Scottish Government Health Directorates Chief Scientist Office

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Vascular injury and repair in premature coronary artery disease: understanding the role of endothelial progenitor cells

Researchers
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Aims
Late outgrowth endothelial cells (EOC) can be isolated from peripheral blood and are thought to derive from a true circulating endothelial progenitor cell, but their origin, phenotype and role in the pathophysiology of coronary artery disease is not known. Our aim was to determine whether the precursors of EOCs originate in the bone marrow or in a vascular niche. We then compared the function of EOC from patients with coronary artery disease and matched control subjects to determine their role in the pathogenesis of disease.

Methodology
To address these aims we undertook three separate clinical studies. ***a)*** In healthy volunteers we compared the phenotype and function of outgrowth cells from peripheral blood and bone marrow with mature endothelial cells. ***b)*** In male patients who received bone marrow transplants from female donors we determined the genotype of EOC isolated from blood and mature endothelial cells from the vessel wall. The genotype was determined by fluorescence in situ hybridisation (FISH) against the X and Y chromosomes combined with staining for the endothelial cell marker CD31, and verified using 16 multiplex short tandem repeat (STRs) analysis. ***c)*** We then compared the phenotype and function of EOC and vessel wall endothelial cells from patients with premature coronary artery disease (n=16) and healthy matched controls (n=16).

Key Results
1. EOC, the progeny from circulating endothelial progenitor cells, are indistinguishable from mature endothelial cells by surface antigen expression, immune-histochemistry, real-time polymerase chain reaction, proliferation, and functional assessments *in vitro* and *in vivo*.
2. In contrast, bone marrow-derived outgrowth cells isolated under the same conditions did not give rise to endothelial cells or contribute to blood vessels *in vivo*.
3. In patients with a sex-mismatched allogeneic bone marrow transplant, we show that EOCs do not have the same genotype as the donor and therefore their precursors must originate from a niche outwith the bone marrow.
4. Finally, in patients with coronary artery disease we demonstrated that vessel wall endothelial cells, but not EOCs derived from a circulating progenitor cell, were dysfunctional compared to matched controls.

Conclusions
Circulating endothelial progenitor cells capable of forming functional endothelial cells do not originate from the bone marrow. Furthermore, deficiencies in the number and function of circulating progenitor cells are not responsible for the development of premature atherosclerosis.

What does this study add to the field?
This represents a paradigm shift in our understanding of endothelial progenitor cell biology that requires a re-evaluation of our approach to harness these cells for therapeutic vascular regeneration.

Implications for Practice
Identification of the origin and phenotype of true endothelial progenitor cells and a better understanding of their role in coronary artery disease may lead to new treatments for patients. Our insights will help design more effective therapeutic approaches to promote vascular regeneration.

Where to next?
Support from this Chief Scientists Office grant has lead to the development of the first ever clinical grade manufacture and production of endothelial progenitor cells for therapeutic use. In a proof of concept clinical trial we will treat patients with acute vascular injury and determine whether these cells can home, integrate and contribute to functional recovery of the blood vessel following injury.

Further details

Tura O et al. Stem Cells. 2013;31(2):338-48.
Brittan M et al. Eur J Prev Cardiol. 2015;22:1557-66.

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