Feeling the Elephant of Cardiovascular Cell Therapy

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There is an ancient and well-known Asian folk-tale that, in a version by the poet Rumi in Tales from the Masnavi, tells of four men who are asked to feel an elephant in a dark room and describe what they are sensing. Each of them touches just one part of the elephant, so they all reach different conclusions and think that they are in the presence of either a water-spout, a fan, a pillar, or a throne, depending on whether they are touching the trunk, ear, leg, or back of the elephant.1

Choice of Therapeutic Cells

Cells that have been used to improve cardiovascular function include adult endothelial progenitor cells, unpurified bone marrow mononuclear cells, adult myocardial stem cells, adult mesenchymal stem cells from the bone marrow or fat, and embryonic stem cells.5 But even within a cell type, there can be significant differences in how cells are isolated, processed, and cultured. For example, endothelial progenitor cells (EPCs) are among the most widely used cell types in cardiovascular cell therapies, but recent analyses have revealed that depending on how EPCs are isolated and cultured, the EPC population can either consist of a minimally proliferative myeloid-monocytic cell population (monocytic EPCs, early EPCs, early outgrowth cells, or cultured angiogenic cells) or primarily consist of a highly proliferative nonmyeloid endothelial cell population (“late” EPCs, colony-forming EPCs, late outgrowth cells).6,7 The use of an often poorly defined label such as “progenitor cell” or “stem cell” for heterogeneous therapeutic cell populations makes it very difficult to compare various studies and reach definitive conclusions about their efficacy.

Mechanisms of Action

The initial paradigm of how cardiovascular cell therapies exert their beneficial effects was that progenitor or stem cells were able to differentiate after transplantation and either replace dysfunctional cardiovascular cells or generate de novo blood vessels and myocardium in the recipient.5–4 The simplicity of the paradigm and the tempting hope that damaged cardiovascular tissues could be regenerated in patients made this paradigm a very attractive explanation for the observed beneficial effects in experimental animal models. However, a novel paradigm has emerged: that the primary mode of therapeutic action of transplanted cells may not be differentiation into cardiovascular cells but release of protective paracrine factors.8 The major question that remains unanswered is the relative contribution of cardiovascular cell differentiation versus other mechanisms such as paracrine activity as mediators of the observed therapeutic effects. The relative contribution of cell differentiation and paracrine activity will likely depend on the choice of the therapeutic cell type and the disease model, but we still need definitive studies to address this question. If indeed the cell differentiation is not the key mediator of observed therapeutic effects, even mature cells could be considered instead of stem or progenitor cells for cardiovascular cell therapies.

Observed Outcomes

The bulk of cardiovascular cell therapy studies have used in vivo angiogenesis or improvement of myocardial function as key outcomes in animal studies or even clinical studies.2,3,5,9 However, cardiovascular cell therapies appear to be beneficial in many additional settings, such as modulating pulmonary vascular permeability in acute lung injury10 or reducing neointima formation.11 It is also important to realize that there is some evidence that cardiovascular cell therapies are potentially harmful and increase atherosclerosis in Apo-E knockout mice.12 It is quite possible that a cell type may be beneficial in one experimental model while being harmful in a different setting. This becomes particularly important when cell therapies are given to cardiovascular patients, who often have multiple comorbidities and may be more vulnerable to potentially harmful outcomes induced by cardiovascular cell therapies.

