Stem cell mobilization versus stem cell homing: potential role for parathyroid hormone?

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See article by Zaruba et al.,1 pp. 722–731.

Stem cells are considered as potential candidates to regenerate the injured myocardium. It has been shown that stem cells are able to differentiate into cardiomyocytes, as recently reviewed.2 It is still an open question, however, whether such myocytes contribute to the functional recovery of the post-infarcted heart. This process is limited by the small number of cells that differentiate into cardiomyocytes, the limited coupling of pre-existing cardiomyocytes to these newly formed myocytes, and the question whether the overall increases in ejection fractions indeed depend on the amount of cardiomyocytes newly formed by stem cells. A specific pattern of matrix proteins may be expressed by these cells, they may mediate anti-apoptotic effects, or they may improve vascularization independent of a possible differentiation into cardiomyocytes. Such effects may be modified by stem cells acting in a paracrine manner. Irrespective of these open questions, research is ongoing to develop treatment protocols that increase the number of systemic stem cells that home to the injured myocardium.3,4

Zaruba et al.1 used a novel and innovative approach to improve the homing of bone marrow-derived stem cells, as described in their article in the current issue of Cardiovascular Research. They tried to improve bone marrow-derived stem cell mobilization by application of parathyroid hormone (PTH), which affects the bone marrow-derived stem cells. This leads to an increased number of circulating stem cells and improves stem cell homing by this mechanism. In order to address this hypothesis, PTH was applied to mice after myocardial infarction to test whether it improves survival, heart function, stem cell mobilization, stem cell homing, vascular endothelial growth factor (VEGF) expression, and apoptosis in a myocardial infarction model. As PTH acts on osteoblasts, and osteoblasts are known to regulate haematopoietic stem cells, they have tested a reasonable hypothesis.

The use of PTH is of special interest for cardiologists. Historically, PTH was considered as a pro-hypertrophic factor responsible at least in part for the development of myocardial hypertrophy in patients with secondary hyperparathyroidism. These patients often develop myocardial hypertrophy and heart failure as a secondary complication that does not become normalized even after parathyroidectomy. In experimental studies, it was found that PTH was able to increase protein synthesis in cardiomyocytes and exerts pro-hypertrophic effects.5 Therefore, PTH was considered as a peptide hormone that favours the progression of heart failure rather than improving cardiac function. In secondary hyperparathyroidism, however, PTH levels are normally very much elevated. The biological effects of PTH may be different in patients with only moderately elevated plasma PTH levels. Interestingly, in patients with heart failure, plasma levels of PTH are often slightly increased without signs of a primary parathyroid malfunction.6 One may wonder if such moderate elevations are not beneficial for the heart and represent part of an endogenous compensatory response to heart failure itself. Studies like the one by Zaruba et al.1 support the suggestion that such moderate elevations of PTH favour homing of stem cells to the heart. Generally speaking, the dosage of PTH may be an important issue. In the study by Zaruba et al., PTH plasma levels in the control groups were probably low. If exogenously applied PTH is beneficial for heart failure, patients may depend on the pre-existing plasma levels of PTH. Experimentally, a logical extension of the present study would therefore be to analyse whether positive effects of exogenously applied PTH are also obtained in animals with established heart failure and already elevated PTH. An interesting field of clinical analysis is that of the cardiac effects in osteoporotic patients receiving PTH.7

Another important question that arises from the current manuscript by Zaruba et al.1 is that concerning the mechanism by which PTH improved survival and heart function in these experiments and reduced the vascular resistance and myocyte apoptosis. Clearly, these data show an improvement of survival and heart function together with elevated bone marrow-derived stem cell mobilization. It is reasonable to assume that the improved mobilization of stem cells found in this experimental study is based on PTH treatment because similar findings were reported previously in a Phase I trial.8 However, this does not establish a causal link...
between stem cell mobilization and improved survival and heart function. PTH may improve the functional recovery in a more direct way. Stimulation of cardiac PTH/PTHrP receptors is known to improve post-ischemic function and to exert beneficial effects on the heart directly. It is unclear how PTH treatment influences the expression of PTHR and that of the common receptor. Finally, as mentioned by the authors themselves, PTH may act on cardiac progenitor cells rather than on bone marrow-derived stem cell mobilization and homing. They measured an increased expression of VEGF in those hearts treated with PTH. VEGF is expressed in stem cells. It might be that PTH increased the endogenous expression of VEGF in resident progenitor cells. Therefore, no conclusion can be drawn about the mechanism by which PTH improved survival and function in the current research report at present.

In summary, the study by Zaruba et al. draws our attention to important issues that need further investigation. Can we improve stem cell homing by improving stem cell mobilization, as suggested by these authors? Is improving stem cell mobilization by PTH better than improving stem cell homing, i.e. by granulocyte-colony-stimulating factor (G-CSF)? The data from the literature on G-CSF and those of the current study may indicate this. Does improved stem cell mobilization lead to a significant differentiation of those cells into functional cells that regenerate the injured myocardium? And finally, what is the precise effect of PTH in cardiac physiology and pathophysiology? What are the target cells, and how are they influenced? Little is known about the effects of low and high concentrations of PTH on cardiomyocytes, although this has been previously studied both in vitro and in vivo. Differences between acute and long-term effects of PTH also need to be investigated. Thus, the excellent set of data presented by Zaruba et al. significantly contributes to the field, but also leads to many new questions that should be addressed in the future.

References