

NEW PERSPECTIVE STUDIES ON THE BLOOD COAGULATION FACTORS AND VASCULAR ENDOTHELIAL GROWTH FACTORS

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In studies of blood coagulation and the vascular system, snake venom toxins have been indispensable in elucidating the complex physiological mechanisms. In the past three decades, much has been learned about coagulations factor, and crystallographic structures of some these factors are available. However, the Gla domains of two blood coagulation factors IX and X were recently determined in our studies of two Gla domain-binding anticoagulants in snake venom. This review describes the finding of studies in which snake venom anticoagulants were used to examine the crystal structure and function of Gla domain in coagulation factors IX and X.

1. Studies on the vitamin K-dependent coagulation factors

We have found that blood coagulation factor IX contains Mg (II)-binding site(s) which is independent on Ca (II) binding sites. The Mg ions had the strong effect on the factor IX clotting activities. In addition to the acceleration of activity by Mg²⁺ ions, folding of the native tertiary structure of factor IX Gla domain appears to require not only Ca²⁺ but also Mg²⁺ ions. The Gla domain of factor Xa is bound to X-bp. The crystal structure of factor X Gla domain peptide complexed with its binding protein X-bp has been determined at 2.3 Å resolutions. The Gla domain-binding site is located on a concave depression surrounded by two subunits of factor-X-bind protein.

Adenoviruses are very often used as gene transfer agents, both clinically and experimentally. Dr. Baker and coworkers have recently demonstrated that coagulation factor X Gla-domain directly binds adenovirus leading to liver infection. In these studies, they have used very effectively factor X-binding protein (Factor X Gla-domain-binding protein) which we have previously isolated and characterized

2. Studies on VEGF and its related proteins.

The family of VEGF ligands has recently grown to include six subtypes: VEGF-A, VEGF-B, placenta growth factor (PLGF), VEGF-C, and VEGF-D from mammal, as well as viral VEGF-E. We have recently isolated two new VEGF which has different its receptor affinities to VEGF receptors. Thus, we defined a novel subtype, seventh member of VEGF family, VEGF-F. We have characterized the unique properties, and crystallized to determine the crystal structure.

Snake venoms are a valuable source of proteins, which could aid in the investigation of coagulation and vascular system in mammals.