

TITLE OF PROJECT

Control of vascular development: a role for the enzyme sphingosine kinase



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Project Description

Endothelial cells (ECs) make up the inner lining of blood vessels which then act as a barrier between the circulating blood and tissues. ECs develop via maturation from their precursor, the endothelial progenitor cell (EPC). Regulation of EPC to EC maturation, as well as their survival, is critical for maintaining health and well being as abnormalities in these cells have been attributed to many debilitating and life threatening diseases (eg rheumatoid arthritis, diabetes, cardiopathies and cancer).

Sphingosine kinase (SK) is a widely expressed enzyme with a known role in regulating cell survival and maturation. We have recently submitted a manuscript suggesting that SK is a regulator of EPC maturation to EC and successfully obtained a 3 year NHMRC grant to investigate the importance of SK in EPC maturation. SK catalyses the formation of sphingosine-1-phosphate (S1P) which is primarily stored and released from activated platelets, but can also be synthesized in other cells (including ECs) in response to various stimuli. Secreted S1P levels are high (100-300 nM) in blood and body fluids and bind to cells expressing the membrane receptors of the S1P receptor family (S1P₁₋₅). The receptor expression for S1P is currently unknown and may be the key to regulating EPC maturation.

Summary

The experiments, utilizing transgenic animals over-expressing SK specifically in the EC compartment, as well as mice depleted of SK should confirm that SK modulates EPC fate (ie differentiation, maturation and survival). By isolating bone marrow cells and generating both EPCs and ECs from these mice (as well as normals) we will determine whether this enzyme holds an essential role in the survival and function of ECs which are critical in blood vessel formation as well as the inflammation associated with a multitude of diseases.

We believe that by understanding the mechanisms in EPC maturation therapeutic targets can be generated.

References

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3. Xia P, et al . An oncogenic role for sphingosine kinase. *Current Biology* 2000, 10: 1527-1530.