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INTRODUCTION

The complexity of the developing and functioning heart has always intrigued scientists. One of the many ambiguous areas in the understanding of cardiac development is the role of a gelatinous substance commonly referred to as cardiac jelly, (Davis, 1924) and more recently the myocardial basement membrane (Little and Rongish, 1995). Researchers have been studying this material to determine its roles. Their studies led them to believe that this jelly-like substance may be involved in vital embryological roles including the actual morphogenesis of the heart, such as heart valve formation and pumping. When cardiac jelly was enzymatically removed, the morphology of the heart changed because cardiac jelly exerted a force on the cardiac tissues which influenced morphogenesis (Mironov et al. 2005). The components of the cardiac jelly are thought to play roles in regulating cell shape, migration, proliferation, and differentiation. They are involved in the binding of growth factors that control cell behavior and cell-to-cell communication and it is targeted in controlling gene expression and maintenance of tissue related functions. With congenital heart malformation leading human birth defects- it occurs in 1% of all births-the analysis of cardiac jelly can lead to a better understanding of the way the heart develops and runs and can ultimately lead to a technique that mends those deformities (Little and Rongish, 1995; Eisenberg and Markwald, 1995).

Development of Cardiac Jelly

Cells commit themselves to become cardiogenic during gastrulation. They arrange themselves into bilateral tubes composed of an inner endocardium and an outer epimyocardium that will later become the muscular outer tube of the heart. Between these two layers lies a primitive extracellular matrix, which will later contribute to the cardiac jelly. In stage 7 or 8 of cardiac development, this matrix contains basement membrane proteins among other components. At stage 9, the bilateral tubes fuse and two concentric layers, the myocardium and endocardium, are apparent. (Little and Rongish, 1995; Moore, 2008). There are two distinct regions present as well; cranial, which contains the primordium of the right ventricle, and caudal, which contains the trabeculated portion of the left ventricle. At stage 10 this tube begins to beat. During the loop stage, stage 12, the primordia of the right ventricle and aorta are present. This stage is characterized by a looping process that changes the shape of the heart drastically. It is at this stage that the extracellular matrix is referred to as cardiac jelly. In stages 14-17, heart chambers and valves are forming. Swelling can be found in the matrix while the endocardium of the atrioventricular canal and outflow tract are transformed into mesenchymal cells which invade the cardiac jelly and are now called cardiac

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cushions. Many of the components found in cardiac jelly aid this transformation (Little and Rongish, 1995).

Composition and Location of Cardiac Jelly

Cardiac jelly is composed of three main substances; collagens (I, III, IV), glycoproteins, like fibronectin, laminin, and fibrillin, and mucopolysoaccharides (glycosaminoglycans) such as hyularonate, chondroitin, and heparin (Hurle et al. 1980; Little and Rongish, 1995). Both the shape of the cardiac jelly and the internal pressure of the heart may come from the glycosaminoglycans and proteins found in the cardiac jelly (Nakamura and Manasek, 1981).

There are also fiber components of cardiac jelly which are arranged in a radial orientation (Taber et al. 1995). It consists of a myocardial basement membrane that has a lamina densa and an extended lamina reticularis and an endocardial basement membrane with only a lamina densa. Together, the matrix is distributed unevenly with thin amounts of jelly located at the ventral and dorsal midlines of the heart and thicker amounts at the original left and right sides of the heart. This arrangement will be extremely important later on in the role of pumping which is aided by cardiac jelly. Because of this uneven distribution, the endocardial tube does not exhibit a circular profile. (Manner et al. 2008). The difference in thickness between the bulbus cordis (embryonic right ventricle and embryonic outflow tract) and the ventricular segment (embryonic left ventricle) of the heart loop are a result of differences in the thickness of the cardiac jelly itself (Manner et al. 2006).

The cardiac jelly also has a distinct shape that reflects the shape of the heart. This allows the outer myocardium to be removed without affecting the shape of the cardiac jelly (Nakamura and Manasek, 1978).

