

## **Differential Actions of S1P Receptors in the Regulation of Microvessel Permeability in Vivo**

**Presenter** Zhang, Gengqian

**Advisor** He, Pingnian

**Collaborators:** Wang, Qian

Sphingosine 1-phosphate (S1P) is a blood-borne biologically active lipid mediator. S1P receptors are widely expressed in mammals and are thought to regulate various physiological actions, including endothelial cell proliferation and migration, adherens junction assembly, and endothelial barrier functions. Three subtypes of S1P receptors, S1P1-3, have been reported in vascular endothelial cells, but their specific functions remain to be defined. Our previous studies demonstrated that S1P prevented PAF-induced endothelial gap formation and permeability increases in intact microvessels. Our present study aims to identify the specific S1P receptors responsible for the protective role of S1P in microvessel permeability in vivo. Microvessel permeability was determined by Lp measurements in individually perfused rat mesenteric venules. Four combined and selective S1P receptor antagonists (VPC23019 against S1P1 & 3, W146 against S1P1; JTE-013 against S1P2; and CAY10444 against S1P3) were used to identify the S1P receptors responsible for the protective role of S1P in PAF-induced permeability increases. In each experiment, after measuring baseline Lp with Ringer-albumin perfusate, the same vessel was first perfused with S1P receptor antagonist (10  $\mu$ M) for 30 min followed by addition of PAF (control) or sequential addition of S1P (10  $\mu$ M, 30 min) and PAF (10 nM) to the perfusate. Each antagonist alone did not affect baseline Lp or PAF-induced Lp increases. While in VPC23019 or W146 perfused vessels, the inhibitory effect of S1P on PAF-induced Lp increases was completely abolished. The mean peak Lp with PAF addition in the presence of S1P was  $8.8 \pm 1.1$  times that of the control, which was similar to that observed in PAF-stimulated vessels in the absence of S1P. In contrast, the selective S1P2 and S1P3 antagonist, JTE-013 and CAY10444 showed no effect on the inhibitory role of S1P in PAF stimulated vessels. Our results indicated that endothelial receptor S1P1, and not S1P2 or S1P3, is responsible for the protective role of S1P in permeability of intact microvessels. Supported by HL56237 and HL084338.