Reparative macrophage transplantation for myocardial repair: a refinement of bone marrow mononuclear cell-based therapy

Authors:
M N Podaru¹, L Fields¹, S Kainuma¹, Y Ichihara¹, M Hussain¹, F Lewis¹, T Ito¹, K Kazuya¹, F D'aquisto¹, K Suzuki¹, ¹St Bartholomew's and Queen Mary University, William Harvey Research Institute - London - United Kingdom of Great Britain & Northern Ireland,

Topic(s):
Basic Science - Cardiac Diseases: Gene Therapy, Cell Therapy

Citation:
Funding Acknowledgements:
British Heart Foundation (RG/15/3/31236); Heart Research UK (RG2618/12/13 and TRP06/15); St Barts Medical School London

Background. Recent research has revealed that reparative (alternatively activated or M2-like) macrophages play an important role in post-myocardial infarction (MI) cardiac repair, proposing that augmentation of these cells will enhance recovery from MI. Transplantation of bone marrow mononuclear cells (BM-MNCs) is an emerging therapy for MI while its therapeutic efficacy in previous clinical trials is not satisfactory. Given that BM-MNCs are a natural source of macrophages, we hypothesized that induced differentiation/polarisation of BM-MNCs to reparative macrophages before transplantation may enhance the effect of BM-MNC transplantation.

Purpose. This study aimed to develop a robust in vitro protocol to produce reparative macrophages from BM-MNCs and to establish the pre-clinical proof of concept data for reparative macrophage transplantation for the treatment of MI.

Methods & Results. Mouse BM-MNCs were treated with M-CSF plus IL-4, IL-10, TGF-β1 or combinations of these in vitro. The concomitant M-CSF+IL-4 protocol (both 20ng/ml) produced the highest rate (89.7±0.7%) and number (1.7-fold larger than the original cell number) of CD11b+F4/80+CD206+ macrophages. Expression and secretion of tissue repair-related factors of the produced cells, including IGF-1, TGF-β1, VEGF and IL1-ra, were more extensive compared to BM-MNCs. Then, 5x10⁵ BM-MNC-derived reparative macrophages, 5x10⁵ BM-MNCs, or saline only (control) were intramyocardially injected in a mouse MI model based on coronary artery ligation. At 4 weeks after treatment, echocardiography demonstrated that reparative macrophage transplantation markedly improved cardiac function (left ventricular ejection fraction; 57.2±1.6%, n=11) compared to both BM-MNC transplantation (48.4±1.3%, n=9) and control group (44.4±2.0%, n=9). Histological studies showed that infarct size was the smallest after reparative macrophage transplantation in association with the greatest tissue repair in the peri-infarct myocardium, including augmented microvascular formation, reduced cardiomyocyte hypertrophy and reduced pathological interstitial fibrosis. These were corresponded to amplified myocardial upregulation of tissue repair-related genes. Of note, survival of donor reparative macrophages in the heart post-transplantation was >10-fold greater compared to BM-MNCs. It was also found that reparative macrophage transplantation increased host-derived cardiac reparative macrophages. This might be a part of the mechanism by which reparative macrophage transplantation augmented myocardial repair, and our in vitro antibody neutralisation study indicated that TGF-β1 played a role in this donor macrophage-to-host macrophage pathway.

Conclusion. M-CSF+IL-4 treatment was effective in producing reparative macrophages from BM-MNCs in vitro. Addition of this pre-treatment improved the therapeutic effect of BM-MNC transplantation. Further preclinical and clinical development of this advanced cell therapy is warranted.
Reparative macrophage transplantation for myocardial repair: a refinement of bone marrow mononuclear cell-based therapy

Authors: M N Podaru1, L Fields1, S Kainuma1, Y Ichihara1, M Hussain1, F Lewis1, T Ito1, K Kazuya1, F D’aquisto1, K Suzuki1

1 St Bartholomew’s and Queen Mary University, William Harvey Research Institute - London - United Kingdom of Great Britain & Northern Ireland,

Topic(s): Basic Science - Cardiac Diseases: Gene Therapy, Cell Therapy

Background. Recent research has revealed that reparative (alternatively activated or M2-like) macrophages play an important role in post-myocardial infarction (MI) cardiac repair, proposing that augmentation of these cells will enhance recovery from MI. Transplantation of bone marrow mononuclear cells (BM-MNCs) is an emerging therapy for MI while its therapeutic efficacy in previous clinical trials is not satisfactory. Given that BM-MNCs are a natural source of macrophages, we hypothesized that induced differentiation/polarisation of BM-MNCs to reparative macrophages before transplantation may enhance the effect of BM-MNC transplantation.

Purpose. This study aimed to develop a robust in vitro protocol to produce reparative macrophages from BM-MNCs and to establish the pre-clinical proof of concept data for reparative macrophage transplantation for the treatment of MI.

Methods & Results. Mouse BM-MNCs were treated with M-CSF plus IL-4, IL-10, TGF-ß1 or combinations of these in vitro. The concomitant M-CSF+IL-4 protocol (both 20ng/ml) produced the highest rate (89.7±0.7%) and number (1.7-fold larger than the original cell number) of CD11b+F4/80+CD206+ macrophages. Expression and secretion of tissue repair-related factors of the produced cells, including IGF-1, TGF-ß1, VEGF and IL1-ra, were more extensive compared to BM-MNCs. Then, 5x10^5 BM-MNC-derived reparative macrophages, 5x10^5 BM-MNCs, or saline only (control) were intramyocardially injected in a mouse MI model based on coronary artery ligation. At 4 weeks after treatment, echocardiography demonstrated that reparative macrophage transplantation markedly improved cardiac function (left ventricular ejection fraction; 57.2±1.6%, n=11) compared to both BM-MNC transplantation (48.4±1.3%, n=9) and control group (44.4±2.0%, n=9). Histological studies showed that infarct size was the smallest after reparative macrophage transplantation in association with the greatest tissue repair in the peri-infarct myocardium, including augmented microvascular formation, reduced cardiomyocyte hypertrophy and reduced pathological interstitial fibrosis. These were corresponded to amplified myocardial upregulation of tissue repair-related genes. Of note, survival of donor reparative macrophages in the heart post-transplantation was >10-fold greater compared to BM-MNCs. It was also found that reparative macrophage transplantation increased host-derived cardiac reparative macrophages. This might be a part of the mechanism by which reparative macrophage transplantation augmented myocardial repair, and our in vitro antibody neutralisation study indicated that TGF-ß1 played a role in this donor macrophage-to-host macrophage pathway.

Conclusion. M-CSF+IL-4 treatment was effective in producing reparative macrophages from BM-MNCs in vitro. Addition of this pre-treatment improved the therapeutic effect of BM-MNC transplantation. Further pre-clinical and clinical development of this advanced cell therapy is warranted.