Modifying the Efficacy of Cardiovascular Cell Therapies

The study by Hristov et al11 published in this issue of Circulation reminds us of the complexity of cardiovascular cell therapy. The authors have previously shown that the
proinflammatory CD40 pathway can participate in neointima formation after carotid injury, and they now show that early outgrowth cells (EOCs, or “early” EPCs) diminish the neointima formation. Furthermore, they also demonstrate that pretreatment of EOCs before transplantation with soluble CD40 ligand (CD40L) can completely abolish the beneficial effects of EOCs. However, EOCs derived from CD40−/− mice not only are more effective in reducing neointima formation but also are not vulnerable to treatment with soluble CD40L. Interestingly, the authors show that the cells express both CD40 and CD40L on an mRNA level. Although the authors do not find CD40L protein on the cell surface, it is possible that CD40L is cleaved and secreted in its soluble form into the culture medium, as EOCs are known to secrete multiple proinflammatory factors. The data presented by Hristov et al illustrate the vulnerability of EOCs to proinflammatory factors. The circulating levels of soluble CD40L in most patients are usually lower than 5 ng/mL, whereas Hristov et al incubated EOCs in 100 ng/mL to 1000 ng/mL of soluble CD40L to abolish the beneficial effects of EOCs. However, inasmuch as CD40−/− EOCs were significantly more effective than wild-type EOCs, it is quite likely that the CD40 pathway of wild-type EOCs is activated either during the EOC culture process by autocrine CD40L or after transplantation by tissue CD40L. This vulnerability of EOCs to stimulation with a single proinflammatory factor is not unique to EOCs, given that even highly proliferative nonmyeloid “late” EPCs can markedly increase their senescence when exposed to the cytokine tumor necrosis factor-α.

This vulnerability raises the question of whether cells used in cardiovascular cell therapies need to be modified to achieve higher efficacy, especially if the diseased tissue of the recipient represents a hostile environment for the transplanted cells. For this reason, multiple studies have identified numerous pathways to augment the efficacy of cardiovascular cell therapy by either blocking the effects of detrimental factors or increasing the expression of beneficial genes. It is important to remember that assessing the efficacy of cardiovascular cell therapies does not allow us to draw conclusions about the biology of cardiovascular regeneration. Many genetic modifications of cells that enhance or suppress efficacy of cardiovascular cell therapy may reflect global changes in cell survival and cell function that can be found in all cells, whether stem cells, progenitor cells, or mature cells. Inasmuch as it is apparent that the therapeutic benefits of cardiovascular cell therapy are not necessarily related to the differentiation of regenerative cells, we have to realize that the observed changes in efficacy during modification of genes or pathways do not implicate these genes and pathways in cardiovascular cell differentiation and regeneration.

Need for a Hierarchy of Cells, Pathways, and Effects in Cardiovascular Cell Therapy

Most of us have our favorite cell type, pathway, and outcome that we like to study. The problem now faced by the field of cardiovascular cell therapy is that we are accumulating numerous isolated findings about relevant pathways and beneficial effects without being able to develop a comprehensive model. It is likely that from the thousands of genes that we can overexpress or knock out, hundreds will either increase or decrease the effects of cardiovascular cell therapies. Chances are that when we study the various cell types used in cardiovascular cell therapies, use multiple disease models, and use multiple in vitro outcomes, some combination will likely yield positive results. However, what we really need is to (a) clearly define and standardize the cell types and treatments used in cardiovascular cell therapies, (b) develop integrative models in which we incorporate positive and negative findings, (c) study multiple cell types and pathways under identical conditions to understand their comparative importance, and (d) distinguish therapeutic effects related to true cell regeneration and differentiation from those related to other mechanisms such as paracrine activity.

The quickest way to resolve the dilemma of the elephant in the dark room would have been for the four people touching the elephant to have discussed their findings with each other. There are not many entities that feel like a water-spout, a fan, a pillar, and a throne. It would have required all of them to recognize their own limitations of looking at only one aspect of the puzzle, and accepting that others may have valid points. However, it is quite possible that the person who thought he was touching a water-spout would have yelled and disagreed with the person describing the fan, each being convinced that his perception was the only correct one. Even though this is a hypothetical scenario, many of us are all too familiar with similar scenarios when we attend meetings and sessions on cardiovascular cell therapies. Once we accept that we all have fairly limited perspectives, and we agree on a common “language” by rigorously defining and comparing cell types, approaches, and outcomes, we should be able to communicate much better.

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