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When the bullet hits the target

Over the last few years the possibility of curing myocardial infarction by taking advantage of hematopoietic stem cells has became closer to reality and hopes have been fostered by quite a large body of studies suggesting that hematopoietic stem cells are not limited to differentiating into mature blood cells but can also mature into hepatic, intestinal, neural, skeletal and cardiac cells. In a questionable jargon expression this phenomenon is usually referred to as *stem cell plasticity*. However, it should be remembered that although many reports support the idea that hematopoietic stem cells can *transdifferentiate* into other cell types, the issue of haematopoietic stem cell plasticity is still matter of debate, and in some cases its existence has been challenged.[1,2]

Investigations suggesting the capacity of hemato-

poietic bone marrow cells to generate cardiomyocytes *in vivo* stem from the famous study by Orlic and Anversa in mice[3] and have continued up to the present with recents reports in human patient.[4-8] In their first study (published in April 2001), Orlic and colleagues showed that lineage-negative, c-kit positive bone marrow cells obtained from transgenic mice expressing the enhanced green fluorescence protein (EGFP), when injected into the peri-infarcted left ventricle of a mouse, were able to contribute to myocardial regeneration. The new developing tissue comprised both proliferating myocytes and vascular structures. This *de novo* generated cardiac tissue was not observed outside the infarcted area and, more importantly, it displayed the expected functional competence.[3] These surprising results were obtained in 40% of the mice which survived the coronary ligation (a method frequently used to induce an ischemic lesion in the experimental animal); on average around 50% of the new myocytes in these mice expressed the EGFP, thus suggesting their origin from the injected bone marrow cells. The fact that in 60% of the cases new generation of cardiomyocytes was not obtained was attributed by the authors to the difficulty of injecting the 2.5 μL of cell suspension into the ventricle wall of a mouse with the heart contracting at 600 beats per minute.[3] A few months after the publication of their paper in Nature, Orlic and Anversa published a new study in which they were able to show that also mobilized bone marrow cells can repair the infarcted heart of the mouse, with an improvement of the hemodynamic parameters and of the survival of the animals.[9] In this report, hematopoietic stem cells, mobilized by stem cell factor and granulocyte colony-stimulating factor, were able to home to the damaged myocardium and to promote myocardial repair: this was accomplished in 100% of the animals. In this way, the authors were able to circumvent the above reported difficulty of injecting cells into the cardiac wall; in addition, bone marrow cell mobilization eliminated the mortality and morbidity related to cardiac surgery in the mouse. However, it should be emphasized that in this experimental setting administration of the two mobilizing cytokines was started a few days before the induction of the infarction by coronary ligation, making this model unsuitable for application in human patients.

In the same year and successively, descriptions of many other experimental models were published and evidence reported that infarcted areas of the myocardium could be rescued (at least in part) by transplantation of different type of bone marrow-derived cells, namely hematopoietic, endothelial, or mesenchymal stem cells.[10-15] Although in most of these studies the intramyocardial transplantation was the prefentially used way to deliver the hematopoietic stem cells, in a few studies intravenous injection was performed.[11,13] At the same time, the first reports of bone marrow-derived cells transplanted into infarcted areas in human patients began to appear. These early reports were aimed to prove the feasibility and safety of this strategy.[4-8] Transplanted cells were obtained either from bone marrow or from peripheral blood. The autologous setting in which these attempts were made, the impossibility of labeling the cells used for transplantation and the association with surgical or interventional revascularisation have made the role and effectiveness of cell transplantation in myocardial recovery difficult to assess. A common feature of all of these attempts was the need for cardiac catheterization for the intracoronary infusion or intraventricular injection of the mononuclear cells. This procedure, even when performed by an expert cardiologist, is not without risk and, of course, it would be appreciable if the delivery of stem cells to the infarcted area could be achieved through a simpler and safer route.

