

Editorial

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Embryonic recall: myocardial regeneration beyond stem cell transplantation

The concept of stem cell transplantation in recovery of the heart never really scrutinized the developmental environment necessary to induce substantial changes. It is now time to shift gear to lessons learned in organogenesis and embryonic development and to study the regenerative forces established during evolution that are evidently lost in mammals. The hypothesis of “regional embryonic recall” is a starting point for the scientific community to improve our knowledge on the principles of myocardial regeneration potentially usable in the clinical arena. We have started a forum of interdisciplinary discussions ranging from the theoretical background to the establishment of clinically feasible methods to recover the heart beyond stem cell research.

The principles of regeneration

Stem cell research has paved the way for new insights into regeneration of the failing heart. Interest in regaining function after acute myocardial injury also widens the horizon for alternative methods such as mimicking embryonic pathways instead of cell transplantation.

There are obvious similarities between cardiac development and regeneration in the adult heart. Signaling to recruit embryonic cells into the developing heart is again expressed in hemodynamic adaptation or myocardial disease [1]. Several species such as amphibians and reptiles are able to regenerate part of the injured myocardium, an ability apparently lost during evolution in mammals [2–4].

We have to ask ourselves whether the loss of the regenerative power during mammalian evolution is for a higher good, such as a benefit of order in homeostasis, or is by chance. The timeframe of different healing principles might be conflicting, making scarless regeneration in most of the vertebrates impossible. In addition, the example of poikilotherm creatures using their ability to regenerate the heart sheds light on the role of environmental and biophysical parameters such as temperature and metabolism, as well as on other epigenetic or, better, epimorphic factors [5]. Regenerative forces might be hidden and could be re-established if the mechanism of signals and timing were understood. The driving forces of tissue generation and possibly regeneration are not only dependent on the gene expression pattern, but also on gradients, spatiotemporal positioning, temperature and metabolism, to name only some of them. For brainstorm-

ing purposes, let us propose and consider that regeneration can potentially be achieved in the adult failing heart and that this pathway is to the benefit of the injured organ and adds to the integrity of the individual.

Lessons learned from cardiac development

In normal organogenesis several important parameters such as intricate signaling, and transcriptional and translational networks regulate cell differentiation, transformation and migration. During early heart development, positioning of cells, cellular gradients, and migrating and transforming cells from different origins induce cardiomyocytes, but also activate pathways leading to cardiac morphogenesis and development of form. Linask describes this staging as an “orchestration of organogenesis involving the incremental activation of regulatory pathways that lead to pivotal transition points, such as cardiac compartment delineation and looping. Each embryonic stage sets up the correct patterning of morphoregulatory molecules that will regulate the next process, until an organ is formed from the mesoderm layer after gastrulation” [6]. Interestingly no report in the literature deals with the obvious and important question of how this orchestration and staging is sensed. This stage valuation seems to lack an important parameter. The stepwise-gained function of the heart, established mirror-like in the pulsatile power of the developing chambers, is at least as important as migration and gene expression patterns. Figure 1 shows a hypothetical loop indicating that morphogenesis is a complex network from different parameters including functional gain and loss in certain areas, as well as measuring the level of organization. This “morphologic clock” was first formulated several years ago and published in this journal [7, 8]. The different time points in this cycle can be interpreted as pivotal transition points, as they are also postulated by Linask in her “orchestration example”. Apoptosis, for instance, is necessary in the formation of functional valves, and blood flow patterns and shear stress during looping of the heart support and drive this hypothetical tissue-generating clock.

Recent critical reports on stem cell transplantation show that we have obviously overlooked an important principle necessary for regeneration. One promising starting point, in analogy to our theoretical tissue-generating clock, seems to be the ability of mechanosensation and transduction of the endocardium and endothelial layers as

The benefit of order: the tissue generating cycle

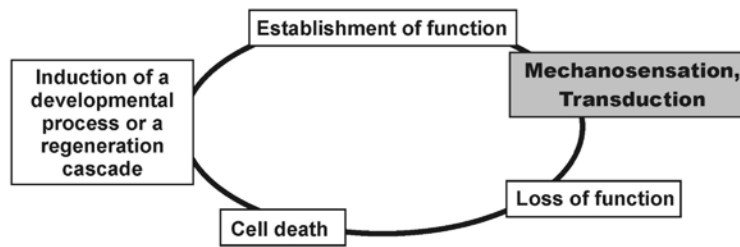


Fig. 1. Tissue-generating clock: orchestration of signals and toll-like registration points. Mechanosensation and transduction of the pulsations and their local distribution of the newly formed heart tube are hypothetically verifications of the achieved/lost function inducing the next morphogenetic steps