In terms of location, the primary heart tube consists of an outer myocardium and inner endocardium (Eisenberg and Markwald, 1995) separated by a layer of cardiac jelly (Armstrong and Bischoff, 2004). Cardiac jelly is located along the entire length of the primitive heart; however, researchers separated cardiac jelly based on its location. Either cardiac jelly is found between the myocardium and the endocardium (MECJ), or it fills up the dorsal mesocardium between the endoderm and endocardium (EECJ). The latter is only present as long as the dorsal mesocardium is around. There are differences in the compositions of MECJ and EECJ which thereby gives these two areas different functions (Hurle et al. 1980). For this paper, we will refer to them synonymously.

Role of Cardiac Jelly in Cardiac Looping

One of the proposed roles of cardiac jelly is its involvement in cardiac, or dextral, looping. This process involves transformation of the "straight bilateral precardiac splanchnic mesoderm" heart tube into the c-shaped heart loop (Nakamura and Manasek, 1981). At this stage, the first signs of left-right asymmetry in the heart can be detected and two distinct regions are apparent; the primitive ventricular region and the primitive outflow tract, or the conus separated by the conoventricular sulcus. The primitive ventricular region will start bending ventrally and toward the right in a C-shape or dextral bend (Manner, 2000). Manasek believed that this bend was a result of the internal pressure of the expanding cardiac jelly (Nakamura and Manasek, 1981). They hypothesized that the dorsal mesocardium acts as a "stiffener" that compels the tube to bend as it inflates due to the pressure of cardiac jelly. They even used rubber models with similar tension and pressure and observed the same results (Taber et al. 1995). This was supported by the observation of increased

mucopolysaccharides in the cardiac jelly specifically at this time (Hurle et al. 1980). However, this was disproved when subsequent scientists degraded cardiac jelly with hyaluronidase with no disturbance of the dextral looping (Taber et al. 1995). Other components of the cardiac jelly besides hyaluronan may be involved in the looping process, so to rule out cardiac jelly as the driving force behind cardiac looping may be premature.

Later on, studies of another event in dextral looping began to indicate a possible role for cardiac jelly in this phase, although slightly indirectly. At the dextral stage, the atrioventricular canal develops between the primitive ventricles and primitive atria (Manner, 2000).

Cardiac jelly within the atrioventricular canal swells and it is now considered the primordia of cardiac cushions (Eisenberg and Markwald, 1995). In other words, this jelly is the precursor of the atrioventricular endocardial cushions. These cushions will eventually be responsible for the division of the primitive atrioventricular canal into the left and right atrioventricular canals. These cushions are also found in the ventricular segments, the outflow tracts, or conus, and the truncus. Although not much is understood about these cushions, they may be related to cardiac looping and deviations in the formation of the loop may have been a result of improper cushion positioning (Manner, 2000).

Temporary Heart Valve Formation- Cardiac Jelly-Endocardial Cushions

In the primitive heart, no valves exist to prevent backflow, allowing a "backlash" or a retrogression of blood. As the embryo grows older, the progression of blood becomes smoother. This was attributed to "mounds" of endocardium piling up within the atrioventricular canal blocking the cardiac lumen. These mounds completely prevented backflow. The expanding cardiac jelly formed the endocardial mounds. Not only was this action found at the atrioventricular canal, but by the ventricular conus and truncus arteriosus-the places where the semilunar valves of the aorta and pulmonary trunk will form-as well. The atrioventricular canal alternates with the truncus so that when one mound is opened the other is closed. This enables cardiac jelly to aid in the pumping of blood (Patten et al. 1948).

Because of this role of cardiac jelly, researchers proposed that the blood passing through the cardiac jelly molds it. In turn, this will influence the mounds and ridges needed to form the valves and septa of the heart (Patten et al. 1948). Here, the two roles allotted to cardiac jelly were its ability to act as a pump while changing its shape and position as the heart develops and as a medium through which the blood flow will shape the heart (Overman and Beaudoin, 2005).

