Targeting bone marrow to treat vascular diseases: Accelerated vascular healing by colony stimulating factor

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Received 31 December 2005; accepted 9 January 2006

Available online 10 February 2006

See article by Yoshioka et al. [6] (pages 61–69) in this issue.

It is a generally accepted view that endothelial damage triggers the pathogenesis of various types of vascular diseases [1]. A growing body of evidence suggests that bone marrow (BM)-derived cells may participate in arterial repair after injury [2,3] by homing to the injured vessel and differentiating into endothelial cells (ECs). Walter et al. suggested that the mobilization of endothelial progenitor cells (EPCs) from BM after vascular injury may mediate accelerated reendothelialization and reduced neointima formation by statin therapy [4]. It was reported that granulocyte colony-stimulating factor (G-CSF), a major regulator of haemopoi-esis and the innate immune system, potently mobilizes EPCs from BM and accelerates reendothelialization [5].

In the current issue of Cardiovascular Research, Yoshioka et al. examined a hypothesis that G-CSF treatment could reduce neointimal formation by increasing the number of circulating EPCs and thereby accelerating reendothelialization after mechanical vascular injury [6]. Pre-treatment with G-CSF before the vascular injury enhanced reendothelialization and decreased neointimal formation. These favourable effects on the injured artery were associated with an increase in the number of putative EPCs (CD34+ Flk-1+ cells) in peripheral blood and a decrease in serum IL-6 level. To assess the effective contribution of EPCs originating from the BM itself, the investigators replaced the BM cells of wild-type mice with those from GFP- or Tie-2/LacZ-transgenic mice and induced vascular injury. Notably, only a few cells in newly formed endothelium were derived from BM, suggesting that additional mechanisms other than enhanced EPC incorporation into the injured artery might be involved in accelerated reendothelialization by G-CSF. These data are concordant with a previous study by Gulati et al. showing that local delivery of fluorescently labelled mononuclear cells promoted reendothelialization and reduced neointimal formation in a rabbit model of balloon carotid injury, although only 5% of total reendothelialized surface was composed of the labelled cells [7]. These findings have raised a new paradigm that BM-derived cells could contribute to the reendothelialization process not only by differentiating into ECs at the site of vascular injury, but also by secreting angiogenic growth factors in a paracrine manner, thus stimulating migration and proliferation of neighbouring resident ECs [7]. In fact, Ziegelhoeffer et al. demonstrated that BM-derived cells formed clusters around growing vasculature and produced angiogenic growth factors such as FGF-2, VEGF, and MCP-1, although those BM-derived cells were not integrated into the new vessels in a mouse model of hindlimb ischemia [8]. Similarly, Kocher et al. [9] showed that EPCs had the capacity to secrete proangiogenic growth factors and chemokines that enhanced proliferation of undamaged endothelium in the vicinity of the infarcted region and hence improved myocardial function by enhancing collateral artery forma-tion in a rat model of myocardial infarction. Besides, enhanced reendothelialization could also result from a direct stimulatory effect of G-CSF on the intact endothelium neighbouring the site of injury. Indeed, G-CSF has been reported to induce proliferation and migration of ECs in vitro and promote angiogenesis in vivo in a rabbit cornea model [10].
Yoshioka et al. found that G-CSF pre-treatment significantly decreased IL-6 level in serum, suggesting that this pathway could also be responsible for accelerated reendothelialization. This hypothesis is supported by the study by Hatzi et al. showing that IL-6 inhibited VEGF- and bFGF-induced EC proliferation in vitro and in vivo [11]. However, such anti-angiogenic properties of IL-6 have been challenged by recent reports indicating that specific blockade of IL-6 receptor α chain inhibited angiogenesis and tumour growth [12]. Hence, further study would be needed to elucidate the molecular mechanism by which the decreased IL-6 level was associated with enhanced reendothelialization by G-CSF.

G-CSF therapy represents an attractive strategy to promote reendothelialization, since G-CSF can mobilize EPCs into the systemic circulation without any invasive procedures [13]. Injection of G-CSF is apparently easier than other cell-based therapies, which often require complicated methods to isolate, expand, and transplant stem cells or progenitors. For clinical application, the protocol of G-CSF injection appears to be critical to improve the therapeutic efficacy. In the present study, Yoshioka et al. compared the effects of G-CSF starting either before or after the vascular injury. Interestingly, the therapeutic efficacy of G-CSF was attenuated when G-CSF was administered only after the injury. These results are consistent with a previous work by Kong et al. which showed that pre-treatment with G-CSF increased reendothelialization of denuded vessels and neointima thickness in a rat carotid balloon angioplasty model [5]. Similarly, Orlic et al. demonstrated that a 5-day administration of G-CSF combined with stem cell factor prior to coronary artery ligation allowed significant recovery by regenerating functional tissue in mice [14], while Askari et al. reported that administration of G-CSF in rats with chronic ischemic cardiomyopathy did not result in myocardial regeneration [15]. Taken together, these data indicate that delivery of G-CSF prior to injury is essential for its efficacy, but mechanisms involved are still to be clarified.

Finally, understanding biological and physiological events induced by systemic G-CSF administration is also key to improving the safety of the treatment. G-CSF has previously been shown to increase migration and proliferation capacities of smooth muscle cells [16]. A recent clinical trial with myocardial infarction patients has shown that G-CSF mobilization of stem cells improved cardiac performance and angiogenesis [17]. However, this improvement was associated with an unexpectedly high rate of in-stent restenosis which led to the premature termination of the trial. One possible explanation for this phenomenon could be differentiation of the mobilized cells into smooth muscle-like cells which could in turn contribute to neointimal formation within the stent, while Yoshioka et al. found that 100 μg/kg/day of G-CSF for 10 days did not significantly affect the number of BM-derived neointimal cells in a murine model of restenosis [6]. Another explanation of the high incidence of restenosis caused by G-CSF therapy could be the participation of the mobilized cells in the inflammatory process. Previous findings indeed suggested that G-CSF may have proinflammatory and procoagulant effects [18,19]. Because G-CSF potentially mobilizes all types of bone marrow cells, the fate of the mobilized BM-derived cells should be carefully monitored following G-CSF treatment. Moreover, dose, frequency, and duration of G-CSF injection should be optimized for clinical use. In this regard, a recent clinical study reported that some patients with coronary artery disease experienced myocardial infarction without objective evidence of cardiac benefit of G-CSF administration [20].

In conclusion, the findings by Yoshioka et al. [6] suggest that treatment with G-CSF could hold therapeutic promise to accelerate vascular healing and attenuate lesion formation in response to mechanical injury. Further study to elucidate the underlying mechanisms would be warranted to confirm the therapeutic effects of G-CSF and improve safety before this new treatment could be applied to wide range of patients.

Acknowledgement

This study was supported in part by grants from the Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor and Welfare, and the Japan Society for the Promotion of Science.

References


