embryos

Science, Anatomy

The cardiovascular system is the first organ system to become fully functional in the vertebrate embryo and its development occurs in a similar way in all vertebrates. It is derived from angioblastic tissue, which arises from mesenchyme, an aggregation of mesenchymal cells derived from the mesodermal tissue of embryos. The main processes involved in the development of the embryonic cardiovascular system are Vasculogenesis, Angiogenesis, Hematopoiesis, Erythropoiesis and Heart Formation. All processes occur under the influence of stimuli from genes and paracrine factors, oligosaccharides, multifunctional cytokines and enzymes.

Vasculogenesis and Angiogenesis

Two distinctive mechanisms, vasculogenesis and angiogenesis implement the formation of the vascular network in the embryo. Embryonic vasculogenesis gives rise to the heart and the primordial vascular plexus within the embryo and its surrounding membranes as the yolk sac circulation. In mammals, it occurs in parallel to hematopoiesis, the formation of blood cells. Vasculogenesis refers to the in situ differentiation and growth of new blood vessels from mesenchymal cells known as angioblasts which aggregate to form isolated angiogenic cell clusters known as blood islands (angiocysts) within the extra-embryonic and intra-embryonic mesoderm. Small cavities appear within these blood islands by the confluence of intercellular clefts.

The peripheral cells within these blood islands flatten to form endothelial cells, triggered by the binding of the Vascular Endothelial Growth Factor (VEGF) to the first of its two receptors, the VEGF-R2 (Flk1) protein, which is

responsible for the differentiation of mesodermal cells into endothelial cells and the subsequent proliferation of the endothelial cells. The core cells give rise to blood cells (haematoblasts). The newly formed endothelial cells arrange themselves around the cavities in the blood islands, forming the primitive endothelium. Cellular vacuoles within the developing endothelial cells coalesce and fuse together without cytoplasmic mixing to forma the blood vessel lumen of the initial endothelial tube.

Extracellular matrix deposition by fibroblasts promotes capillary-like tube formation under the influence of the binding of VEGF to its second receptor, VEGF-R1 (Flt1). This is followed by the interaction of the endothelial blood vessel with the supporting mesodermal cells. The Angiopoietin-1 growth factor binds to the Tie2 receptor tyrosine kinase on the cell membrane of the endothelial cells, allowing the blood vessel to recruit the peri-endothelial cells that will surround it as pericytes and the smooth muscle tissue of the blood vessel, thus maintaining the stability of the blood vessels.

The growth and multiplication of this primordial vascular plexus occurs through the process of angiogenesis in which new blood vessels arise from pre-existing vascularity. This process requires the combination of two signals, Angiopoietin 2 and VEGF, in order to promote the loosening of the support cells and the ability of newly exposed endothelial cells to multiply by budding and sprouting into new vessels. Replacement of Ang1 by Ang2 on the Tie2 receptor tyrosine kinase destabilizes the vessel integrity thus facilitating vessel sprouting in response to the VEGF signal. The new endothelial tubule then interacts with the surrounding mesenchymal cells in

part as a response to Ang1 which acts on the endothelial cell Tie2 in order to trigger the association of the new tubule with the periendothelial cells.

Hematopoiesis and Erythropoiesis

Blood develops from endothelial cells (haematoblasts) by a process known as hematopoiesis initially in various parts of the embryonic primitive mesenchyme (yolk sac and allantois), and then in the liver and later on in the spleen, bone marrow and lymph nodes. In embryonic development it is known as primitive hematopoiesis. All blood cells develop from pluripotential stem cells committed to three, two or one hemopoietic differentiation pathways but morphologically undistinguishable. These pluripotent stem cells divide infrequently to generate either more pluripotent stem cells (self-renewal) or committed progenitor cells (colony-–forming cells, CFCs) which are irreversibly determined to produce only one or a few types of blood cells.

These colony-forming cells are known as Lymphocyte Forming Colony (LCFC), Megakaryocyte Forming Colony (MCFC), Erythrocyte Forming Colony (ECFC) and Monocyte Granulocyte Forming Colony (MGFC). The progenitor cells are stimulated to proliferate by specific growth factors (colony-stimulating factors, CSFs) but progressively lose their capacity for division and develop into terminally differentiated blood cells which usually live for only a few days or weeks. Erythrocytes (red blood cells) develop by the process of erythropoiesis. In embryos, erythrocytes are nucleated and express embryonic globin chains.