Role of Cardiac Jelly in Endothelial-Mesenchymal Transdifferentiation

Endothelial-Mesenchymal Transdifferentiation or EMT is the process by which endocardial endothelial cells migrate into the cardiac jelly and transform into mesenchymal cells. The cushion cells will come from endocardial endothelial cells that are transformed into mesenchyme by this process (Armstrong and Bischoff, 2004). This process only occurs in the atrioventricular canal and ventricular outflow tract. Small particles develop and deposit themselves within the cardiac jelly, forming larger complexes called adherons. The components of the adherons include the ES antigens, which are multiprotein complexes that may provide the signal for EMT (Eisenberg and Markwald, 1995). The ES antigens join fibronectin and other components of the cardiac jelly to regulate this transformation (Little and Rongish, 1995). Therefore, cardiac jelly containing the transdifferentiated cells is the precursor of cardiac cushions which in turn are responsible for heart valve and septum formation.

The early heart has four different segments: the ventricular outflow tract, ventricle, atrioventricular canal and atrium. After dextral looping, the cardiac jelly associated with the atrioven tricular canal and outflow tract regions begins to expand. In the outflow tract region, the cardiac jelly forms "parietal and septal ridges" (Nakajima et al. 1997). The expansion is accompanied by an invasion of mesenchymal cells known as EMT (Eisenberg and Markwald, 1995). At stage 39, the first invasion of mesenchymal cells occurs in the atrioventricular region while the outflow tract is only invaded beginning from stage 40 and becomes populated with cells at stage 41 (Lee and Jeannet, 2009). The cardiac jelly cells, or cushion primordia, grow until these cushions are ready to undergo valvuloseptal formation where the cushions become valves and septa (Eisenberg, 1995).

The important role that cardiac jelly plays in the process of cushion formation is the signal it provides to initiate the endocardial differentiation, EMT. These signals are soluble factors found in the jelly and can cause EMT to begin. It has been found that the extracellular matrix regulates the growth of these cells.

All three of the glycosaminoglycans found in cardiac jelly have been shown to play a role in cardiac development (Armstrong and Bischoff, 2004). When chondroitin sulfate was not expressed in the heart, no atrioventricular formation occurred and cell migration was impaired (Peal et al. 2009).

Hyaluronic acid (HA) has been targeted as a major component for the process of EMT. It has been linked to chamber septation and heart valve formation (Camenisch et al. 2002). Hyaluronic acid is one of the glycosaminoglycans found in cardiac jelly. It is a hydrated gel that allows the extracellular space to expand in addition to regulating its ligand availability. Experiments were performed that removed the enzymes responsible for forming hyaluronic acid. The cardiac jelly did not form and in consequence, neither did the endocardial cushions.

When early researchers used hyaluronidase, they discovered that the overall shape of the heart was not changed, but the heart shrunk and became flaccid. They concluded from here that the myocardium, although it can retain its shape without cardiac jelly, needs the jelly to retain its size (Nakamura and Manasek, 1981).

EMT and migration of endocardial cells were greatly reduced in the presence of hyaluronidase (Nakamura and manasek, 1981). It has been shown that both the migration as well as the transformation of cells requires hyaluronic acid. Additionally, hyaluronic acid promotes transformation into prevalvular mesenchyme and provides a medium for the cells that are entering. Scientists believed that components within the cardiac jelly, such as hyaluronan, might be responsible for the initiation of EMT. However, hyaluronic acid does not act alone in regulating these tasks. They are regulated by the ErbB family of receptor tyrosine kinases. Cells undergoing EMT express ErbB3 in the membrane of endocardial and mesenchymal cushion cells. Hyaluronic acid allows for endothelial cells to become mesenchymal cells by activating the ErbB family during EMT. Hyaluronic acid activates the ErbB receptor complex on the atrioventricular canal endocardium in order to induce EMT. These cells become mixed into the cardiac jelly and will remodel the cushions into cardiac valves. There is currently insufficient research to say if hyaluronic acid is involved directly in transformation or if it is responsible for forcing endothelial cells to become mesenchymal. However, the research providing evidence that connects hyaluronic acid and ErbB and the roles they play may be of critical importance in understanding cardiac formation and repair. Mice without ErbB3 died with hypoplastic cardiac cushions and decreased mesenchyme. (Armstrong and Bischoff, 2004; Camenisch et al. 2002)

Heparin, which is also found in cardiac jelly, has been found to play a role in proper cardiac valve formation (Camenisch et al. 2002).

