



EDITORIAL COMMENT

One answer, many further questions

Uma resposta, muitas novas questões

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The discovery of adult progenitor or stem cells has aroused the enthusiasm of medical researchers, attracted the interest of biotechnology entrepreneurs and caught the attention of politicians and religious leaders. The presence in an adult organism of cells that can proliferate and differentiate into different phenotypes appears to hold the promise of regenerative medicine in many clinical fields, in particular for organs that traditional paradigms considered to be post-mitotic.

The mammalian heart has been considered a post-mitotic organ because in traditional histology studies cardiomyocytes were never seen to divide. Two clinical observations first raised the possibility that there is cardiomyocyte renewal during human adult life. First came the observation of dividing cardiomyocytes after myocardial infarction¹; then biopsies from human heart transplants with donor-recipient sex mismatches were shown to harbor newly formed cardiomyocytes from the recipient². Later human and other mammalian resident cardiac cells — identified by the stem cell membrane markers c-kit, Sca-1, and MDR1 — were isolated. These cells are clonogenic and self-perpetuating, and can differentiate into cardiomyocytes and regenerate myocardium³⁻⁸, which identifies them as true cardiac stem cells. It is estimated that approximately 3×10^6 are generated every day in the human heart⁹.

Since the description of adult stem cells, i.e. cells within different organs capable of asymmetric division and therefore of differentiation, the prevailing theory has been that each organ has its own pool of stem or pluripotent cells, which maintain cell turnover for the different cellular

phenotypes characteristic of that organ, through controlled proliferation. These tissue-specific stem cells would be in a state of development similar to that of the embryonic stem cells that originated that organ, and therefore would have the same transcription factors^{10,11}. Furthermore their differentiation would reproduce the embryonic pattern of gene expression¹². However, to prove this theory it would be necessary to isolate pure embryonic populations as well as pure adult stem cells and to compare their transcription profile¹².

An alternative or complementary view is that there is a pool of circulating stem cells, located in the bone marrow or elsewhere, that can turn into different cell types on homing to a specific organ¹³. This raises the question of adult stem cell plasticity, by which stem cells would be able to turn into a phenotype of any adult organ, meaning that adult stem cells could have very broad possibilities of cell fate determination. Whether this happens *in vivo*, as a normal physiologic process to maintain cell turnover, or only *in vitro* as a result of experimental conditions, is also debatable. However, a dual origin of mesenchymal stem cells, organ-resident and possibly circulating, has been identified¹⁴.

Endothelial progenitor cells (EPCs) are a particular class of adult stem cells that are relevant to the biology of angiogenesis and repair mechanisms as well as to atherosclerosis; they may participate in vascular regeneration following acute ischemic syndromes, and in establishing collateral circulation during chronic ischemia, while their role in atherosclerosis is unknown.

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According to current knowledge, EPCs originate in bone marrow and migrate through the circulation to different organs. In this issue of the *Journal*, Bettencourt et al¹⁵ identified EPCs in the peripheral blood of symptomatic patients with suspected coronary artery disease and diverse risk factors. They found a direct correlation between classic risk factors and EPC counts, establishing EPCs as an apparently independent variable in coronary artery disease. Unfortunately there was no control group, so it is impossible to tell whether there is an increase or decrease of EPCs in these cases, compared to normal values.

This is an interesting static study of a dynamic phenomenon, i.e. the transit of EPCs from bone marrow into peripheral organs; any measurement of EPCs in peripheral blood could reflect an increase of production and egress from the bone marrow as well as peripheral homing to repair endothelial damage, which makes it difficult to interpret the results.

For example, the authors defined major risk factors such as hypertension, diabetes and dyslipidemia by the fact that the patients were receiving therapy. Whether the results in these groups, and the differences from other studies, result from the pathophysiology of these processes or from the effect of treatment is another open question.

The question also arises whether, in a particular clinical situation, an increase or decrease of EPCs in peripheral blood is beneficial or detrimental. The risk factors for atherosclerosis in the study population — hypertension, diabetes and dyslipidemia — are important causes of endothelial damage, leading to atherosclerosis. The main question arising from this and other studies is whether EPCs participate in the regeneration of damaged endothelium or in atherosclerotic plaque formation.

As so often happens with interesting studies, this paper answers one important question, as it establishes the independence of EPCs from risk factors, and raises many other fruitful questions, that will be interesting to follow in future publications.

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