Heart Formation

In vertebrate embryos the heart tube, the earliest formed heart structure, arises in the heart field, an embryonic clustering of cells which arises soon after gastrulation. These early stages of development are almost identical among all vertebrates unlike the subsequent septation of the chambers and of the outflow tract which varies between species.

The heart field is that region of the precardiac mesoderm that contains the cardiac progenitor cells (endocardial and myocardial precursor cells) and is competent in responding to inductive signals.

Precardiac cells from the epiblast lateral to the primitive streak invaginate through the streak and migrate cranio-laterally to form part of the lateral plate. This pattern is maintained in the eventual anteroposterior placement of structures in the heart, with the most cranial cells contributing to the bulbus cordis at the extreme anterior end of the heart and the most caudal cells contributing to the sinoatrial region and the extreme posterior end.

As mentioned above, the cell progeny of this region contributes to all layers of the heart tube (myocardium, endocardium and parietal pericardium), as well as to the endothelial cells in the vicinity of the heart. In the lateral plate the cells maintain their anteroposterior position.

The lateral plate splits to form two epithelial layers, the somatic mesoderm (which also includes migratory precursors for limb musculature) and the splachnic mesoderm which remains an epithelial sheet and includes the cardiac precursors.

The embryo then folds ventrally carrying the splachnic mesoderm with it and bringing it ventral to the foregut which is generated as the lateral folds meet in the ventral midline. The precursors of the endocardium are included in the splachnic mesoderm and begin to form clusters on the foregut side of the epithelial sheet.

The heart fields fuse at the midline to form a primary heart tube, the process beginning cranially and proceeding caudally. This tubular heart consists of an outer myocardial mantle and an endocardial inner lining. Between these two concentric epithelial layers an acellular matrix, the cardiac jelly, is found. As the ventricular region of the heart begins to bend to the right (" cardiac looping"), the cardiac jelly disappears from the future major chambers of the heart (atria and ventricles) and begins to accumulate in the junction between the atria and ventricles (atrioventricular junction, AVJ) and in the developing outflow tract (OFT).

This results in the formation of the endocardial cushion tissues in the AVJ which later contribute to the formation of AV (atrioventricular) septal structures and valves, septation of the OFT and formation of the semilunar valves of the aorta and pulmonary artery.

The vertebrate heart tube is aligned along the antero-posterior axis. Arterial flow is directed from the ventricle at the anterior end of the heart, through the ventral aortic vessel and branchial arches and subsequently travels posteriorly to the dorsal vessel. Blood flow returns to the heart through the venous system to the atrium lying at the posterior end of the heart chamber.

Formation of the Mammalian Embryonic Cardiovascular System

1) Formation of the primitive cardiovascular system

a) Extra-embryonic blood vessels

The wall of the yolk sac mesenchyme proliferates and forms isolated cell clusters known as blood islands. Peripheral cells within these islands flatten and differentiate into endothelial cells in order to form endothelial tubes. Centrally- located cells develop into primitive blood cells (hematoblasts). Endothelial tubes approach and fuse with each other forming a primitive vascular network. This primitive endothelial network appears in the chorionic membrane and body stalk and connects to the vitelline circulation.

b) Intra-embryonic blood vessels

The endothelial tube network appears in the intraembryonic mesenchyme to form an intraembryonic endothelial tube network. The intraembryonic and extra embryonic tube networks connect to each other forming a diffuse endothelial tube network which either fuses or disappears to form a primitive cardiovascular system.

2) Development of the Heart

The primitive cardiovascular system consists of the primary heart tube, formed from the fusion of the two bilateral heart fields of the precardiac mesoderm. The primary heart tube gives rise to the endocardium. Blood flows through this primitive heart tube in a cranial position. The mesenchyme surrounding the tube condenses to form the myoepicardial mantle (the future myocardium). Gelatinous connective tissue, the cardiac

jelly, separates the myoepicardial mantle from the endothelial heart tube (the future endocardium).

A series of constrictions (sulci) divides the heart into sections: the sinus venosus, in which the common cardinal veins, the umbilical veins and the vitelline veins drain; the primitive common atrium; the primitive common ventricle; and the bulbus cordis through which blood flows to the paired dorsal aortae. The paired dorsal aortae arise when the branchial or pharyngeal arches are penetrated by six pairs of arteries called aortic arches. These arteries arise from the aortic sac and terminate in a dorsal aorta. Initially, the paired dorsal aortae run along the whole length of the embryo but soon fuse to form a single dorsal aorta just caudal to the branchial or pharyngeal arches.

