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Mobilization of bone marrow stem cells with StemEnhance® improves muscle regeneration in cardiotoxin-induced muscle injury

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Abbreviations: BMSC, bone marrow-derived stem cells; SE, stemenhance; CTX, cardiotoxin

Bone marrow-derived stem cells have the ability to migrate to sites of tissue damage and participate in tissue regeneration. The number of circulating stem cells has been shown to be a key parameter in this process. Therefore, stimulating the mobilization of bone marrow stem cells may accelerate tissue regeneration in various animal models of injury. In this study we investigated the effect of the bone marrow stem cells mobilizer StemEnhance (SE), a water-soluble extract of the cyanophyta *Aphanizomenon flos-aquae* (AFA), on hematopoietic recovery after myeloablation as well as recovery from cardiotoxin-induced injury of the anterior tibialis muscle in mice. Control and SE-treated female mice were irradiated, and then transplanted with GFP$^+$ bone marrow stem cells and allowed to recover. Immediately after transplant, animals were gavaged daily with 300 mg/kg of SE in PBS or a PBS control. After hematopoietic recovery (23 days), mice were injected with cardiotoxin in the anterior tibialis muscle. Five weeks later, the anterior tibialis muscles were analyzed for incorporation of GFP$^+$ bone marrow-derived cells using fluorescence imaging. SE significantly enhanced recovery from cardiotoxin-injury. However, StemEnhance did not affect the growth of the animal and did not affect hematopoietic recovery after myeloablation, when compared to control. This study suggests that inducing mobilization of stem cells from the bone marrow is a strategy for muscle regeneration.

Introduction

Over the past few years, a large number of studies have demonstrated not only the ability of bone marrow stem cells to differentiate into a wide variety of somatic cells,[1-4] including myocytes,[5-7] but that this phenomenon takes place spontaneously after tissue damage.[8-12] For example, within hours after acute myocardial infarction (AMI), granulocyte-colony stimulating factor (G-CSF), which triggers stem cell mobilization, can be measured in the blood.[13,14] Within a few days after AMI, the number of stem cells circulating in the blood increases by about 3–4-fold when compared to healthy individuals.[13,15] Similar increases have been documented after bone fracture,[16,17] skin burn[18] and muscle injury.[19] Within 24 to 72 hours after AMI, the heart releases stromal-derived factor 1 (SDF-1), a cytokine known to attract stem cells and trigger their extravasation.[20] As they migrate in the infarcted cardiac tissue, stem cells proliferate and differentiate into functional cardiomyocytes.[21]

Bone marrow-derived stem cells (BMSC) contribute to the repair of various tissues. G-CSF-induced stem cell mobilization, as a therapeutic approach, has shown promise in a number of disease models, including diabetes,[22,23] coronary heart disease,[24,25] stroke[26] and wound healing.[27] However, G-CSF has been associated with severe side effects in humans and cannot be used for periods of time long enough to maximize the benefits of BMSC mobilization.[28]

Recently, a water-soluble extract of the cyanophyta *Aphanizomenon flos-aquae* (AFA) (StemEnhance®, "SE") was shown to act as a mild mobilizer of BMSC, increasing the number of circulating stem cells by 25% within one hour of oral consumption.[29] We tested the hypotheses that StemEnhance® would increase the rate and extent of regeneration in cardiotoxin-induced injury of the tibialis muscle in mice,[30] as well as hematopoietic recovery after myeloablation.

Results and Discussion

Toxicity. There was no evidence of toxicity due to SE administration. No animals in either group died or had signs of toxicity or discomfort. As shown in **Figure 2**, animals in both groups

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Table 1. Quantification of hemoglobin (HGB) and hematocrit (HCT), as well as counts for white blood cells (WBC), red blood cells (RBC), platelets, polymorph nucleated cells (PMN), lymphocytes (Lymph), monocytes (Mono), eosinophils (Eos) and basophils (Baso), at day 16 and 30 after irradiation and transplant of BMSC in both PBS and SE-treated groups

