Chapter 1 : Bone Marrow in Hypoxia and Rebound - CORE

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Licence This is an open access article distributed under the terms of the Creative Commons Attribution License , which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. Abstract Decline in the therapeutic potential of bone marrow-derived mesenchymal stem cells MSC is often seen with older donors as compared to young. Although hypoxia is known as an approach to improve the therapeutic potential of MSC in term of cell proliferation and differentiation capacity, its effects on MSC from aged donors have not been well studied. MSC from old donors exhibited a reduction in proliferation rate and differentiation potential together with the accumulation of senescence features compared to that of young donors. However, MSC cultured under hypoxic condition showed enhanced self-renewing and proliferation capacity in both age groups as compared to normal condition. Bioinformatic analysis of the gene ontology GO and KEGG pathway under hypoxic culture condition identified hypoxia-inducible miRNAs that were found to target transcriptional activity leading to enhanced cell proliferation, migration as well as decrease in growth arrest and apoptosis through the activation of multiple signaling pathways. Overall, differentially expressed miRNA provided additional information to describe the biological changes of young and aged MSCs expansion under hypoxic culture condition at the molecular level. Introduction Mesenchymal stem cells derived from bone marrow BM-MSCs are adult multipotent stem cells with the self-renewing capacity and the ability to differentiate into cells of various connective tissue lineages. They are regarded as a promising and potential alternative source in the repair of many cells and tissues due to its multilineage differentiation capability into not only mesoderm but also ectodermic and endodermic lineages such as osteoblasts, chondrocytes, adipocytes, neurocytes and myoblasts Wei et al. MSCs are clinically used in engraftment of post-transplantation or as gene therapy vehicles in osteogenesis imperfecta because of their immunosuppressive capacity and are widely used in the treatment of cardiac disorder, musculoskeletal and cancer Baxter et al. Outstanding features of MSC are that it can be easily obtained from various sources of adult tissue adipose and bone-marrow and postnatal tissues Wharton-jelly and umbilical cord and can be expanded in vitro Oliveira et al. The challenge for MSC-therapy is that it requires high yield and good quality of stem cells. In order to get sufficient yield, stem cells need to be expanded under prolonged passage, which can lead to deterioration of its self-renewal and differentiation capacity. Prolonged passage has been reported to be directly linked with the shortening of telomere length that leads to decrease in cell proliferation and increase of senescence Samsonraj et al. Age is another factor that is associated with progressive loss of cell proliferation resulting in cellular senescence. Biological markers of cellular senescence were highly expressed in MSC from aged donors along with oxidative damage indicators Reactive oxygen species ROS and nitric oxide Stenderup et al. The acceleration of senescence was related with the decrease of cell proliferation and their life span as well as contributing to the accumulation of DNA damage leading to stem cell exhaustion Rube et al. These marked the compromised quality of MSCs with age as well as prolonged passage under normal condition. Despite that, in the case of autologous MSC transplantation for severe autoimmune diseases and old age related diseases in aged patients, the use of MSC of aged donor is still highly in demand Wang et al. Hypoxia is known to stimulate pro-angiogenic effects in stem cells while maintaining the telomere length Efimenko et al. Although the hypoxic condition has been demonstrated as a mode to improve the therapeutic potential of MSC Cicione et al. Interestingly, the miRNA expression patterns in MSC when subjected to various factors and culture conditions such as hypoxia and serum deprivation differ considerably Nie et al. Cumulative population doubling CPD was counted using Typan blue assay. To calculate the CPD, population doubling in each passage was determined and compared with the population doubling of earlier passages Stolzing et al. Multipotent differentiation The multipotency of MSCs were evaluated using adipogenic and osteogenic assays Pandey et al. Change of medium was performed every 3 days until 21 days when the matrix mineralization and lipid droplets were fully formed. Prior to

amplification, indices for sample multiplexing were incorporated. Pathway analysis Target genes were identified using a target prediction program miRDB. Normalization was done using the average value of miRa, miRp and miR evaluated using geNorm algorithms. Primer sequences for qPCR are listed in Table 1. The accession number and target sequence of the primers used in the quantitative real-time PCR assay.