In this issue of Haematologica, Ciulla and colleagues show how bone marrow mononuclear cells home to the injured myocardium after injection into a peripheral vein in the rat.[16] In their experimental model they used a freeze-thaw technique to produce necrotic damage to the left ventricular wall of the heart of a rat and seven days later they injected labeled bone marrow derived-mononuclear cells into the femoral vein. One week after injection, the animals were sacrificed and the presence of the injected population assessed in the heart and in other organs. Interestingly, labeled cells were detected only in the injured myocardium, whereas they were never found in other sites, with the exception of the spleen and the bone marrow. The authors also showed that most of the labeled cells in the infarcted area were $Thy^{-}1^{+}$ and some of them $CD34^{+}$, suggesting their hematopoietic origin. Thus, according to the data reported in this paper, peripherally injected bone marrow mononuclear cells can traffic and home to an injured area of the heart. This could provide the rationale for designing protocols in human patients based on the peripheral intravenous administration of hematopoietic cells. Ciulla's paper also raises the important question of what mechanism underlies the homing of bone marrow cells to the damaged myocardium. Based on the data reported by the authors it is difficult to identify putative candidates involved in this process. Moreover, the animals were sacrificed only seven days after the injection, no quantification of the contribution of the labeled cells to the injured area is reported and no evidence of myocardial regeneration is assessed. In this regard, the fact that labeled cells found in the heart expressed CD34 and Thy-1 does not rule out the possibility that these cells were of endothelial origin. Nevertheless, the absence of labeled cells in healthy organs (with the above mentioned exception of the spleen and the bone marrow) and their presence only within the injured areas of the heart sug-

gests that chemoattraction to these areas takes place, possibly through a network of cyto- and chemokines (and their cognate receptors on bone marrow cells) which can be released by the damaged heart. We do not yet know which molecules and receptors drive bone marrow cells to the infarcted areas, but recently we have learnt how the SDF-1/CXCR4 axis plays a pivotal role in the mobilization of hematopoietic stem cells from the bone marrow to periphery and in homing after transplantation.[17] It is possible to envisage a similar mechanism for the migration of bone marrow mononuclear cells to the infarcted heart. If, in coming years, the scientific community can clarify the real contribution of (hematopoietic) stem cells to the repair of damaged myocardium and identify the molecules that regulate their migration, then we really will be close to the possibility of curing myocardial infarction in human patients through a simple injection of bone marrow cells into a peripheral vein, as the study by Ciulla and colleagues so tantalizingly suggests.

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Thrombosis and malignancy: an underestimated problem

Malignancy is a thrombophilic condition and there is clinical evidence that patients with cancer have a significantly increased risk of thrombosis. The pathogenesis is multifactorial and, in great part, relies on the capacity of tumor cells to interact with the hemostatic system and activate it in several ways. The association between cancer and thrombosis is clinically relevant because, on the one hand, thrombosis can represent the first symptom of an occult cancer and, on the other hand, thrombotic events in patients with a known malignancy can influence the morbidity and mortality of the underlying disease. Furthermore, it is important to be aware that many factors, such as surgery and chemotherapy, may increase the thrombotic risk in cancer patients. Recently, a number of strategies for prevention and management of thrombosis in cancer have been under evaluation.

The association between cancer and venous thromboembolism (VTE) has been known for over a hundred years. Since the beginning, this association appeared to have a dual significance. First, there is the concept that the occurrence of VTE is a common complication of cancer, as underlined by Armand Trousseau in 1865, who observed that «*in cancer there is a special condition of the blood predisposed to spontaneous coagulation even in the absence of inflammatory reactions*».[1] Second, the possibility of a relation between the clotting mechanism and the development of metastases was postulated as early as 1878 by Billroth, who described cancer cells within a thrombus and interpreted his finding as evidence of the spread of tumor cells by thromboemboli.[2] We here focus our attention mainly on the first aspect.

The mechanisms of thrombus promotion in malignancy include some general host responses to the tumor (acute-phase, inflammation, angiogenesis,