6-4 Sphingosine 1-Phosphate-Related Metabolism in the Blood Vessel

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Summary. Sphingosine 1-phosphate (S1P) is an important intercellular lipid mediator, especially in vascular biology. Blood platelets store S1P abundantly and release this bioactive lysophospholipid extracellularly upon stimulation. Vascular endothelial and smooth muscle cells respond dramatically to this platelet-derived lipid. Regulating S1P biological activities may be valuable to treat vascular disorders, and, as such, requires a better understanding of those mechanisms that mediated vascular S1P. Various factors may mediate the level and function of plasma S1P in vivo, these include S1P release from platelets and S1P distribution between albumin and lipoproteins as well as S1P receptor (S1P) expression and lipid phosphate phosphatase activity on vascular cells. In atherosclerotic diseases, where the plasma levels of lipids and lipoproteins or endothelial cell functions are altered, modulating effects of S1P may be of pathophysiological importance.

Keywords. Sphingosine 1-phosphate, platelets, vascular endothelial cells, vascular smooth muscle cells, vascular biology, lipid phosphate phosphatase
1. Introduction

Sphingosine 1-phosphate (SIP) is a bioactive sphingolipid capable of inducing a wide spectrum of biological responses, mainly through a family of G protein-coupled cell-surface receptors named SIP_1-5 (originally EDG-1, 5, 3, 6, and 8, respectively) (Kluk and Hla 2002, Lynch 2002, Spiegel and Milstien 2002, Takuwa 2002, Hla 2003, Spiegel and Milstien 2003). SIP is an important intercellular lipid mediator, especially in vascular biology (Liu et al. 2000, Yatomi et al. 2001, Karliner 2002, Okajima 2002, Panetti 2002, Siess 2002, Ozaki et al. 2003). Blood platelets store SIP abundantly and release this bioactive lysosphospholipid extracellularly upon stimulation. Vascular endothelial cells (ECs) and smooth muscle cells (SMCs) respond dramatically to this platelet-derived lipid. Recent reports detail the functional roles of SIP in platelet-vascular cell interactions (Liu et al. 2000, Yatomi et al. 2001, Karliner 2002, Okajima 2002, Panetti 2002, Siess 2002, Ozaki et al. 2003). SIP interactions with ECs may sustain vascular system integrity and mediate physiological wound healing processes such as vascular repair. This important lipid, however, can become atherogenic and thrombogenic, thereby causing, or aggravating, cardiovascular diseases. Furthermore, SIP interaction with SMCs induces a variety of responses, including vasoconstriction. Hence, it seems likely that the manipulation of SIP would have invaluable therapeutic benefits for treating vascular disorders. To this end, it is essential to fully understand the mechanisms that contribute to the regulation of SIP levels in blood vessels. One such mechanism is SIP-related metabolism in the blood vessel.

2. SIP release from activated platelets: source of plasma SIP

SIP forms intracellularly through the phosphorylation of sphingosine (Sph) that is catalyzed by Sph kinase (Kohama et al. 1998, Olivera et al. 1998). The SIP lyase, which degrades SIP into phosphoethanolamine and fatty aldehyde, seems the most important enzyme for degradation of SIP (van Veldhoven and Mannaerts 1993), but phosphatase activity for SIP should not be neglected. Platelets possess a highly active Sph kinase (Stoffel et al. 1973, Yatomi et al. 1995, Yatomi et al. 1997b) but are devoid of SIP lyase, a nearly ubiquitous enzyme present in almost all tissues van (Veldhoven and Mannaerts 1993, Yatomi et al. 1997b) (Figure 1). As a result, platelets store SIP abundantly (Yatomi et al. 1997a, Yatomi et al.