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Disease[edit] The normal bone marrow architecture can be damaged or displaced by aplastic anemia , malignancies such as multiple myeloma , or infections such as tuberculosis , leading to a decrease in the production of blood cells and blood platelets. The bone marrow can also be affected by various forms of leukemia , which attacks its hematologic progenitor cells. Many of the symptoms of radiation poisoning are due to damage sustained by the bone marrow cells. To diagnose diseases involving the bone marrow, a bone marrow aspiration is sometimes performed. This typically involves using a hollow needle to acquire a sample of red bone marrow from the crest of the ilium under general or local anesthesia. Plain film x-rays pass through soft tissues such as marrow and do not provide visualization, although any changes in the structure of the associated bone may be detected. For example, normal fatty "yellow" marrow in adult long bones is of low density to Hounsfield units , between subcutaneous fat and soft tissue. Tissue with increased cellular composition, such as normal "red" marrow or cancer cells within the medullary cavity will measure variably higher in density. MRI enables assessment of the average molecular composition of soft tissues, and thus provides information regarding the relative fat content of marrow. In adult humans, "yellow" fatty marrow is the dominant tissue in bones, particularly in the peripheral appendicular skeleton. Because fat molecules have a high T1-relaxivity , T1-weighted imaging sequences show "yellow" fatty marrow as bright hyperintense. Furthermore, normal fatty marrow loses signal on fat-saturation sequences, in a similar pattern to subcutaneous fat. When "yellow" fatty marrow becomes replaced by tissue with more cellular composition, this change is apparent as decreased brightness on T1-weighted sequences. Both normal "red" marrow and pathologic marrow lesions such as cancer are darker than "yellow" marrow on T1-weight sequences, although can often be distinguished by comparison with the MR signal intensity of adjacent soft tissues. Normal "red" marrow is typically equivalent or brighter than skeletal muscle or intervertebral disc on T1-weighted sequences. Diffuse marrow T1 hypointensity without contrast enhancement or cortical discontinuity suggests red marrow conversion or myelofibrosis. Falsely normal marrow on T1 can be seen with diffuse multiple myeloma or leukemic infiltration when the water to fat ratio is not sufficiently altered, as may be seen with lower grade tumors or earlier in the disease process. Bone marrow examination is the pathologic analysis of samples of bone marrow obtained via biopsy and bone marrow aspiration. Bone marrow examination is used in the diagnosis of a number of conditions, including leukemia, multiple myeloma, anemia , and pancytopenia. The bone marrow produces the cellular elements of the blood, including platelets , red blood cells and white blood cells. While much information can be gleaned by testing the blood itself drawn from a vein by phlebotomy , it is sometimes necessary to examine the source of the blood cells in the bone marrow to obtain more information on hematopoiesis; this is the role of bone marrow aspiration and biopsy. The ratio between myeloid series and erythroid cells is relevant to bone marrow function, and also to diseases of the bone marrow and peripheral blood , such as leukemia and anemia. The normal myeloid-to-erythroid ratio is around 3: The preferred sites for the procedure In a bone marrow transplant , hematopoietic stem cells are removed from a person and infused into another person allogenic or into the same person at a later time autologous. If the donor and recipient are compatible, these infused cells will then travel to the bone marrow and initiate blood cell production. Transplantation from one person to another is conducted for the treatment of severe bone marrow diseases, such as congenital defects, autoimmune diseases or malignancies. The procedure is minimally invasive and does not require stitches afterwards. This procedure is similar to that used in blood or platelet donation. In adults, bone marrow may also be taken from the sternum , while the tibia is often used when taking samples from infants. The earliest fossilised evidence of bone marrow was discovered in in Eusthenopteron , a lobe-finned fish which lived during the Devonian period approximately million years ago. Pathology of bone marrow and blood cells 2nd ed. North-Western Journal of Zoology. Tissue Engineering

Part B:

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In these days, it was reported that bone marrow BM cells might take part in the remodeling of some systemic vascular diseases; however, it remains unknown whether the BM cells were involved in the vascular remodeling of pulmonary arteries and the progression of pulmonary hypertension PH. The purpose of this study was to investigate whether BM-derived cells contribute to pulmonary vascular remodeling in hypoxia-induced PH. Marked vascular remodeling including medial hypertrophy and adventitial proliferation was observed in the pulmonary arteries of PH mice. Strikingly, a number of GF[P. Metaspectrometer measurements using confocal laser scanning microscopy confirmed that this green fluorescence was produced by GFP, suggesting that these GF[P. Most of them expressed [alpha]-smooth muscle actin, a smooth muscle cell, or myofibroblast phenotype, and contributed to the pulmonary vascular remodeling. A semiquantitative polymerase chain reaction of the GFP gene revealed that the BM-derived GFP-positive cells in the PH group were observed more than eightfold as often compared with the control mice. The BM-derived cells mobilize to the hypertensive pulmonary arteries and contribute to the pulmonary vascular remodeling in hypoxia-induced PH mice. The causes of primary PH remain unknown, but it frequently leads to RV failure and death. Although much effort has been devoted to the treatment of PH, there is still no effective therapy available to prevent it. The pathogenesis of PH remains unclear, but is likely to at least in part be mediated by hypoxia. Acute exposure to hypoxia induces a selective pulmonary arterial vasoconstriction and an increase in pulmonary arterial pressure. Chronic hypoxia causes sustained PH and pulmonary vascular remodeling. Medial hypertrophy results from the proliferation of smooth muscle cells SMCs , and intimal thickening is caused by fibrosis, and the proliferation of endothelial cells, SMCs, and myofibroblasts. However, the precise mechanism of vascular remodeling in PH remains unresolved. Studies of the pathogenesis of vascular remodeling in general systemic vascular diseases have focused largely on the role of SMCs, which are derived locally from the adjacent medial layer, in vascular remodeling. However, there is accumulating evidence of the existence of circulating progenitor cells such as smooth muscle progenitor cells, endothelial progenitor cells, and fibroblasts. These cells can mobilize to sites of tissue injury and contribute to vascular remodeling in models of vascular disease such as postangioplasty restenosis, graft vasculopathy, and hyperlipidemia-induced atherosclerosis. In PH, the seminal study of Davie et al 13 raised the concept of BM cell mobilization to hypoxia-induced remodeled pulmonary arteries by demonstrating the existence of c-[kit. However, a more recent study by Hu et al 14 demonstrated the presence of Sca-[1. To clarify whether BM-derived cells can migrate to the hypoxia-induced PH lung, we generated chimeric mice by the transplantation of BM cells from enhanced green fluorescent protein GFP -transgenic mice into normal donor mice. We investigated BM cell mobilization to remodeled pulmonary arteries following prolonged exposure to hypoxia using a hypoxic chamber. In this report, we demonstrate directly that BM-derived cells can home to remodeled pulmonary arteries in PH mice and contribute to pulmonary vascular remodeling. For analysis of the engraftment of donor BM cells, peripheral blood was obtained from the retroorbital plexus of the recipient mice using micropipettes Drummond Scientific Co; Broomall, PA. Chamber gases were monitored continuously using an [O. The last 10 mice were kept in the normoxic condition as a control. Hemodynamics Mice were anesthetized with ketamine and xylazine, and a 1. Isolated lungs were immersion-fixed overnight at 4[degrees]C with rocking and subsequently were cryoprotected in sucrose solutions at 4[degrees]C. Cryostat sections 6 [micro]m thick were stained with hematoxylin-eosin and elastica van Gieson stain. The sections were incubated for 4 h at 4[degrees]C with secondary antibodies that had been conjugated Alexa ; Molecular Probes; Eugene, OR. Statistical significance was evaluated using the unpaired Student t test for comparisons between two mean values. Multiple comparisons among more than three groups were performed using analysis of variance. There was marked vascular remodeling including medial hypertrophy and adventitial proliferation in both the distal pulmonary artery Fig 2, top right, E, and upper middle, F and the proximal pulmonary artery Fig 2, lower