an important stimulus to induce a cascade of molecular events necessary in normal angiogenesis [9, 10]. How can mechanosensation and transduction be achieved in the developing heart? Until now we only know about endothelial activation but little about its endocardial analogon in embryonic life. Localized differences in shear stress of the flowing blood and pulsatile stretch induce changes in the developing heart, as was discussed in our symposium on “Regeneration and Angiogenesis beyond Stem Cell Research” and published in the Proceedings in this issue of the journal by Hierck [11]. As knowledge unfolds in this field, we will be able to connect historical reports with modern developmental biology. It is at least an attractive theory that the still unknown function of venoluminal channels, first described by Thebesius, are actually the areas in which mechanosensation and transduction in the developing heart occur, enhancing further development of the coronary circulation and maturation of the myocardium [12]. Another very interesting fact is that coronary venous endothelium and the coronary sinus originate from a vascular source active in the development of the coronary vasculature. It can very well be that pluripotency of these cells and patterns in activation will be a source in regeneration of the failing heart.

Linking development to regeneration

If we postulate that regeneration can be induced by myocardial jeopardy and cardiac failure, applying analog mechanisms which are responsible for recruiting cells in the embryo and to induce maturation of the myocardium, we have to link the expertise gathered in both fields.

Species that are able to induce regenerative pathways dedifferentiate specialized cells forming a so-called blastema together with proliferating and recruited cells [13, 14]. Although dedifferentiation is not unchallenged in the development of a blastema formation, it represents a morphogenetic embryonic pattern-forming mechanism which may have survived in mammalian evolution but cannot take place because of the loss of some coordinating mechanism or repression by a too efficient wound-healing capability inducing fibrous growth and scarring. Since biophysical forces play an important role in development as an “epimorphic” parameter, similar mechanisms may be involved in regeneration and neoangiogenesis in the adult heart.

The hypothesis of “regional embryonic recall”

It seems that regeneration is not lost or abandoned but is latent, waiting to be revived. The stimulus of regional ischemia induces restoring mechanisms evidently unable to fully recover the heart; instead they frequently induce a vicious cycle of remodeling. It is now our hypothesis that adding embryonic mechanisms such as the formative biophysical power of blood flow and pressure on the regional endothelium will lead to a reset of the formative clock of organogenesis and to the induction of hidden regenerative forces. Furthermore, we postulate that this mechanism can be used in the adult jeopardized heart, applying pulsatile stretch on the cytoskeleton of venous endothelium and locally recalling an embryonic milieu. PICSO (pressure controlled intermittent coronary sinus occlusion), a method proven valid to reduce infarct size, seems to use this mechanism to induce myocardial survival and recovery [15, 16]. There are several examples showing that the pressure amplitude acting on the coronary venous endothelium induces beneficial effects through changes of gene expression patterns of vasoactive and neoangiogenic genes [17]. Figure 2 shows the coronary sinus pressure during PICSO in a phase 2 clinical trial. Unlike the theoretical role of endocardium stimulation during development, coronary venous endothelium has to be activated periodically in order not to hinder normal myocardial perfusion. To optimize endothelial activation in a myocardial risk zone without impairment of coronary perfusion is one of the secrets of this method.

As reported by Kasahara in this journal, PICSO has also shown a long-lasting clinical benefit in patients with acute coronary syndromes [18].

From bench to bedside

Clinical transplantation of hematopoietic stem cells into the failing myocardium has been popular, but it seems that the high expectations of regeneration cannot be met in relation to a scientific benchmark [19]. The concept of induction of a developmental process or a regeneration cascade offers an alternative to the established concept of stem cell transplantation. Our hypothesis of regional embryonic recall mimicking the developing heart by changing the regional environment in order to induce

