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Commentary: It takes two to tango: Revascularization and viable cells

Ari A. Mennander, MD, PhD

Ongoing myocardial ischemia may lead to irreversible infarction and loss of viable tissue. The key to successful treatment is to intervene during reversible ischemia before complete tissue destruction ensues. First, the irreversible ischemic damage is limited to as small as possible an infarct area by securing adequate and early revascularization. Second, the presence of viable cells that induce paracrine mediators is ensured to aid angiogenesis of the developing scar after infarction.¹ However, bringing external fresh myocardial cells by injecting stem cells or cardiosphere-derived cells (CDCs) into the ischemic myocardium has not yet offered a final mind-blowing solution.^{1,2} It seems that external cells do not incorporate sufficiently and do not revitalize the scarred infarction tissue.

In a well-presented experimental setup, Saha and colleagues³ hypothesized that the externally applied CDCs needed additional hypoxia-inducible factor 1- α (HIF-1 α) to activate paracrine factors enabling ischemic tissue salvage. Fresh CDCs were isolated from both neonate and adult human tissue samples. HIF-1 α molecules were manufactured using polymerase chain reaction and incorporated within shuttle vectors that slipped HIF-1 α into lentivectors. These enriched HIF-1 α -containing carrier molecules were forced into the allogeneic CDCs, but elegantly, both naïve CDCs and CDCs with empty vectors served as controls. Meanwhile, the left anterior descending artery of athymic rats were ligated and 10 minutes later, the CDCs with HIF-1 α were injected around the induced myocardial infarction area. Cardiac echocardiography and myocardial histology were performed. The paracrine and proliferation capacities of the CDCs with and without HIF-1 α were quantified using

The second-best environmental-friendly transport option.

CENTRAL MESSAGE

After prevention, means to limit infarction is the second-best option. Cardiosphere-derived cells boosted with hypoxia-inducible factor 1- α may enable paracrine cell viability of the myocardium.

enzyme-linked immunosorbents assays and Alamar blue, respectively. Cellular migration and wound healing were tested using in vitro assays.

The gene and protein expressions of HIF-1 α and paracrine factor release were prominent in neonate CDCs, which showed increased proliferation, migration, and wound-healing capacities. After 28 days of implementing CDCs with HIF-1 α , the hearts showed improved function, less myocardial scar, and increased angiogenesis-like formation as compared with controls.

What are the hurdles against further clinical application?² The CDCs were procured from patients with different characteristics, including coronary artery disease. The timely and early application of the cells is an unsolved clinical challenge; when exactly would the most suitable time to implant the CDCs be after myocardial ischemia and infarction? Would harmful effects, such as arrhythmias, development of malignant tumors, or graft versus host kind of rejection, also occur while implanting allogeneic CDCs with HIF-1 α into the myocardium? Importantly, the overexpression of HIF-1 α may also hamper the beneficial paracrine effect.⁴

Some temperate stress phenomena may induce cell recovery. In a controlled milieu, hypoxia, preconditioning, and inflammation are all examples that may be harnessed to aid beneficial outcome after reversible cellular injury.^{5,6}

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Should HIF-1 α be incorporated in vitro to the CDCs and only thereafter the cells implanted in the myocardium, or should growth factors be applied straight to the myocardium?² Neither revascularization alone of myocardial infarction nor administration only of additional viable allogeneic cells around the devitalized myocardial tissue may suffice for total functional myocardial recover. Cell transfer without paracrine effect is like revascularization without viable tissue.

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Commentary: The inconsistent field of cell-based therapy for postinfarct repair

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Saha and colleagues¹ take another shot at cell-based therapy for postinfarct repair. Two decades since the earliest experimental work in this area appeared in the literature, it seems that many of the same pitfalls remain. Fundamentally, it is not known which cell type produces the most efficient and effective myocardial repair. Obvious challenges with cell-based therapy include achieving cell survival in the hostile environment of an infarct, delivering cells into the infarct zone without trauma, and determining the best time frame for cell therapy after infarction. Early in this

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CENTRAL MESSAGE

Investigators revisit a decade-old hypothesis in cell-based therapy after myocardial infarction, producing contrary results.

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field, investigators reported that treatment with stem cells derived from adult tissues, including bone marrow, adipose tissue, and the heart, could achieve myocardial regeneration. This concept, which challenged the basic tenet that the adult heart was terminally differentiated, was largely refuted in later work. Currently, most in the field posit that the salutary effects of cell-based therapy are mediated by secretory products released in the infarct milieu (ie, a paracrine effect).