	WBC ($10^3/\mu l$)		RBC ($10^3/\mu l$)		HGB ($10^3/\mu l$)		HCT ($10^3/\mu l$)		Platelet ($10^3/\mu l$)	
Day	14	28	14	28	14	28	14	28	14	28
PBS	1.93	5.05	10.10	10.11	14.20	14.13	48.47	45.97	518	976
SE	1.26	6.12	9.16*	9.47*	12.80*	13.00*	44.03*	43.27*	761	759
Reference Values	4.54 ± 1.84		9.89 ± 0.44		15.2 ± 0.6		48.8 ± 1.8		1336 ± 82	
	PMN ($10^3/\mu l$)		**Lymph ($10^3/\mu l$)**		**Mono ($10^3/\mu l$)**		**Eos ($10^3/\mu l$)**		**Baso ($10^3/\mu$)**	
Day	14	28	14	28	14	28	14	28	14	28
PBS	0.65	0.85	1.07	3.84	0.05	0.07	0.14	0.26	0.01	0.02
SE	0.50	1.14	0.58*	4.43	0.04	0.10	0.12	0.40	0.01	0.02
Reference Values	0.41 ± 0.26		4.08 ± 1.62		0.05 ± 0.08		0 ± 0		0 ± 0	

Asterisks (*) indicate statistically significant differences between the two groups.

showed identical body-weight growth patterns (p = 0.9). At each weekly time point, body weights and change in body weights, for the two groups did not show any statistical difference. No visual or behavioral differences were seen between the two groups.

Hematopoietic recovery. Overall, all hematopoietic parameters were close to normal values 28 days after cardiotoxin administration in both the SE-treated and control groups, except for HGB, HCT and platelets. In both groups, PMN were slightly elevated. SE did not appear to have an effect on hematopoietic recovery (**Table 1**).

Recovery from CTX-induced injury. In the injury part of the study, the extent of the recovery was evaluated by measuring the area covered by fluorescence in the recovering muscles. To take into account the overall process of recovery, in each fluorescence photomicrograph all green pixels were counted. Greater regeneration of the anterior tibialis muscle in the SE-treated group (21.7 ± 2.8 mm^2) was observed 5 weeks after CTX injury when compared to control (17.5 ± 3.0 mm^2) ($p < 0.05$) (**Fig. 3**). Less fluorescence was seen in the uninjured left anterior tibialis muscles of both groups (SE: 8.4 ± 1.0 mm^2; control: 7.8 ± 0.8 mm^2) and the slight difference in fluorescence was not statistically significant, indicating that migration of BMSC was more significantly directed toward the injury. Fluorescence was also seen in most of the main organs, such as the heart, brain, kidney, liver and lung, though no difference was visually seen between the two groups. Histological or colorimetric assays could not be performed on the various organs and tissues due to the loss of the frozen tissue samples.

Animals received 300 mg/kg of StemEnhance (SE), which is roughly 10 times the dose given to humans.[29] At that level, growth was normal and animals showed no signs of toxicity. SE is a 5:1 concentrate of the cyanophyta *Apahnizomenon flos-aquae* (AFA). Our observations are consistent with Schaeffer et al.[31] who reported that consumption 16,666 mg/kg of AFA (equivalent to >3,000 mg/kg SE) led to no signs of toxicity in mice.

Support of hematopoietic recovery by SE was not observed in this study. This observation is nonetheless consistent with the report by Jensen et al.[29] that SE selectively increased the number of circulating CD34$^+$ cells without affecting RBC, WBC, HGB, HCT or platelet count (also unpublished data).

Many studies have reported the ability of BMSC to migrate into various tissues and differentiate into functional somatic cells of these tissues, including muscle.[32] In this process, the number of circulating stem cells has emerged as a critical parameter whereby more circulating stem cells means that more stem cells are available for migration and differentiation.[33,34] The present study found that increasing the number of circulating stem cells using a daily intake of SE accelerated and enhanced the recovery of CTX-induced muscle injury, and that this was linked to the migration of BMSC. Interestingly, significant recovery was also seen in the control group, supporting the view that BMSC naturally contribute to tissue regeneration. Similar observations have been made using various muscle injury models and different mobilizers such as G-CSF[21,35] or autologous transplant.[36]

In both experimental and control groups, BMSC migrated to a much lesser extent in the non-injured left anterior tibialis muscles, confirming that BMSC primarily migrate towards sites of injury or tissue damage. Indeed, following sex-mismatched bone marrow transplant, male donor-derived cells were reported in relatively high concentration in the livers of female recipients following liver damage, indicating the migration of bone-marrow derived cells to repair the liver tissue.[8] Such directed migration has been documented in the gut after section of an intestinal segment,[37] in the heart after AMI,[7,38] or induced cardiomyopathy,[39] in the brain after stroke,[40,41] and in the liver after drug-induced liver damage.[42]

In conclusion, increasing the number of circulating stem cells with daily administration of SE enhanced recovery from CTX-induced muscle injury. This study supports the view that inducing endogenous bone marrow stem cell mobilization could

