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EDITORIAL

Growing the Coronary Tree: The Quail Saga

Coronary vessel development has become an active area of research thanks to the rediscovery of the precursors of the epicardium and coronary vessels and the deployment of new techniques. A long-time leader in the field, Dr. Robert Tomanek provides us with a paper in this issue that calls our attention to several important aspects of coronary vessel development in the quail, a valuable animal model for these investigations. His findings also bring up many "why" questions that underscore how much more work is required to understand fully how normal and abnormal coronary vessels develop and function or malfunction. Insights from these data would be relevant for therapy in adult diseases where new vessel growth is required, such as after heart attacks, or needs to be suppressed, as in cancer.

Once the size and metabolic activity of an animal exceed the limits of diffusion, a circulatory system becomes a necessity. The same rule applies to individual organs, and the heart is an interesting example of an organ that solved this problem in unique ways, both phylogenetically and ontogenetically. The primitive pulsatile vessels or even sophisticated hearts of more complex invertebrates such as large marine crustaceans or mollusks are devoid of coronary vascularization. Instead, if an increase in myocardial mass is desired, the heart muscle is organized into a spongy meshwork of trabeculae. The same arrangement of myocardium can be found even in some lower vertebrates, typically cold-blooded, relatively sedentary animals with low blood pressure, notably some fish (Ostadal and Schiebler, 1971; Tota et al., 1983) and amphibian species such as Xenopus, that has a coronaryless ventricle, although with rudimentary coronary vessels supplying the atrioventricular canal and the arterial pole (Sedmera et al., 2003).

Unlike most organs in the vertebrate body, the heart has to function continuously from very early stages of its development to support the embryo's growth. Consequently, the coronaryless stages are recapitulated in the ontogenesis of the higher vertebrates, and the lacunar system of the trabeculated heart was recognized more than a century ago (Minot, 1901; Rychter and Ostadal, 1971) as a means to increase surface:volume ratio to facilitate exchange of nutrients and oxygen.

The coronary blood supply becomes necessary at the point when increasing circulatory demands cannot be met by the trabeculated heart. Obviously, it would be too late to start recruiting parts and constructing coronary vessels when they are acutely needed; indeed, their development starts at the early trabeculated stages as soon as the heart becomes covered by the epicardium (reviewed in Tomanek, 2005). Interestingly, this is the time when hypoxia can be detected in the OFT myocardium by hypoxia indicator EF5 (Sugishita et al., 2004).

The development of coronary arteries is typically divided into three steps. In the first step, delamination of migratory cells from the epicardial mesothelium occurs, and these multipotent precursors invade the heart. Proliferation and coalescence of these precursors produce the primitive vascular network (vasculogenesis), and some of these pluripotential cells give rise also to blood islands. This was demonstrated by Tomanek et al. (2006) using retrovirus lineage tracing that proved the blood cells and endothelial cells share common precursors. In the second step, further growth occurs by sprouting (angiogenesis) from this primitive network. The critical event culminating in this period is the connection of this network to the circulation, similar to plumbing systems, with the venous end connected first, then the arterial end later (Vrancken Peeters et al., 1997). The last step, involving differentiation and patterning of the arterial and venous parts of the coronary system, occurs after the connection to circulation and is probably in part controlled by the hemodynamic signals from the lumen. Differential hypoxia of the myocardium and subsequent activation of hypoxia-inducible factors such as HIF-1 may play a role in organizing the large vessels of the coronaries at the atrioventricular and interventricular sulci (Wikenheiser et al., 2006).

Much of our knowledge about the coronary development comes from studies in the avian systems, in particular the Japanese quail (*Coturnix coturnix japonica*). Apart from the advantages inherent in in ovo systems (easy access for experimental manipulations, low cost), avian systems offer the opportunity of simple lineage tracking experiments using quail-chick chimera with detection of transplanted cells using quail-specific antibodies (QCPN, quail nuclear marker; QH1, quail endothelial and hemangioblast marker). Studies employing these techniques have shown that epicardial-derived cells give rise to all cell

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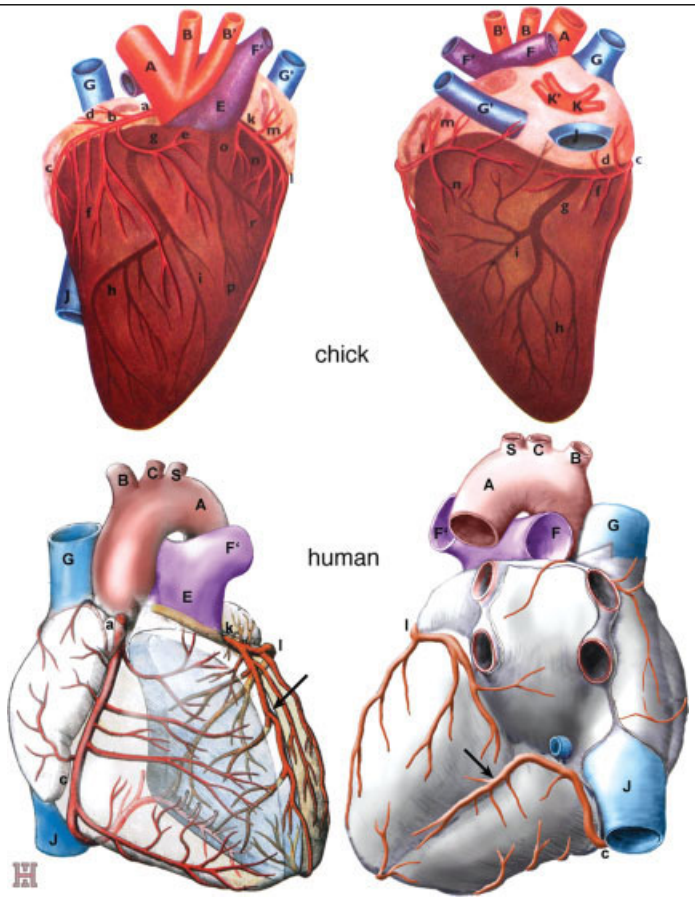

