

COMMENTARY

Bone marrow cell therapy in cardiovascular disease drives us slowly to a better identification of the active cell component

David M Smadja^{1,2,3}See related research by Lamirault *et al.*, <http://stemcellres.com/content/4/6/152>**Abstract**

Endothelial progenitor cell therapy and stem cell therapy have been proposed in regeneration of acute myocardial infarction (AMI). In the previous issue of *Stem Cell Research & Therapy*, Lamirault and colleagues described a strong analysis of progenitors in blood and bone marrow of patients collected after AMI, and correlated these levels to bone marrow mononuclear cell (BM-MNC) therapy efficacy and smoking status. The main results are that BM-MNCs can override smoking alteration in endothelial lineage and confirm that endothelial progenitor cells are probably not by themselves the active component of BM-MNC in AMI. This paper allows one to better appreciate the cellular complexity of cell therapy approach in AMI.

Endothelial progenitor cell (EPC) therapy and stem cell therapy have been proposed in regeneration of myocardial infarction and peripheral arterial disease. However, there remains an ongoing need to understand what could be the cellular active component appropriate for each clinical situation to make this cell therapy approach impossible to circumvent. In the previous issue of *Stem Cell Research & Therapy*, Lamirault and colleagues described a strong analysis of hematopoietic progenitors and EPC in blood and bone marrow (BM) of patients collected after acute myocardial infarction (AMI), and correlated these levels with bone marrow mononuclear cell (BM-MNC) therapy efficacy and smoking status [1].

The first insight from this study is the specific impairment of the endothelial lineage in active smokers. Indeed, the authors described BM activation during the days following AMI whereas EPC numbers were found lower in active smokers, suggesting a specific lack of activation of the endothelial lineage [1]. This is not the first description of a specific EPC impairment and/or lack of mobilization. Indeed, our group in 2008 described a defect in EPC mobilization in the context of extracorporeal circulation in patients having numerous cardiovascular risk factors [2], while the hematopoietic lineage was strongly enhanced whatever the risk factor status.

These results are not in favor of a mixed lineage between hematopoietic and endothelial lineages and the hemangioblast existence in adults. Indeed, EPCs have been described as clonally different from hematopoietic progenitors in patients with myeloproliferative disorders [3]. This different ontogeny and the presence of clonogenic endothelial cells extracted from umbilical cord blood or lung led Yoder to suggest that EPCs could have a vascular origin [3]. This hypothesis led us to think that EPCs could be efficiently mobilized after vascular stimulation induced by local ischemia. However, because local ischemia does not mobilize any subtypes of EPCs [4], the origin and regulation of EPCs remain controversial and not fully understood. Finally, we have to carefully conclude that since EPCs isolated from smokers, despite the same level in blood as nonsmokers, have increased DNA damage and senescence [5]. This could explain the discrepancy between EPC numbers and an absence of correlation with efficacy.

The second highlight of this study is that cardiac BM cell therapy overrides EPC impairment observed in AMI patients. The cell subset responsible for the beneficial effects of BM cell therapy are not yet identified, but a multitude of studies have been published and have demonstrated that intracoronary BM-MNC delivery led to a

Correspondence: david.smadja@egp.aphp.fr¹Université Paris Descartes, Sorbonne Paris Cité, Faculté de Pharmacie, 75006, Paris, France²Inserm UMR-S1140, 4 avenue de l'observatoire, 75006, Paris, France

Full list of author information is available at the end of the article

left ventricular ejection fraction (LVEF) improvement. However, most of these trials did not have real biological exploration in parallel to BM-MNC therapy and several remaining questions exist about the active component and patient's eligible for BM cell therapy.

Although Lamirault and colleagues' results shows an absence of correlation between the EPC level and improvement after BM-MNC injection that is descriptive, the findings from this study provide strong evidence that, despite EPC involvement in physiological regeneration due to correlation with the LVEF in placebo group patients, EPCs are probably not the cell type responsible for clinical improvement in the BM-MNC therapy approach. This result is in accordance with several previous hypotheses. First, strong data from preclinical models suggest that BM-MNCs do not differentiate into endothelial cells, and that their paracrine effect is most probably responsible for the angiogenic process [6]. Second, the correlation previously described with BM-MNC efficacy has been achieved with angiogenic cells not able to build vessels by themselves and different from real vasculogenic EPCs [7]. Thus, the more we know about EPCs, the more evidence seems to discredit them as the sole active component.

A recent meta-analysis found that younger patients and patients with a more severely depressed LVEF at baseline benefit from this adjunctive therapy and also 5 to 7 days after AMI produced a superior improvement in global cardiac function (LVEF) when compared with an earlier or delayed delivery time [8]. However, the time lag of a few days between myocardial infarction and treatment excludes the preparation of cell therapy products from cells purified following expansion *in vitro* as mesenchymal stem cells or EPCs. Mesenchymal stem cells induce blood flow recovery *in vivo* to the same degree as in healthy controls, in contrast to the reduced ability that has been described for BM-MNCs and EPCs from patients with cardiovascular disorders [9] – thus mesenchymal stem cells should be a good candidate for cell therapy. So, despite the observation that BM-MNCs secrete lower amounts of angiogenic and anti-apoptotic growth factors than the mesenchymal stem cell subtype [10], BM-MNCs are probably the best cell therapy product for AMI.

