Dimorphisms in the Membrane-Spanning Domain of EPCR Impact Systemic Coagulation

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The role of vascular coagulation receptors, particularly modest changes in the levels of these proteins in terms of controlling downstream coagulation factor activation, remains largely unknown. The study reported by Ireland and colleagues in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology demonstrates that a moderately common dimorphism in the endothelial cell protein C receptor (EPCR) influences the levels of markers of ongoing coagulation (Figure). Several of the key components, thrombomodulin and the EPCR, are subject to downregulation by inflammatory mediators that could play a role potentially in local thrombotic events. EPCR is an important regulatory factor in that it binds protein C and activated protein C, augments protein C activation by the thrombin-thrombomodulin complex, facilitates activated protein C cytoprotective activity, binds factor VII and VIIa, and leads to the internalization and degradation of both factor VII and protein C. In addition, the EPCR gene has a relatively common dimorphism in which there is a Ser to Gly substitution in the membrane spanning domain. This substitution leads to increased shedding, probably catalyzed by TACE (tumor necrosis factor-α converting enzyme), of EPCR as a soluble form from the endothelial cell surface. Shedding increases the levels of circulating EPCR at the expense of membrane-bound EPCR and hence should impact EPCR function. Indeed the 3 genotypes Ser-Ser, Ser-Gly, and Gly-Gly were identified in the human population and studied in the analysis by Ireland et al. for alterations in a variety of markers of ongoing coagulation, particularly factor VII and VIIa levels, prothrombin fragment 1 to 2, and factor IX activation peptide. The fundamental observations of interest are that in individuals with the Gly variants, the levels of factors VII and VIIa were elevated. These studies are the first human studies to indicate in vivo that EPCR apparently serves as a significant reservoir for factor VII. These results are consistent with mouse studies in which the role of EPCR in controlling factor VII levels could be evaluated more directly than in the human studies. Also of interest is the finding that the people with the EPCR Gly variants had elevated levels of markers of coagulation factor activation.

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Figure. EPCR shedding influences systemic coagulation. There is a common amino acid dimorphism in the membrane spanning domain, illustrated as either Ser or Gly. The Gly variant is shed more rapidly by endogenous enzymes, probably TACE (tumor necrosis factor-α converting enzyme). The Gly EPCR variant is shed much more rapidly than the Ser variant. Humans with the Gly variant have elevated plasma EPCR levels and, as shown in this study, elevated factor VII/VIIa, fragment 1 to 2 and factor IX activation peptide levels. EPCR indicates endothelial cell protein C receptor; PC, protein C; APC, activated protein C.

See accompanying article on page 1968

Ireland and colleagues consider many of the possible mechanisms for perturbation of downstream coagulation by the Gly variants including decreased clearance of Factor VII/VIIa, decreased protein C activation, and hence less effective regulation of coagulation. Other possibilities include potential contributors to elevated coagulation activation markers. Because EPCR is important for APC cytoprotective effects, including suppression of adhesion molecule expression on the surface of the endothelium, it is also possible that the decrease in endothelial cell surface expression of EPCR could result in increased cell activation and this, in turn, could result in increased downstream coagulation. At present, we do not know several things about the system that might help distinguish the mechanisms responsible for enhanced coagulation activation. Although we assume that increased shedding reduces the cell surface EPCR expression, we do not know how much the expression is reduced or whether release is widely distributed over the cell surface or localized, which could have different impacts on signaling. In addition, we do not know whether the EPCR Gly variants influence EPCR release differentially in specific vascular beds.

The findings of Ireland and colleagues also add to the limited but emerging information that EPCR deficiency might contribute to thrombotic disease. A small number of patients within a family were identified with a mutation that results in failure to express one allele and hence is the equivalent of heterozygous deficiency. These patients had an apparent association with increased risk of both venous and arterial thrombosis but because the affected family mem-
bers were relatively few, a clear indication of the causal association of the deficiency with thrombosis was not possible. The EPCR Gly variant would be expected to have less effect on vascular levels of EPCR than that seen in the patients, hence demonstrating that this modest decrease leads to elevated markers of ongoing coagulation would be consistent with the clinical picture observed in the patients with heterozygous deficiency. They are also consistent with the observed association of EPCR haplotype with increased risk of thrombosis, an association not observed in other clinical studies.

Disclosures

None.

References

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