The arterial and venous ends of the heart tube are fixed by the branchial or pharyngeal arches and the septum transversum, respectively. At this stage the heart is beating and the contractions are of myocardial origin and likened to peristalsis.

The primitive atrium loops up behind and above the primitive ventricle and behind and to the left of the bulbus cordis forming the bulboventricular loop.. This looping process brings the primitive areas of the heart into the proper spatial relationship for the further development of the heart.

Embryonic venous circulation consists of three pairs of veins: the vitelline veins which drain blood from the yolk sac, the umbilical veins which bring oxygenated blood from the chorion (early placenta), and the common cardinal veins which return blood to the heart from the body of the embryo.

Arterial circulation consists of three paired arteries: the intersegmental arteries, which form 30-35 branches of the dorsal aortae and carry blood to the embryo, the vitelline arteries which pass to the yolk sac and later to the primitive gut, and the umbilical arteries which carry oxygen-depleted blood to the placenta.

3)   Formation of the Heart Chambers

As mentioned above, during cardiac looping the cardiac jelly disappears from

the future major chambers of the heart and begins to accumulate in the atrioventricular junction (AVJ) and developing outflow tract (OFT). This results in the formation of the endocardial cushion tissues in the dorsal and ventral walls of the AVJ. These cushions are invaded by mesenchymal cells, approach each other and fuse, dividing the atrioventricular canal into the right and left atrioventricular canals.

The primitive atrium is divided into right and left atria by the formation, modification and fusion of the septum primum and the septum secundum. The septum primum grows towards the fusing endocardial cushions from the roof of the primitive atrium creating a curtainlike septum, the foramen primum between the free edge of the septum and the endocardial cushions.

This foramen becomes progressively smaller and eventually disappears when the septum primum fuses with the fused endocardial cushions (atrioventricular septum). The septum secundum grows from the ventrocranial wall of the atrium to gradually overlap the foramen secundum

in the septum primum, forming an incomplete separation between the atria in the form of an oval opening, the foramen ovale.

The sinus venosus initially opens into the center of the dorsal wall of the primitive atrium and its left and right horns are of about the same size. The right horn progressively begins to enlarge inrespectto the left horn until it receives all the blood from the head and neck via the superior vena cava and the placenta and caudal regions of the body via the inferior vena cava. The left horn forms the coronary sinus.

The wall of the left atrium is formed by the incorporation of the primitive pulmonary vein which develops as an outgrowth of the dorsal atrial wall. As the atrium expands, the primitive pulmonary vein and its branches are gradually incorporated into the wall of the left atrium forming four pulmonary veins with separate openings.

The division of the primitive ventricle into the right and left ventricles is initially indicated by a muscular ridge with a concave free edge in the middle of the ventricular floor near its apex. Initially, most of its increase in height results from the dilation of the ventricles on its each side. Later, however there is active proliferation of myoblasts, forming the thick muscular part of the interventricular septum.

At the beginning a crescentic interventricular foramen exists between the free edge of the interventricular septum and the fused endocardial cushions allowingcommunicationbetween the right and left ventricles. This foramen closes as the result of the fusion of tissue from three sources: 1) the right bulbar ridge, 2) the left bulbar ridge and 3) the endocardial ridges. The

membranous part of the interventricular spetum is derived from tissue extension from the right side of the endocardial cushions. It merges with the aorticopulmonary septum and the thick muscular part of the interventricular septum. When the interventricular foramen closes, the pulmonary trunk is in communication with the right ventricle and the aorta communicates with the left ventricle.

Active proliferation of mesenchymal cells in the walls of the bulbus cordis gives rise to the formation of the bulbar ridges. Similar ridges form in the truncus arteriosus and are continuous with the bulbar ridges. Both the bulbar and the truncal ridges have a spiral orientation and result in the formation of a spiral aorticopulmonary septum when the bulbar and truncal ridges fuse. This septum divides the bulbus cordis and the truncus arteriosus into the aorta and pulmonary trunk.

Due to the spiral orientation of the aorticopulmonary septum, the pulmonary trunk twists around the aorta. The bulbus cordis is incorporated into the walls of the ventricles. In the left ventricle it forms the walls of the aortic vestibule just inferior to the aortic valve. In the right ventricle it forms the infundibulum or conus arteriosus.

Ventricular trabeculation begins in the apical region of the ventricles soon after cardiac looping. The trabeculation serves primarily as a way of increasing the oxygenation of the myocardium in the absence of a coronary circulation. The compactation of the trabeculae adds to the proportion and thickness of the compact myocardium.