CAESAR: A New Paradigm to Study Cardioprotection (p 572)

Jones et al bring clinical-level rigor to preclinical assessments of cardioprotective interventions.

Despite forty years of effort and considerable financial investment, the cardioprotection field has yet to develop a single drug capable of reducing infarct size in heart attack patients. This failure in translating preclinical studies to the clinic has been ascribed in part to the lack of reproducibility and rigor of preclinical studies. To address this problem, the Consortium for preclinical Assessment of Cardioprotective therapies (CAESAR) was established with the aim of ensuring consistent methods across multiple centers and improving accuracy by adopting approaches such as randomization of animal subjects and blinding of investigators to treatment groups. To evaluate the efficacy of this approach, the consortium performed experiments and suggest bone marrow cells are valuable targets for boosting heart regeneration. The adult heart has only a limited capacity for regeneration. Therefore, identifying specific cells that contribute and could be boosted to improve recovery from injury could lead to significant advances in the field. It is widely accepted, for example, that bone marrow stem cells can differentiate into cardiomyocytes, but it is unclear whether they actually contribute to regeneration in vivo. Indeed, bone marrow transfer experiments have shown that donor cells can home to an injured heart, engraft, and express cardiomyocyte markers. But parabiosis experiments, where the circulatory systems of two mice—one with labeled cells and one wild type—are joined, have shown only the engraftment of cells, with no sign of differentiation into cardiomyocytes. Wu and colleagues wondered whether the timing of parabiosis—which in previous experiments was performed immediately prior to heart injury—might be a crucial factor. They found that in parabiotically-paired mice, it takes 7 to 10 days to establish a fully shared circulatory system. Informed by these findings, the team delayed heart injury until that time and observed that cells from the labeled mouse not only integrated into the injured heart of the unlabeled mouse, but also developed into cardiomyocytes. They suggest that in prior experiments, early injury signals failed to pass through the shared circulation, which was only partially complete. Importantly, these findings support the role of bone marrow transfer experiments and suggest bone marrow cells are valuable targets for boosting heart regeneration.

Circulating Cells Contribute to Myocardial Repair (p 633)

Wu et al confirm bone marrow cells can promote cardiac regeneration in vivo.

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Cell Therapy for Hypoplastic Left Heart Syndrome (p 653)

Ishigami et al perform the first clinical trial for cell therapy in hypoplastic left heart syndrome.

Hypoplastic left heart syndrome (HLHS) is a congenital heart malformation caused by the incomplete development of the left ventricle, aorta and valves. Infants with HLHS are unable to properly pump blood through the body and therefore require immediate surgical intervention—either to adapt the patient’s own heart, or to replace it with a transplanted one. The former approach is unable to fully restore circulation and further surgeries are generally required, while the latter approach depends upon an all-too-scarce donor. Thus additional therapeutic approaches are needed for the treatment of HLHS. Ishigami and colleagues investigated the possibility of progenitor cell therapy as one such approach. Recent research has shown that in HLHS patients, cardiac myocyte proliferation declines during development—a problem that might be resolved by the transfer of progenitor cells. Moreover, initial clinical trials in myocardial infarction patients indicate that progenitor cell therapy thickens cardiac muscle. The team thus isolated and expanded progenitor cells from seven HLHS patients and then transferred the cells back into the patients’ hearts by intracoronary infusion one month after palliative surgery. Eighteen months later, patients exhibited improved right ventricle function and reduced heart failure status, suggesting that the approach warrants additional clinical trials.