The future of stem cells: Should we keep the "stem" and skip the "cells"?

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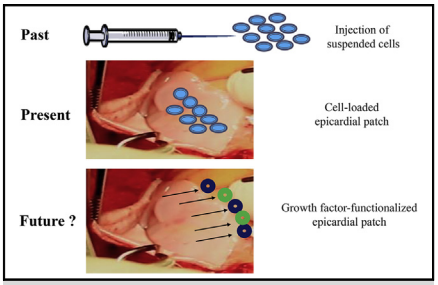
ABSTRACT

There is accumulating evidence that the cardioprotective effects of stem cells are predominantly mediated by the release of a blend of factors, possibly clustered into extracellular vesicles, which harness endogenous repair pathways. The clinical translation of this concept requires the identification of the cell-secreted signaling biomolecules and an appropriate transfer method. The study by Wei and colleagues has addressed these 2 requirements by showing that the epicardial delivery of a collagen patch loaded with the cardiokine follistatin-like 1 improved left ventricular function in animal models of myocardial infarction. Beyond the choice of the factor and its vehicle, these data may open a new therapeutic path whereby the functionalization of biomaterials by bioactive compounds could successfully substitute for the current cell transplantation–based strategy. (J Thorac Cardiovasc Surg 2016;152:345-9)



Possible evolution of cardiac stem cell therapy.

Central Message

The activation of endogenous repair pathways holds promise for improving the function of failing hearts, as shown by the benefits of a collagen patch loaded with the cardiokine follistatin-like 1.

See Article page 570.

See Editorial Commentaries page 350 and 583.

Editor's Note—*This article is one of the first in our series that will highlight important new discoveries that may impact thoracic surgeons in the not too distant future. The* Journal *has recruited a number of Featured Editors to scan the literature to identify important new information that we believe will be of interest to our readers. Feature Editor Craig Smith identified this important article in* Nature *by Wei and colleagues that identified factors that stimulated endogenous cardiac stem cells to regenerate the heart after a myocardial infarction. The Editors invited Professor Philippe Menasche to write the Expert Opinion piece because of his experience with clinical trials of regenerative approaches. We hope that you enjoy this series and the contribution of Dr Menasche.*

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In the September 24, 2015, issue of *Nature*, Wei and colleagues[1] reported that the epicardial delivery of a collagen patch loaded with the cardiokine follistatin-like 1 (Fstl-1) improves cardiac function in mouse and swine models of myocardial infarction. The premise of this study was that Fstl-1 is a regenerative factor that is normally present in uninjured hearts but is down-regulated after myocardial infarction, thereby supporting the concept of restoring it through its release from an epicardial bioengineered construct.

The beneficial effects of the Fstl-1-loaded patch were observed after permanent coronary artery ligation, with immediate patch application, and after occlusion/reperfusion; in the latter setting, the patch was applied according to a more clinically relevant scenario, ie, at a later time (1 week later). However, 2 methodologic features of the study protocol call for caution in extrapolating the results for use in clinical practice. First, the study was performed in primarily mouse hearts; and large animal data, although encouraging (reduced scar size and improvement in contractile recovery), are limited to 2 swine. Second, when cardiomyocytes at various developmental stages were tested for their response to Fstl-1, only those featuring an immature phenotype were found to proliferate. The precise identity of the Fslt-1-responsive cells could not be tracked precisely, which calls into question the applicability of Fsl-1 effects to heart failure patients.

Abbreviation and Acronym
Fstl-1 = cardiokine follistatin-like 1

Despite these caveats, the data reported in this paper convey at least 3 clinically relevant messages. The first is that an appropriately selected factor can foster endogenous repair pathways, thereby contributing to improvement of the functional outcome of infarcted hearts. In this particular case, such an improvement seems to have been mediated by a combination of effects (reduction of fibrosis, stimulation of angiogenesis, host cardiomyocyte proliferation) induced by Fstl-1, a cardiokine located in epicardial cells and the levels of which are depleted after myocardial infarction. The fact that delivery of Fslt-1 by the patch improved post-infarction function is therefore consistent with the role of epicardium-derived signals in cardiac regeneration.[2] For cardiac surgeons, the common observation of a thick layer of fibrosis overlaying the scarred myocardium can call into doubt the concept that local delivery of any factor can reverse the phenomenon, and convert an akinetic into a contractile area.

