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RACP Foundation Research Awards

FINAL REPORT

Project Title		A novel role for Adventitial Macrophage Progenitor Cells (AMPCs) in providing a local source of macrophages in atherosclerosis
Name		Dr Peter James Psaltis
Award Received		2018 RACP Fellows Career Development Fellowship
Report Date		1 February 2019
Chief Investigator / Supervisor		Peter J Psaltis - CI Stephen J Nicholls - Supervisor
Administering Institution		South Australian Health and Medical Research Institute
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PROJECT SUMMARY

As the main cause of heart attack and stroke, atherosclerosis causes enormous burden to patient morbidity, mortality and health care expenditure. A better understanding of how atherosclerosis develops is therefore crucial to national and global health, to improve preventive and treatment strategies. Specialised white blood cells (macrophages) play an integral role in formation of atherosclerotic plaque, that leads to arterial narrowing, as well as plaque rupture and clot formation that result in arterial occlusion. For a long time, it has been thought that all macrophages in atherosclerotic arteries come from cells called monocytes, that originate in bone marrow, circulate in blood and enter the artery wall to become macrophages. We have discovered a new population of "stem" cells, called Adventitial Macrophage Progenitor Cells (AMPCs), that are present in the outer layer of arteries (adventitia), and can generate macrophages independently of circulating blood monocytes. We have found that these AMPCs are more abundant in atherosclerotic blood vessels. In this project, we have been studying the hypothesis that AMPCs become activated in atherosclerosis and provide a local source of macrophages, that contribute to the build-up of plaque and its destabilisation, from the outside of the artery wall inwards. This research is ongoing but in time could lead to new insights into atherosclerosis, and in turn new treatment strategies, with great scope to impact on human cardiovascular disease

PROJECT AIMS / OBJECTIVES

AIMS:

(1) To study macrophages origins in atherosclerotic arteries by lineage tracing.

(2) To examine the direct contribution of AMPCs to plaque macrophages by adoptive transfer.

(3) To assess how depletion of AMPCs affects plaque formation.

RESEARCH PLAN:

(1) FLT3-mTmG-ApoE-/- mice fed Western diet (WD) have been studied to track the contributions of bone marrow (BM) haematopoiesis (FLT3+, GFP+) versus local myelopoiesis (FLT3-, tdTom+) to macrophages in early, established and advanced aortic plaques.

(2) Unstable plaque will be induced by carotid tandem stenosis surgery in WD-fed ApoE-/- mice. GFP+ AMPCs will be injected into carotid adventitia to study their contribution to plaque Mϕs.

(3) Different mouse pairings, involving CX3CR1(null)-ApoE-/- mice that are deficient in AMPCs, have been bred. We will soon be performing irradiation-BM transfer studies to assess how AMPC depletion affects aortic plaque formation.

SIGNIFICANCE AND OUTCOMES

Atherosclerosis is the underlying disease process responsible for the vast majority of myocardial infarctions. Current prevention and treatment strategies for atherosclerosis focus mainly on risk factor modification, and are far from curative. Inflammation is at the core of atherosclerotic plaque formation, with macrophages a central player. It follows that understanding precisely how macrophages develop in plaques is vital to optimising atherosclerosis management. We have discovered and characterised the existence of resident adventitial macrophage progenitor cells (AMPCs) in healthy and atherosclerotic arteries. Our data so far indicate that this novel population of stem-like cells contributes to macrophage self-renewal and proliferation in blood vessels, but also the formation of endothelial cells and vasa vasorum in the atherosclerotic vessel wall. By systematically studying the contribution of AMPCs to different macrophage subsets in plaque and the development of vasa vasorum during plaque growth, our work is re-challenging long-standing paradigms about macrophage and endothelial cell biology in atherosclerotic blood vessels. This is helping to uncover new insights into the inflammatory basis of atherosclerosis and in time has the potential to open up new opportunities for cell-targeted therapies for vascular diseases.

PUBLICATIONS / PRESENTATIONS

1. Toledo-Flores D, Williamson A.....Psaltis PJ. Vasculogenic properties of adventitial Sca-1+CD45+ progenitor cells in mice: a potential source of vasa vasorum in atherosclerosis. In Revision 2019.

2. Franke K.....Psaltis PJ. Current State-of-Play on Spontaneous Coronary Artery Dissection. In Submission 2019.

3. Williamson A, Toledo-Flores D.....Psaltis PJ. Discovery of postnatal tissue-resident haemangioblast progenitor cells that arise from extra-embryonic yolk sac. In Preparation 2019.

Abstract:

1. Williamson A.....Psaltis PJ. Postnatal murine aorta contains self-renewing progenitor cells with bipotent myeloid and endothelial plasticity and vasculogenic capacity. Australian Vascular Biology Society ASM Nov 2018. Adelaide. Young Investigator Awards - Oral Presentation - Finalist.

2. Liyanage S.....Psaltis PJ. Discovery and characterisation of haemangioblasts in postnatal murine skin: implications for wound healing. Australian Vascular Biology Society ASM Nov 2018. Adelaide. Young Investigator Awards - Oral Presentation - Winner.

3. Schwarz N.....Psaltis PJ. FLT3 lineage-mapping reveals the origins of aortic macrophages during atherosclerosis development in mice. Australian Atherosclerosis Society ASM Nov 2018. Early Career Investigator Awards - Minioral Presentation - Winner