In conclusion, Lamirault and colleagues fill a gap in our knowledge by identifying in a large biological study associated with a cell therapy trial that BM-MNCs can override smoking alteration in endothelial lineage. This result allows us to confirm that EPCs are probably not by themselves the active component of BM-MNCs in AMI, and contributes to better appreciation of the cellular complexity of the cell therapy approach in AMI.

Abbreviations

AMI: Acute myocardial infarction; BM: Bone marrow; BM-MNC: Bone marrow mononuclear cell; EPC: Endothelial progenitor cell; LVEF: Left ventricular ejection fraction.

Competing interests

The author declares that he has no competing interests.

Acknowledgements

DMS' research is supported by INSERM, Paris Descartes University and Région Ile de France-CORDDIM (Domaine d'intérêt majeur Cardiovasculaire Obésité Rein Diabète).

Author details

¹Université Paris Descartes, Sorbonne Paris Cité, Faculté de Pharmacie, 75006, Paris, France. ²Inserm UMR-S1140, 4 avenue de l'observatoire, 75006, Paris, France. ³AP-HP, Hôpital Européen Georges Pompidou, Hematology Department, 20 rue Leblanc, 75015, Paris, France.

Published: 27 Jan 2014

References

1. Lamirault G, Susen S, Forest V, Hemont C, Parini A, Le Corvoisier P, Piot C, Richard MJ, Delasalle B, Rouard H, Sportouch C, Persoons V, Van Belle E, Roncalli J, Lemarchand P: **Difference in mobilization of progenitor cells after myocardial infarction in smoking vs. non-smoking patients: insights from the BONAMI trial.** *Stem Cell Res Ther* 2014, **4**:152.
2. Smadja DM, Godier A, Susen S, Packard RR, Fabiani JN, Aiach M, Gaussem P: **Endothelial progenitor cells are selectively mobilised immediately after coronary artery bypass grafting or valve surgery.** *Thromb Haemost* 2009, **101**:983–985.
3. Yoder MC: **Is endothelium the origin of endothelial progenitor cells?** *Arterioscler Thromb Vasc Biol* 2010, **30**:1094–1103.
4. Mauge L, Sabatier F, Boutouyrie P, D'Audigier C, Peyrard S, Bozec E, Blanchard A, Azizi M, Dizier B, Dignat-George F, Gaussem P, Smadja DM: **Forearm ischemia decreases endothelial colony-forming cell angiogenic potential.** *Cytotherapy* 2013 [Epub ahead of print].
5. Paschalaki KE, Starke RD, Hu Y, Mercado N, Margariti A, Gorgoulis VG, Randi AM, Barnes PJ: **Dysfunction of endothelial progenitor cells from smokers and COPD patients due to increased DNA damage and senescence.** *Stem Cells* 2013, **31**:2813–2826.
6. Dudley AC, Udagawa T, Melero-Martin JM, Shih SC, Curatolo A, Moses MA, Klagsbrun M: **Bone marrow is a reservoir for proangiogenic myelomonocytic cells but not endothelial cells in spontaneous tumors.** *Blood* 2010, **116**:3367–3371.
7. Walter DH, Krankenberg H, Balzer JO, Kalka C, Baumgartner I, Schluter M, Tonn T, Seeger F, Dimmeler S, Lindhoff-Last E, Zeiher AM: **Intraarterial administration of bone marrow mononuclear cells in patients with critical limb ischemia: a randomized-start, placebo-controlled pilot trial (PRO-VASA).** *Circ Cardiovasc Interv* 2011, **4**:26–37.
8. Delewi R, Hirsch A, Tijssen JG, Schachinger V, Wojakowski W, Roncalli J, Aakhus S, Erbs S, Assmus B, Tendera M, Goekmen Turan R, Corti R, Henry T, Lemarchand P, Lunde K, Cao F, Huikuri HV, Sürder D, Simari RD, Janssens S, Wollert KC, Plewka M, Grajek S, Traverse JH, Zijlstra F, Piek JJ: **Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis.** *Eur Heart J* 2013 [Epub ahead of print].
9. Smadja DM, d'Audigier C, Guerin CL, Mauge L, Dizier B, Silvestre JS, Dal Cortivo L, Gaussem P, Emmerich J: **Angiogenic potential of BM MSCs derived from patients with critical leg ischemia.** *Bone Marrow Transplant* 2012, **47**:997–1000.
10. Li TS, Cheng K, Malliaras K, Smith RR, Zhang Y, Sun B, Matsushita N, Blusztajn A, Terrovitis J, Kusuoka H, Marbán L, Marbán E: **Direct comparison of different stem cell types and subpopulations reveals superior paracrine potency and myocardial repair efficacy with cardiosphere-derived cells.** *J Am Coll Cardiol* 2012, **59**:942–953.

10.1186/scrt405

Cite this article as: Smadja: Bone marrow cell therapy in cardiovascular disease drives us slowly to a better identification of the active cell component. *Stem Cell Research & Therapy* 2014, **5**:16