Development and regeneration: two sides of the same coin
1. First develop, then regenerate

Embryonic development of multicellular organisms is a highly patterned process which is regulated in space and time by complex gene networks and signalling pathways. Embryonic patterning is crucial to the rise of adult cardiac form and function.

Regeneration of a given adult tissue or organ also requires the activity of patterned gene expression and signalling. Moreover, regeneration involves cellular mechanisms of de-differentiation (allowing for the transformation of a somatic, differentiated cell into a progenitor cell type), de novo differentiation or even transdifferentiation (change in state of one cell type into another).

At least a part of the events taking place during regeneration processes are based on the activity of ancestral, evolutionary conserved signalling pathways crucial to embryogenesis like WNTs, NOTCH, BMPs/TGFβs, FGFs or IGFs.

However, the persistence or reactivation of defined developmental signals in the adult might not have the same effects in developing embryonic tissues than in regenerating ones. The activation of such signals is related to constraints affecting the genetic toolbox of different animal groups.
Regeneration involves the renewal, restoration and growth of tissues/organs. In non-vertebrate animals regeneration is mediated by a proliferative blastema that can comprise multi- or pluri-potent stem cells (epimorphic regeneration).

In some vertebrates, mostly anamniotes, regeneration is restricted to a few structures (fins, limbs, tails and hearts). In general, amniotic vertebrates cannot regenerate damaged tissues, just repair them.

Repair of a tissue or organ involves the quick restoration of gross defects. The compensatory growth is frequently dependent on fibrosis and mediated by inflammation. It does not always restore the normal architecture and function of the original tissues. Restoring function is a condition sine qua non for true regeneration.
3.-Why did higher vertebrates lose their regeneration abilities?

Most experts agree that one of the main reasons for the loss of regeneration abilities in higher vertebrates relates to the post-natal arrest of cell proliferation. Note that most invertebrate and anamniotic animals remain growing until the end of their lives (independently from the lifespan of the organism).

It is also assumed that mitosis cessation in most somatic tissues of adult amniotic vertebrates is an evolutionary selected mechanism to avoid metaplasia and cancer progression. However, classic post-mitotic adult tissues have been shown to retain a low division rate associated with the presence of resident stem cells.

Important aspects that need to be taken into account when analyzing tissue regeneration are:

1) The number of cells with reparative/regenerative properties over the total number of damaged cells in the organ.

2) The relative importance of cell de-differentiation and cell progenitor activation versus resident stem cell contribution.

3) The spatial distribution of stem cell niches in the organ.

4) The specific characteristics of each blastema, as some of them have been shown to be constituted of several distinct, restricted progenitor cell pools. Under these circumstances the blastema becomes a ‘mosaically built structure’ (Tanaka & Reddien, 2011. Developmental Cell 172-185).
4.- Requirements for heart regeneration

Ideal heart regeneration would require:

1) Local renewal of the lost myocardial mass with heart chamber-matched cardiomyocytes.

2) Fast maturation of new cardiomyocytes into a population of cells electrically-coupled to the host tissue.

3) Persistent neovascularization of the newly formed myocardium.

4) Reduced or absent scarring.

Proposed sources for new cardiomyocytes include:

1) Foetal cardiomyocytes.

2) Adult stem cells (e.g. bone-marrow derived).

3) Embryonic stem cells (ES).

4) Resident cardiac stem cells (CSCs).

5) Induced pluripotent stem cells (iPS).

Retinoic acid is essential for epicardial embryonic development and seems to be a crucial morphogen during vertebrate heart regeneration. Data from studies on the role of epicardium in zebrafish heart regeneration emphasize the relevance of the signals provided by the damaged tissues, suggesting that the characteristics of the wound determine the reparative/regenerative response.
Again, spatio-temporal control of signalling molecules during embryonic development is required for the proper differentiation of epicardial derivatives. Critical molecules involved in the process include Notch receptors, BMPs, FGFs and Retinoic Acid, among others.
As indicated, spatio-temporal control of signalling molecules during embryonic development is required for the proper differentiation of epicardial derivatives. A critical gene in the process is Wilms tumor supressor 1 (\(Wt1\)) a gene sensitive to RA that has been recently shown by our group to directly regulate RA synthesis via Raldh (Guadix et al., 2011. Development 138, 1093-1097).

The multipotent properties of the embryonic epicardial cell lineage suggest that epicardial derivatives in the adult could be good candidates for a cell-based therapy to regenerate the damaged heart.

Epicardial-derived cells (EPDC) contribute to the formation of coronary blood vessels and ‘cardiac interstitial cells’ (CIC).
8.-The epicardium and CICs

What are CICs?

CICs are a heterogeneous cell population including CSCs, fibroblast progenitors, fibroblasts, myofibroblasts and other non characterized cell types of different origin.

EPDC are the first cells that colonize the cardiac interstitium. The major postnatal contributor to the cardiac interstitium is the bone marrow.

The fibroblastic and smooth muscle-like phenotypes seem to constitute an embryonic developmental continuum, and are two well defined developmental fates for epicardial derivatives.
9.- How does the embryo respond to heart damage?

Chick embryo (HH20). Ventricular microcryocauterization

- cTnl mRNA
- Col III mRNA
- BMP2 mRNA

MF20+
Raldh2+
CK+
Distinct subpopulations of epicardial-derived cells display very different proteolytic properties.
11.- Cells at the cardiac interstitium constitute a complex community

Bone marrow cells show a special affinity for epicardial-derived cells (EPDC).

EPDC could have a relevant role as stromal cells for different cardiac progenitors, thus helping to sustain adult heart homeostasis.

The specific response of the epicardial-derived CICs to heart damage is not known.

The quantitative and qualitative contribution of epicardial-derived cells to heart fibrosis remains a mystery.
1.-Cardiac regeneration is partially dependent on the genetic toolbox of embryonic developmental processes.

2.-Cell proliferation abilities of adult somatic tissues, as well as the numbers and distribution of progenitor/stem cells, determine their regeneration potential.

3.-The epicardium is a key element in lower vertebrate heart regeneration; such regeneration involves the activation of an epicardium-specific developmental genetic program.

4.-Some adult EPDCs seem to retain the full developmental potential of embryonic EPDCs (endothelium, smooth muscle, fibroblasts and cardiomyocytes).

5.-An important part of CICs have an epicardial origin. Epicardial-derived CIC pioneer the colonization of the cardiac interstitium and contribute to a highly reactive subpopulation of cardiac fibroblasts.
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