Fig. 1. Anatomy of coronary arteries in the chick. Note that in contrast to human heart [redrawn by Ivan Halekal based on Cihak's (2004) textbook of human anatomy], there are no distinct superficial interventricular branches (marked by arrows in human) on either surface. The origin and course of the circumflex branches in the atrioventricular sulcus (a–c, k–l) are, however, comparable. Other differences in the bird include right-sided aortic arch (A), two (right and left) brachiocephalic arteries (B, B′), and left superior caval vein (G′). Reproduced from Komarek et al. (1982) with permission.

types found in the coronary vessels (Vrancken Peeters et al., 1997).

While there is little doubt that the main principles governing coronary vessel development are conserved between birds and mammals, when it comes to typical adult pattern of coronary arteries, there are some important differences to account for. Both birds and mammals have typically two coronary arteries, originating from the left and right aortic sinuses. However, it is the branching pattern that presents significant deviations (Fig. 1). These differences would be important to understand in order to extrapolate from findings using avian model systems.

While the human (as an example of mammals that is thoroughly described in a host of widely available anatomical atlases) has prominent anterior and posterior interventricular arteries (thick enough for surgeons to put a bypass graft on), the stems of the chicken coronary arteries stay in the atrioventricular sulcus, sending only rather small branches to the atria and ventricles. On the other hand, consistently present is a major septal artery (off the right coronzary) that does not have a counterpart in mammals. Differences exist also in the arrangement of cardiac veins, with the chick lacking the coronary sinus and having the left superior caval vein (Komarek et al., 1982).

The paper by Tomanek et al. in this issue fills in some significant gaps of our knowledge of normal coronary patterning in birds. Focusing on the quail as the most popular model system of coronary vasculogenesis, it gives us a detailed account of what is going on during incubation days 6–18, a period that has received scanty attention from previous investigators. Using a combination of powerful morphological techniques (TEM, serial sections, double immunohistochemistry), the authors provide a detailed chart of arterial differentiation and patterning. They show that anastomoses between the coronary network and the ventricular lumen described previously (Rychter and Ostadal, 1971) are exceptions rather than the rule. Smooth muscle actin staining shows a gradient in differentiation from the base toward the ventricular apex, providing a valuable time line for future experimental studies. This time chart includes changes in extracellular matrix and sympathetic innervation. Of particular interest is the detection of apoptotic figures in the vessel wall, suggesting programmed cell death as a mechanism of pruning of anastomoses to achieve the definitive pattern. Likewise, it is involved in the mechanism of establishing the connection of the left and right coronary artery with the aorta. The development of coronary arterialization is correlated with increasing thickness of the compact myocardium, corroborating the results obtained in previous studies (Sedmera et al., 2000).

Apart from answering some important questions, this study also leads to new ones. Among the most in

triguing is how the exact site of penetration of the aorta by the periaortic vascular ring is determined. The site of penetration seems to be tightly regulated and conserved among species. Uncovering this mechanism would improve our understanding of occasional abnormal position of coronary artery orifices. These coronary anomalies, such as anomalous left coronary artery originating from the pulmonary artery (ALCAPA), may be rare, but can have serious consequences such as sudden cardiac death (Kandzari et al., 2002). The elimination of intercoronary anatomoses during the remodeling phase seems to be dependent on flow through the network and shows significant variability between species. Enhancement of such anastomoses could help alleviate myocardial ischemia, which is one of the major diseases in developed countries. Both of these processes mentioned above seem to involve apoptosis, but the spatiotemporal control of apoptosis certainly needs further investigations. Sympathetic control of coronary blood vessels is physiologically important, but the signals that control this innervation are not known. Blood vessels and nerves tract together and recent work suggests that they may use the same signals to find their way and that they also communicate with each other (reviewed in Eichmann et al., 2005). The findings from and techniques used in these studies in other systems such as the retina may provide insight into the location of cardiac ganglia, control of innervation of coronaries, and the preferential concentrated innervation of the parts of the pacemaking and conduction system. Lastly, impaired coronary vascularization is associated with various forms of noncompacted cardiomyopathy (Jenni et al., 2001). Total failure of coronary artery development in mouse mutants is associated with a thin compact myocardium and mid-gestation lethality (reviewed in Sedmera et al., 2000). Partial localized defects correlate with persisting trabecular (sinusoidal) myocardium and lead to impaired ventricular contractility or sudden cardiac death (Varnava, 2001). Dissection of the molecular cross-talk between the myocardium and coronary arteries, which might direct the growth of vessels and induce conduction fiber differentiation by the arteries (reviewed in Gourdie et al., 2003), would shed more light on this so far obscure entity.

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