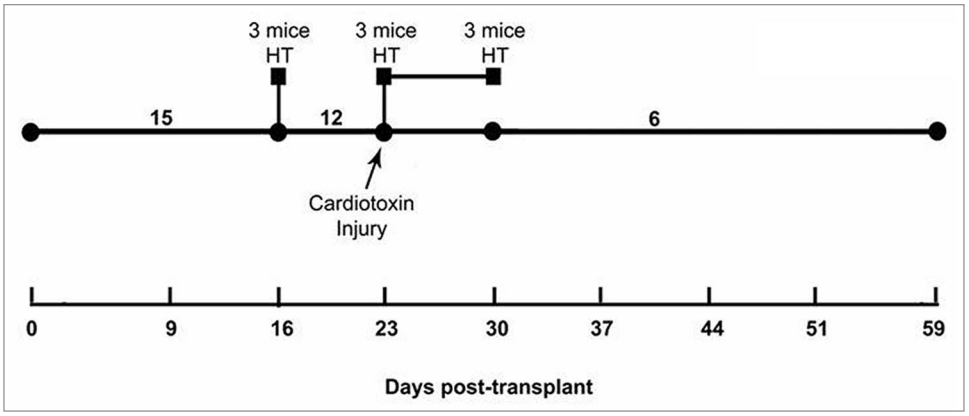

Figure 1. Timeline of the treatment and testing for both the control (A) and experimental (B) groups. Numbers on the timeline indicate the number of animals treated, dots mark the time points at which animals were sacrificed for testing, and squares indicate when hematology testing was performed (HT; Day 16, 23 and 30), at which times three mice were sacrificed for each testing. All animals were injected with 10 μm of cardiotoxin in 100 μL of PBS in the anterior tibialis muscle of the right leg on Day 23.

constitute an effective approach to facilitate recovery from various injuries, particularly muscle-related traumas.

Methods

Experimental animals. Thirty C57BL/6-GFP[43,44] female donor mice (bred at AntiCancer, Inc.,) and 30 C57BL/6 female recipient mice, 8–10 weeks old (Purchased from Harlan Laboratories, Livermore, CA), were used for this study. All animals were weighed using an electronic balance (Spectrum; APX-203, Gardena, CA). The mice were housed 5 per cage. An inspection was performed before the administration and transplantation to ensure their suitability for the study.

The animals were maintained in a HEPA filtered environment in a Micro-VENT full ventilation rodent housing system (Allentown Caging Equipment Co., Allentown, NJ). Animal room controls were set to maintain temperature and relative humidity at 22°C ± 2°C and 55% ± 15%, respectively. The rooms were lit by artificial light for 12 hours each day. Cages and bedding were autoclaved. Water was purified by Milli-Q Biocel System (Millipore, Billerica, MA), autoclaved and supplied ad libitum to each cage via water bottles. Ampicillin (0.008% w/v) was added to drinking water during the period of acclimatization. Autoclavable rodent diet 5010 was obtained from PMI Nutrition International Inc., (Brentwood, MO).

All recipient mice were irradiated with a lethal dose of 8.0 Gy total body radiation. The day after irradiation, the mice received 1 x 10^7 bone marrow cells from GFP^+ donor mice via the tail vein. The mice were then randomly split into two groups, control (A) and experimental (B), and caged individually. The day of bone marrow cell transplantation was set as Day 0. Animals were monitored for behavioral changes during the whole study.

Materials and consumable preparation. StemEnhance (SE), a water-soluble extract of the cyanophyta *Aphanizomenon flos-aquae*, was supplied by STEMTech HealthSciences, Inc., SE was stored at room temperature and protected from light and humidity. Each cage was clearly marked with one mouse per cage. Experimental animals (Group B) were gavaged with 300 mg/kg of SE dissolved in 1 ml PBS while control animals (Group A) were gavaged with 1 ml PBS alone. Cardiotoxin (CTX) was purchased from Sigma (St. Louis, MO). To cause an injury, 10 μm of CTX in 100 μl PBS was injected directly into the anterior tibialis muscles of the right leg.

Study design. For both Group A and Group B, three mice were sacrificed at Day 16 after transplantation for hematology tests (**Fig. 1**). At Day 23, the remaining animals in each group were divided into two subgroups. For assessment of hematopoietic recovery, six animals were randomly selected from each group. Three animals in each group were sacrificed for hematology testing at days 23 and 30. For the assessment of the effect of SE on the regeneration of CTX-induced muscle injury, the remaining six animals in each group were treated on day 23 with CTX, as described previously. The animals continued to be treated with placebo or SE during the following 5 weeks and were sacrificed at Day 59 after transplantation for analysis of the presence of fluorescence in tissues.