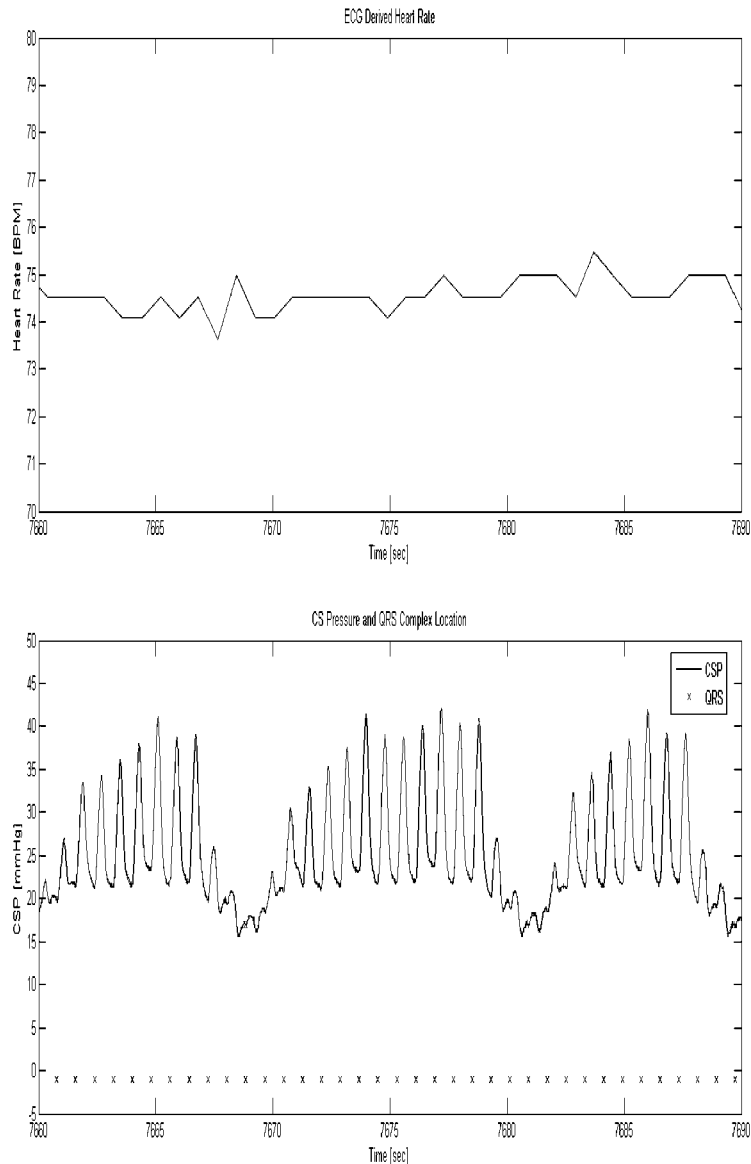


Fig. 2. Original tracing of the coronary sinus pressure during PICSO (phase 2 trial). Each pressure amplitude is stretching the vascular endothelium inducing a mechanotransduction. Periodicity of the occlusion/release cycles are necessary to allow normal coronary perfusion

recovery is in agreement with recent findings on resident cardiac stem cells, cardiomyocyte cell division and the role of epicardial cells in regeneration [20].

The proof of this hypothesis might open a new horizon of how we view the ability of the mammalian heart to regenerate. In addition, the simple method of a quasi physiologic principle using biophysical force and the dynamics of blood flow on the coronary venous endothelium can be applied clinically without ethical concern or methodological difficulties.

If the principles of mechanosensation and transduction applying pulsatile stretch on the endothelium can be substantiated in further experiments, we will be able to bring this alternative method beyond stem cell research from bench to bedside. Future multidisciplinary studies on this method will merge the interests of the clinician to

recover the failing heart with the experience of developmental biologists as well as the clinician on the basis of organogenesis and its application in regeneration.

Clinical implications

The principles of regional embryonic pattern formation in the adult heart might therefore be rearranged and orchestrated by evaluating wound-healing mechanisms and their signals, as well as properties of the “epimorphic systems” surviving embryonic life. The questions to be asked are how to reintegrate these signals to recover the failing heart. The necessary medium of this mission is a conceptual paradigm shift from stem cell transplantation to manipulation of the environment. The route to clinically feasible methods of regeneration will integrate or-

chestration of multiple molecular and epigenetic signals. Let us start with the concept of mechanotransduction and activation of coronary venous endothelium, or the manipulation of temperature, as poikilotherm creatures demonstrate during regeneration of their injured limbs. Perhaps the myth of Prometheus and the nightly regeneration of his liver ripped out by an eagle during the day are leading us in the right direction. In the early 1990s I was in Oxford at a symposium on myocardial protection, where I presented a talk on "Myocardial protection to recover the heart". At that time and what I presented was that I never envisioned it would be possible to rejuvenate the adult and failing heart; evidently things may have changed, as the proceedings of our symposium on cardiac regeneration and angiogenesis beyond stem cell research appearing in this volume teach us that the potential of regeneration is on the horizon.

We are at the beginning of an interesting era in the scientific perception of mammalian regeneration, linking answers available from embryology with questions formulated in the distress of failing hearts, and it seems possible that even clinical applications of restoration and recovery will be waiting on the finishing line. The race is on!

Werner Mohl

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