Title: LRG1 as a novel target for therapeutic angiogenesis

Ischemic cardiovascular diseases (CVDs) are caused by atherosclerosis-related restriction of blood flow to the heart (coronary artery disease), brain (cerebrovascular disease) and peripheral muscles (peripheral arterial disease). CVDs are the leading cause of death worldwide. An estimated 17 million people die of CVDs every year accounting for 30% of all global death (The World Health Organization (WHO)). Several intervention options are available to control CVDs, however, a substantial proportion of patients are not responsive or suitable for these procedures [1]. Accelerating blood vessel formation by pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) and basic Fibroblast Growth Factor (bFGF) has been considered as an attractive therapeutic option to bypass occluded vessels, re-vascularize ischemic tissues and restore tissue function [2-4]. Although therapeutic angiogenesis approach is supported by an impressive body of preclinical evidence, the translation of this seemingly simple principle has proven highly problematic partly due to the complex nature of angiogenesis and human ischemic diseases, and the difference in pathophysiology and tissue recovery between animal models and human diseases. Novel treatment options targeting alternative or complementary angiogenic pathways may synergistically induce functional blood vessel formation to restore perfusion in ischemic tissues.

We recently identified a novel angiogenic factor, namely Leucine rich alpha-2-glycoprotein 1 (LRG1), and found that LRG1 promotes blood vessel formation through switching the endothelial transforming growth factor (TGF) β signalling towards the pro-angiogenic pathway [5]. Whilst this angiogenic switch in TGFβ signalling has been known for many years, our work is the first to show that LRG1 is a major player in this phenomenon and explains in part the context-dependency of TGFβ signalling. Given the multifunctional role of TGFβ at various stages during angiogenesis, it is likely that LRG1 is also involved in other TGFβ regulated processes. Preliminary data shows a significant reduction of LRG1 expression in heart biopsies in patients with diabetes-related myocardial infarction (Figure 1). In addition to its ability to promote vessel formation on its own in combination with VEGF (Figure 2), we also found that LRG1 is involved in the TGFβ mediated extracellular matrix (ECM) deposition and contractile protein expression in VSMC (Figure 3). We therefore hypothesize that LRG1 influences the context-dependent behaviour of TGFβ in both ECs and mural cells, and LRG1 overexpression promotes functional blood vessel formation and ischemic tissue function. To test this hypothesis, we aim to: 1) to investigate the role of LRG1 in endothelial cell, vascular smooth muscle cell and pericyte signalling and function, 2) to study the role of LRG1 in endothelial cells/mural cell interaction, 3) to characterize the consequence of LRG1 and LRG1/VEGF combination treatment on blood vessel formation in vivo, and 4) to evaluate the therapeutic potential of LRG1 and LRG1/VEGF combination treatment for heart failure using TAC and left anterior descending (LAD) coronary artery ligation model. We anticipate that the outcome of this project will provide novel insights into the molecular mechanism of angiogenesis, and aid the development of novel therapeutics to treat ischemic CVDs.

Figure 1: Reduced LRG1 expression is observed in the infarcted heart. Heart biopsies were collected from human patients with diabetic ischemic heart disease. The expression of LRG1 was analysed by qRT PCR. Biopsies from healthy heart were used as the control. All data are mean ± s.e.m. of n=3 independent experimental groups. *P < 0.05; *** P < 0.001 (Student’s t-test).


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