Hematology testing. After transplantation, blood cell counts (WBC, RBC, hemoglobin, hematocrit, platelets, PMN, lymphocytes, monocytes, eosinophils and basophils) were done at days 15 and 30. Samples of whole blood were sent to Rabbit & Rodent Diagnostic Associates (RRDA, San Diego, CA) for reticulocyte counts.

Fluorescence imaging. At day 59 after transplantation, all mice were sacrificed. Open-mouse imaging was conducted with the Olympus OV 100 Small Animal Imaging System (Olympus America, Melville, NY). The mice were evaluated for incorporation of GFP bone-marrow cells into tissues, including heart muscle, liver, kidneys, intestinal wall, brain, skin and lung. To evaluate the effect of SE on the recovery from CTX-injury, the number of GFP-positive muscle fibers was estimated using Photoshop 7.0 (Adobe Systems Inc., San Jose, CA), by quantifying the number of pixels covering the fluorescent area.

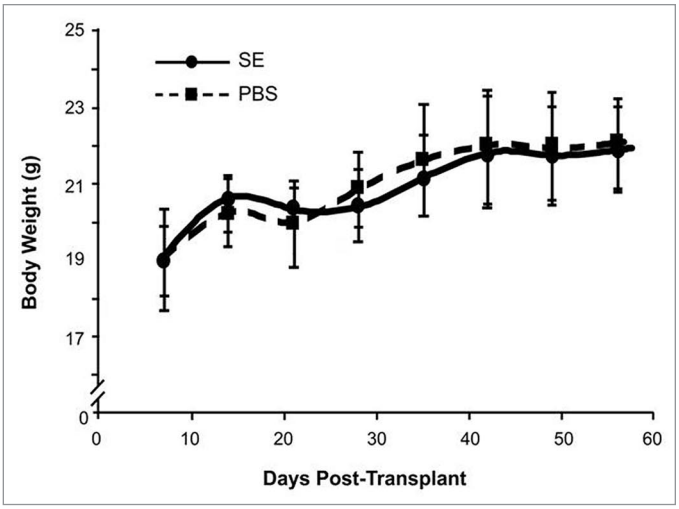

Figure 2. Animals were weighed every week during the 8 weeks of the study. SE did not affect growth pattern, as both groups showed identical growth curves. Both groups experienced a similar growth decrease during the two weeks after irradiation but resumed a normal growth pattern thereafter.

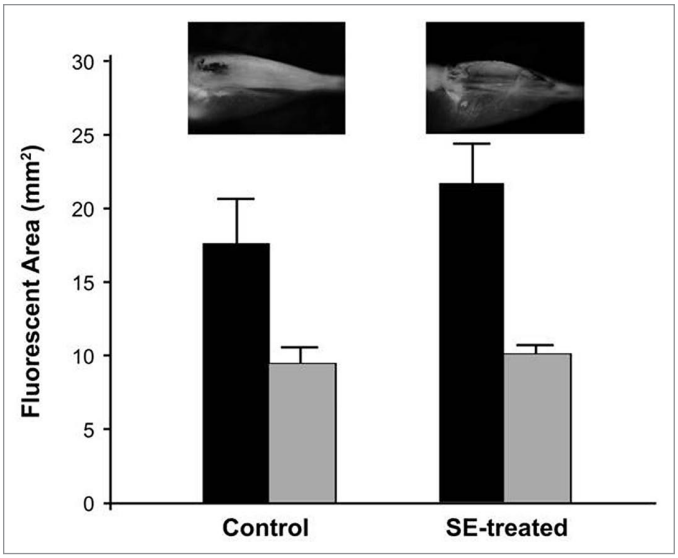

Figure 3. Graph showing the area covered by fluorescence in the CTX-treated right anterior tibialis (black) and untreated left anterior tibialis (gray), 5 weeks after CTX-injury. Fluorescence was due to migration of GFP bone-marrow cells. Migration of BMSC and incorporation of fluorescence was much less in the contralateral non-injured left leg ($p < 0.05$). On top of the graph are representative pictures of the right tibialis muscles from control group and SE-treated group, 5 weeks after CTX-induced injury.

Statistical analysis. Incorporation of fluorescence in the tibialis muscles of both groups was analyzed using Monte Carlo simulation (Resampling Stats for Excel 2007, Statistics.Com, Arlington, VA). Data is reported as mean ± standard error.

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