Diabetes distresses bone marrow stem cells by damaging their microenvironment

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New research has shown the presence of a disease affecting small blood vessels, known as microangiopathy, in the bone marrow of diabetic patients. While it is well known that microangiopathy is the cause of renal damage, blindness and heart attacks in patients with diabetes, this is the first time that a reduction of the smallest blood vessels has been shown in bone marrow, the tissue contained inside the bones and the main source of stem cells.

These precious cells not only replace old blood cells but also exert an important reparative function after acute injuries and heart attacks. The starvation of bone marrow as a consequence of microangiopathy can lead to a less efficient healing in diabetic patients. Also, stem cells from a patient's bone marrow are the most used in regenerative medicine trials to mend hearts damaged by heart attacks. Results from this study highlight an important deficit in stem cells and supporting microenvironment that can reduce stem cells' therapeutic potential in diabetic patients.

The research team, led by Professor Paolo Madeddu, Chair of Experimental Cardiovascular Medicine in the School of Clinical Sciences and Bristol Heart Institute at the University of Bristol, investigated the effect of diabetes on bone marrow stem cells and the nurturing of small blood vessels in humans.

The new study, published in the American Heart Association journal Circulation Research, was funded by the British Heart Foundation

(BHF).

The researchers have shown a profound remodelling of the marrow, which shows shortage of stem cells and surrounding vessels mainly replaced by fat, especially in patients with a critical lack of blood supply to a tissue (ischaemia). This means that, as peripheral vascular complications progress, more damage occurs in the marrow. In a vicious cycle, depletion of bone marrow stem cells worsens the consequences of peripheral ischaemia.

Investigation of underpinning mechanisms revealed that exposure of bone marrow stem cells to the high glucose level typical of diabetes mellitus impacts on "microRNAs", which are tiny RNA molecules controlling gene expression and hence biological functions. In particular, microRNA-155, that normally controls the production of stem cells, becomes dramatically reduced in bone marrow cells exposed to high glucose. Diabetes-induced deficits are corrected by reintroducing microRNA-155 in human stem cells. The authors foresee that microRNAs could be used to regain proper stem cells number in diabetes and fix stem cells before reintroduction into a patient's body.

Professor Madeddu said: "Our study draws attention to the bone marrow as a primary target of diabetes-induced damage. The research suggests that the severity of systemic vascular disease has an impact on bone marrow causing a precocious senescence of stem cells. More severe bone marrow pathologies can cause, or contribute to, cardiovascular disease and lead to worse outcomes after a heart attack, through the shortage of vascular regenerative cells. Clinical evidence indicates that achieving a good control of glucose levels is fundamental to prevent vascular complications, but is less effective in correcting microangiopathy. We need to work hard to find new therapies for mending damaged microvessels."

Professor Costanza Emanueli, Chair of Vascular Pathology and Regeneration at University of Bristol and co-author of the paper, added: "MicroRNAs represent an attractive means to repair the marrow damage and generate "better" stem cells for regenerative medicine applications. We are working at protocols using microRNA targeting for enhancing the therapeutic potential of stem cells before their transplantation to cure heart and limb ischaemia, which are often associated with diabetes mellitus. More work is, however, necessary before using this strategy in patients."

The findings advance the current understanding of pathological mechanisms leading to collapse of the vascular niche and reduced availability of regenerative cells. The data provides a key for interpretation of diabetes-associated defect in stem cell mobilisation following a heart attack. In addition, the research reveals a new molecular mechanism that could in the future become the target of specific treatments to alleviate vascular complications in patients with diabetes.

Professor Jeremy Pearson, Associate Medical Director at the BHF said: "Professor Madeddu and his team have shown for the first time that the bone marrow in patients with diabetes can't release stem cells which are important for the repair of blood vessel damage commonly found in people with the disease.

"If we could restore the ability of the marrow to release stem cells there is potential to reduce the effects of diabetes, and prevent the devastating consequences of the condition such as blindness and amputation. Understanding more about injured blood vessel repair will also aid in the fight to mend hearts damaged after a heart attack, a vital research area we fund through our Mending Broken Hearts Appeal.'

More information: Global Remodeling of the Vascular Stem Cell

Niche in Bone Marrow of Diabetic Patients: Implication of the miR-155/FOXO3a Signaling Pathway, Gaia Spinetti, Daniela Cordella, Orazio Fortunato, Elena Sangalli, Sergio P. Losa, Ambra Gotti, Franco Carnelli, Francesco Rosa, Stefano Riboldi, Fausto Sessa, Elisa Avolio, Antonio Paolo Beltrami, Costanza Emanueli, and Paolo Madeddu, *Circulation Research*, originally published online December 18, 2012.

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