Singling out heart cells

Michael Basson

Three studies identify multipotent progenitor cells that can give rise to major cell types of the heart. The findings may lead to improved approaches for heart repair.

Results from clinical trials using stem cells to repair damaged hearts have so far been disappointing, perhaps because the types of stem cells that have been used are unable to generate heart cells efficiently. Using cells that are programmed to generate the heart during development might have a better chance of success. Three recent reports give this strategy a boost by identifying progenitor cells that can give rise to three major cell types of the heart—cardiac muscle, smooth muscle and endothelial cells[1–3].

A flurry of recent work has led to the view that cardiac muscle cells are generated from two areas in the embryo, the so-called primary and secondary heart fields[4]. Work on the secondary heart field has been aided by the observation that these cells are marked by expression of the Isl1 transcription factor[5]. *In vivo* lineage-tracing studies showed that Isl1-expressing cells contribute to specific areas of cardiac muscle and that Isl1-expressing cells are found in the hearts of newborn animals[6].

Chien and colleagues[3] now show by the same lineage-tracing technique that Isl1-expressing cells, isolated from embryos, contribute not only to cardiac muscle—but also to pacemaker, smooth muscle and endothelial cells. In cultures of differentiating embryonic stem cells, a single Isl1-expressing cell could be expanded to form colonies containing cardiac muscle, smooth muscle and endothelial cells, or only one or two of these cell types. Analysis of these colonies suggested that the tripotent progenitor expresses two other markers (Nkx2.5 and Flk1) in addition to Isl1.

A hierarchy was proposed in which progenitors expressing only two of the three markers have a more limited developmental potential. To verify that these progenitors exist *in vivo*, the researchers identified cells expressing these three markers in embryo (**Fig. 1**), and found that these cells in culture could similarly form colonies containing the three cell types.

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Two other groups of researchers have also identified heart progenitor cells, albeit expressing different markers. Keller and colleagues[1] isolated cells expressing two markers (Brachyury and Flk1) at a specific time during the differentiation of embryonic stem cell cultures. Like the cells isolated by Moretti *et al.*[3], these cells could generate cardiac muscle, smooth muscle and endothelial cells, and cells expressing the two markers were seen at the appropriate stage of embryonic development.

Orkin and colleagues[2] identified yet another type of heart progenitor cell (expressing the markers c-Kit and Nkx2.5). This progenitor was observed in the embryo and in cultures of differentiating embryonic stem cells; these progenitors, however, seemed to have a more restricted developmental potential as they could generate cardiac muscle and smooth muscle cells but not endothelial cells.

Although the marker proteins identified in these new studies have previously been implicated in heart development, precisely how multipotent progenitor cells contribute to the heart will need to be further explored. For example, how the progenitor cell populations in these three studies—defined by different markers—are related to one another is an unresolved question. Addressing these questions may also shed light on what goes wrong in congenital heart disease.

Although it may be too early to draw conclusions on how these progenitor cells fit into the overall scheme of heart development, the findings highlight the similarities in the developmental potential of these cells—which can give rise to multiple cell types in the heart—and hematopoietic stem cells—which generate all of the cell types in the blood.

Previously, other types of progenitor cells have been found within adult hearts; for example, adult hearts contain c-Kit–expressing cells, which are able to generate a variety of cell types and regenerate cardiac muscle *in vivo*[7]. Although more recent work indicates that this type of progenitor cell might be derived from the bone marrow[8], it will be interesting to investigate the relationship between adult heart progenitor cells and those now identified in the developing embryo. From this standpoint, it may be worth noting that Isl1-expressing progenitors were previously reported not to express c-Kit or another marker of adult cardiac progenitor cells, Sca-1 (ref. 6); in contrast, the progenitor cells identified by Wu *et al.* were partially defined by their expression of c-Kit.

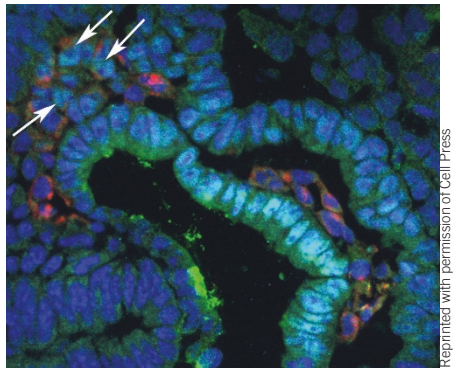

Figure 1 Cells expressing the markers of tripotent cardiac progenitors—Isl1 (green), Nkx2.5 (cyan) and Flk1 (red)—are found in day 8.25 embryos. DAPI staining (blue) marks cell nuclei.

From a therapeutic perspective, the multipotent progenitors identified in these new studies would be expected to be able to regenerate both cardiac muscle and vasculature in damaged hearts, which may have advantages compared to treatments using cells with a more restricted developmental potential. Of course, for therapy, a ready supply of the progenitors would be necessary. It is therefore encouraging that these cells can be derived from mouse embryonic stem cells, and the question of whether similar cardiac progenitors can be derived from human embryonic stem cells will no doubt soon be answered.

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