

Abstract No. Daut0243

The Structure of the Endothelial Protein C Receptor and a Bound Phospholipid

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Beamline(s): X9B

The endothelial cell protein C receptor (EPCR) shares ~20% sequence identity with the major histocompatibility complex class 1/CD1 family of molecules, accelerates the thrombin-thrombomodulin-dependent generation of activated protein C, a natural anticoagulant, binds to activated neutrophils, and can undergo translocation from the plasma membrane to the nucleus. Blocking protein C/activated protein C binding to the receptor inhibits not only protein C activation but the ability of the host to respond appropriately to bacterial challenge, exacerbating both the coagulant and inflammatory responses. To understand how EPCR accomplishes these multiple tasks, we solved the crystal structure of EPCR alone and in complex with the phospholipid binding domain of protein C. The structures were strikingly similar to CD1d. A tightly bound phospholipid resides in the groove typically involved in antigen presentation. The protein C binding site is outside this conserved groove and is distal from the membrane-spanning domain. Extraction of the lipid resulted in loss of the protein C binding, which could be restored by lipid reconstitution. CD1d augments the immune response by presenting glycolipid antigens. The EPCR structure is a model for how CD1d binds lipids and further suggests additional potential functions for EPCR in immune regulation, possibly including the anti-phospholipid syndrome.