However, beyond the choice of a given compound, the relevance of this study lies in the evidence that exogenously induced paracrine signaling plays a major role in heart repair. Although mechanical unloading of the left ventricle is one intervention that can induce such paracrine effects, as suggested by the increase in the number of cycling cardiomyocytes in myocardial biopsies taken before and after placement of a left ventricular assist device,[3] the main triggers of these effects that have been studied so far are stem cells. The consistent discrepancy between the fact that stem cells are quickly cleared from transplanted tissue, yet a functional benefit persists over time is strong evidence that these cells release paracrine factors that trigger endogenous cardioreparative pathways.[4]

The practical, yet unsettled, question is thus to assess which factor(s) is the most effective. Some investigators have reported successful results with intramyocardial injection of conditioned medium released by mesenchymal stem cells in animal models of myocardial infarction.[5,6] Likewise, in the study by Wei and colleagues,[1] the conditioned medium collected from cultured epicardial cells increased the proliferation of mouse embryonic stem cell–derived cardiomyocytes. The drawback of this strategy is that conditioned medium contains large proteins, which may be unstable in vivo and are unlikely to cross cell membranes and permeate the cells. An alternate strategy consists of focusing on a single growth factor, which was the case in the study by Wei and colleagues[1] after mass spectrophotometry of the epicardium-derived conditioned medium had identified Fstl-1 as the only protein (among 1596 peptide reads) endowed with cardiogenic activity.

However, focusing on a single pathway may be somewhat reductionist in view of the multiplicity of interconnected networks that synergistically regulate cell survival, proliferation, differentiation, and function. For this reason, much attention is currently paid to extracellular vesicles as key mediators of these paracrine effects. These vesicles primarily encompass small-sized exosomes ($\leq$150 nm) that originate from cytosolic endosomes and microvesicles (up to 1000 nm), which are produced as buds off of the plasma membrane. All these vesicles are rich in biomolecules, particularly noncoding nucleic acids, lipid rafts, and protein fragments, all of which they can shuttle to target cells. Transfer of this payload can result in changes in the transcript profile of the recipient cells, as typically illustrated by the ability of fibroblasts incubated in the presence of cardiosphere-derived microvesicles to exert antifibrotic, anti-apoptotic, and angiogenic effects.[7] Extracellular vesicles, therefore, are currently considered to be major mediators of intercellular communication, and their ability to turn on pathways that are instrumental in the control of key events, such as neovascularization, cell proliferation, and apoptosis likely accounts for the improved functional outcomes reported after their delivery in animal models of myocardial infarction.[8]

In our laboratory, the functional benefits of transplanting human embryonic stem cell–derived cardiac progenitors in a mouse model of postinfarction chronic heart failure have thus been equaled by the delivery of the sole vesicles collected from those same cells.[9] Thus, extracellular vesicles quite conceivably may become substitutes for transplantation of the parent cells, provided that their production can be achieved by a scalable and cost-effective purification method, along with the development of standardized and reliable quality controls. Overall, the ''pharmaceuticalization'' of cell-derived biologics would offer the advantages of ''off-the-shelf'' product availability and the elimination of the potential side effects associated with cells, such as uncontrolled proliferation or immune responses. This approach would likely result in greater cost effectiveness, a streamlined regulatory path, and at the end, more clinical applications.

The second important finding from the study by Wei and colleagues[1] is the potential for biomaterials to foster cardioreparative mechanisms. They used a collagen-made patch, which makes sense both theoretically (collagen is the main component of the extracellular matrix) and practically (medical-grade collagen-based materials are widely available and have a longstanding safety record). However, their collagen was engineered so as to yield an elasticity modulus matching that of the embryonic epicardium ($\sim$12 kPa), with the objective of optimizing myocyte contractility.

In practice, materials available for generating cardiac constructs are broadly categorized as follows: natural polymers (such as collagen); synthetic polymers, which are often used in a blended fashion; and decellularized extracellular matrices. All of them have advantages and