Biological Science

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Structural basis for the cooperative interplay between the two causative gene products of combined factor V and factor VIII deficiency

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Introduction

Combined deficiency of coagulation factors V and VIII (F5F8D), an autosomal recessive disorder characterized by coordinate reduction in the plasma levels of factor V (FV) and factor VIII (FVIII), is genetically linked to mutations in the transmembrane lectin ERGIC-53 and the soluble calcium-binding protein MCFD2. For better understanding of the mechanisms underlying the functional coordination of ERGIC-53 and MCFD2, we provided the structural basis for the interaction between MCFD2 and the carbohydrate recognition domain (CRD) of ERGIC-53 [1].

Experimental Procedure

Crystals of the complex between the CRD of ERGIC-53 and MCFD2 were obtained in trigonal $P3_121$ form by the hanging drop vapor diffusion method. Diffraction data sets were collected at Photon Factory BL5A. The crystal structure was solved by molecular replacement. The refined model of the complex between ERGIC-53-CRD and MCFD2 has an R of 18.8 % and R_{free} was 20.0% for data between 49.8 and 1.84 Å resolution (Fig. 1). In this crystal structure, two different packing interactions were observed between ERGIC-53-CRD and two MCFD2 molecules, one of which is from the next unit cell.

Results and Discussion

By X-ray crystallographic analysis in conjunction with NMR and ultracentrifugation analyses, it was revealed that ERGIC-53-CRD binds MCFD2 through its molecular surface remote from the sugar-binding site, giving rise to a 1:1 complex in solution (Fig.1). The interaction involves most of the missense mutation sites of MCFD2 so far reported in F5F8D. Our structural data lead us to propose a model of functional coordination between ERGIC-53 and MCFD2. In this model, MCFD2 is converted into the active form upon complex formation with ERGIC-53 and thereby becomes able to capture polypeptide segments of FV and FVIII in cooperation with ERGIC-53 interacting with their carbohydrate moieties.

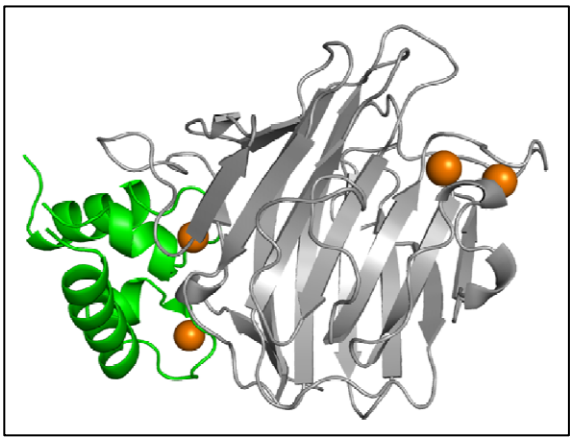

Fig.1 Crystal structure of the complex between ERGIC-53-CRD and MCFD2.

Reference

[1] M. Nishio et al.,
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