Role of Cardiac Jelly in Heart Pumping

Pumping is another vital function of the heart attributed to cardiac jelly. As early as the 1940s, studies showed that had the endocardial and myocardial portions of the cardiac tube been in direct contact with each other without the cardiac jelly layer in between, no heart pumping would have been possible. They showed that the width of the cardiac jelly layer must be 45% of the radius of the lumen in diastole for pumping to take place (Barry, 1948; Manner et al. 2008). Others found that cardiac jelly provides the physical size necessary for the heart to pump blood and acts like a valve to ensure that blood is only flowing in the forward direction (Gessner et al. 1965). The heart begins to pump blood by waves of contractions known as peristaltoid. The details of these contractions are beyond the scope of this research paper. During the systole phase of heart pumping, the myocardial tube contracts concentrically while the endocardial tube narrows eccentrically. As was mentioned earlier, the eccentric formation of the endocardial tube is a consequence of the uneven distribution of the cardiac jelly. At the ventral and dorsal midlines of the heart, the cardiac jelly is extremely thin. This elliptical form of the endocardial tubes enables blood to be pumped more efficiently compared to the circular shape and minimizes the mechanical stress caused by contractions. Both the thickness that cardiac jelly provides as well as its uneven shape enables the heart to perform one of its most vital functions, pump blood (Manner et al. 2008).

Clinical Significance

Although many roles have been attributed to cardiac jelly, most researchers are still hypothesizing what this substance really does. Therefore, the ramifications of an altered or absent jelly cannot be directly linked to any specific malformation or deformity of the heart. However, several ideas have been presented.

Decreased mucopolysaccharides have been linked to congenital malformations. Sulfate mucopolysaccharides in the limbs of a chick embryo were found to cause skeletal defects. These glycosaminoglycans decrease as the embryo gets older while cardiac jelly naturally diminishes after day 14. The greatest effect of decreased sulfate occurs on day 13 which is coincidentally the day that cardiac jelly is most actively involved (Overman and Beaudoin, 2005).

Mitral Valve Prolapse is a condition where the heart valve exhibits changes in its shape and rigidity. Data shows an increase of chondroitin sulfate, also one of the glycosaminoglycans found in cardiac jelly, in these valves. However, chondroitin sulfate has not yet been conclusively targeted as the cause of this condition. (Peal et al. 2009).

When EMT and cells began to invade the cardiac jelly, many genes, such as Sox9, were activated. When this gene was not present, other genes, such as ErbB, were unable to be activated. A human disease linked with this is campomelic dysplasia whose symptoms include “endochondral bones, XY sex reversal and occasional kidney and pancreas deformities (Akiyama et al. 2004)”.

Altering the collagen composition in the embryo by blocking certain receptors may prevent cardiac cushions from forming, and as noted before, various defects are associated with cardiac cushion flaws (Lamparter et al. 1999).

In Cardiac Lethal Mutant Axolotl, the myocardium is unable to assemble myofibrils. The cardiac jelly is affected here because it doesn’t allow sufficient hyaluronate or proteoglycan

production. Once cardiac jelly is altered, mesenchymal cells won't migrate and cushion tissue does not form (Lemanski and Fitzharris, 1989).

CONCLUSION

Although there has been an increase in the understanding of the primitive heart and its components, further research is necessary to determine the roles of this magnificent organ. Cardiac jelly found in the extracellular matrix of the heart has been linked to many vital morphogenic processes integral for proper heart formation and function such as heart valve formation and pumping, among others. How and why this unique jelly-like substance operates within the heart is not yet clearly defined but with further research, scientists may grasp its significance and use their knowledge to treat the various malfunctions that arise.

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