middle right, G, and bottom right, H of the PH mice compared to control mice Fig 2, top left, A, upper middle left, B, lower middle left, C, and bottom left, D. The exposure of these animals to hypoxia led to extensive vascular remodeling of the pulmonary arteries, which was characterized by medial hypertrophy and adventitial proliferation, leading to PH. Under high magnification, GF[P. It may also represent a reaction to injury associated with the presence of PH. There was a significant increase in numbers of GF[P. Moreover, the number of mobilized GF[P. Absorbance frequency analysis with a metaspectrometer LSM Metaspectrometer; Carl Zeiss confirmed that the green signals were not due to a nonspecific background Fig 4, bottom, C. Taken together, these results provide strong evidence that BM-derived cells, which were mobilized to the pulmonary arteries, contributed to pulmonary vascular remodeling in hypoxia-induced PH mice. Myofibroblasts play key roles in tissue remodeling, wound healing, and various fibrotic disorders, 16,17 and have been proposed to also be involved in the pathophysiology of vascular remodeling. Our present results strongly suggest that BM-derived cells that are mobilized to the pulmonary artery wall during hypoxia-induced remodeling can differentiate into myofibroblasts. These findings may indicate a reaction to injury that is associated with the presence of PH. It has generally been accepted that differentiation is the major mechanism by which stem cells acquire a vascular cell phenotype. Further studies are needed to clarify this mechanism. It will also be important in future studies to determine which BM cells are mobilized to remodeled pulmonary arteries to acquire an [alpha]-SM[A. There is evidence that both hematopoietie and mesenchymal stem cells can differentiate into SMCs. Hayashida, Fujita, Ogawa, and Fukuda, and Mrs. Kentaro Hayashida and Jun Fujita contributed equally to this study. Cellular and molecular mechanisms of pulmonary vascular remodeling. Annu Rev Physiol ; Hypoxia-induced pulmonary vascular remodeling: J Chn Invest ; Physiol Res ; Contribution of adventitial fibroblasts to neointima formation and vascular remodeling: Circ Res ; Hypoxic activation of adventitial fibroblasts: Chest ; suppl: Hypoxia induces differentiation of pulmonary artery adventitial fibroblasts into myofibroblasts. Am J Physiol Cell Physiol ; Host bone-marrow cells are a source of donor intimal smooth-muscle-like cells in murine aortic transplant arteriopathy. Nat Med ; 7: Circulating smooth muscle progenitor cells contribute to atherosclerosis. Hematopoietic stem cells differentiate into vascular cells that participate in the pathogenesis of atherosclerosis. Nat Med ; 8: Bone marrow-derived progenitor cells in pulmonary fibrosis. J Clin Invest ; Hypoxia-induced pulmonary artery adventitial remodeling and neovascularization: Abundant progenitor cells in the adventitia contribute to atheroselerosis of vein grafts in ApoE-deficient mice. FEBS Lett ; The roles of the myofibroblast in idiopathic pulmonary fibrosis: Am J Pathol ; Thrombin differentiates normal lung fibroblasts to a myofibroblast phenotype via the proteolytically activated receptor-1 and a protein kinase c-dependent pathway. J Biol Chem ; Adventitial myofibroblasts contribute to neointimal formation in injured porcine coronary arteries. Direct in vivo evidence demonstrating neointimal migration of adventitial fibroblasts after balloon injury of rat carotid arteries. Smooth muscle cells in human coronary atherosclerosis can originate from cells administered at marrow transplantation. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. Transplanted adult hematopoietic stems cells differentiate into functional endothelial cells. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. Little evidence for developmental plasticity of adult hematopoietie stem cells. Changing potency by spontaneous fusion. Regulation of smooth muscle actin expression and contraction in adult human mesenchymal stem cells. Exp Cell Res ;

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viii. effect of hypoxia and postâ€•hypoxic polycythaemia (rebound) on mouse marrow and spleen.

Chapter 7 : Formats and Editions of Bone marrow in hypoxia and rebound. [calendrierdelascience.com]

longed exposure to hypoxia. The bone marrow pluripotential stem cells were To assess whether there was a "rebound" accumulation of pluripotential.

Chapter 8 : The science behind the hypoxic niche of hematopoietic stem and progenitors

The immunohistological findings in the thymus after bone marrow transplantation were studied in autopsy samples from 12 patients who had received allogeneic grafts as treatment for acute leukemia.