Heparin and Bone Marrow–Derived Cell Therapy
Friend or Foe?

Edward T.H. Yeh, James T. Willerson

Cell therapy has been shown to be useful in treating some patients with acute myocardial infarction, congestive heart failure, and ischemic limbs.1–3 In harvesting, storing, or injecting the bone marrow–derived mononuclear cells (BMCs), an anticoagulant, such as heparin, is often added to prevent cell clumping. In this issue of Circulation Research, Drs Stephanie Dimmeler, Andreas Zeiher, and their colleagues (Seeger et al8) show in detailed studies that heparin may impair the functional capacities of BMCs. This discovery has significant implications for the processing of BMCs before administration of cell therapy and potentially in the treatment of patients with acute coronary syndromes, chronic ischemic and nonischemic cardiomyopathies, and peripheral vascular disease.

In their report, the authors show that heparin impairs migration and homing of BMCs by blocking a key cytokine and its receptor on the surface of BMCs. SDF-1 and CXCR4 are the ligand/receptor pair that play an important role in the homing of BMCs to ischemic tissues.9,10 Heparin was shown to block internalization of CXCR4 and its intracellular signaling pathways. It was shown that heparin binds to both SDF-1 and CXCR4, thus interfering with the SDF1/CXCR4 axis. That heparin binds to SDF1 has been shown by others.11 A minimum size of 12 to 14 monosaccharide units is required for efficient binding between heparin and SDF-1. However, binding of heparin to CXCR4 had not been shown previously. Interestingly, binding of heparin to the CXCR4 receptor did not block SDF-1 binding, suggesting that heparin binds to a different surface of CXCR4. Importantly, bivalirudin, a direct thrombin inhibitor distinct from heparin, did not affect the SDF-1/CXCR4 axis. In the present report, incubating heparin with BMCs altered in vitro “invasion” capacity and in vivo homing to experimentally injured murine ears and experimentally created myocardial infarcts in mice. Bivalirudin did not alter BMC migration or homing in any of these experiments.

Is blocking the SDF-1/CXCR4 axis necessarily harmful to cardiac repair, which is the most relevant effect clinically? Losordo and colleagues12 used a CXCR4 antagonist, AMD3100, to address this question previously. In their report, acute administration of AMD3100 increased circulating epithelial progenitor cells (EPCs), enhanced EPC incorporation into ischemic myocardium, and improved cardiac function. On the other hand, continuous CXCR4 blockade with AMD 3100 impaired EPC incorporation, increased adverse cardiac remodeling, and reduced recovery of cardiac function. The study by Dimmeler (Seeger et al) shows that heparin affects the SDF-1/CXCR4 axis, but it did not evaluate whether acute or chronic administration of heparin promoted or impaired cardiac repair. It will be helpful to determine the effects on cardiac repair of both acute and chronic administration of heparin in both of these in vivo models used by Dimmeler and Zeiher (Seeger et al).

The findings presented in this report should make all who work with BMCs in cardiac injury models very careful to not include heparin in the cell preparation steps. Whether the systemic administration of heparin in conjunction with BMC therapy also influences BMC migration, homing, and or retention in humans with acute coronary syndromes and other ischemic tissue injuries is uncertain presently, but one should be careful. On the other hand, the direct thrombin inhibitor bivalirudin appears to be safe to use with BMCs, at least in ischemic injury models in mice. These studies by Dimmeler and her team (Seeger et al) are a definite contribution to the field of BMC treatment of ischemic tissue in animal models (and very likely in humans), but, like all good studies, they also raise other issues of relevance that still must be addressed.

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Disclosures

None.

References


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