【Grant-in-Aid for Scientific Research(S)】

Integrated Disciplines (Complex systems)

Title of Project : Dynamics of molecular pattern recognition in protein interaction

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Research Area : Biomolecular chemistry
Keyword : Molecular mechanism of activity expression

【Purpose and Background of the Research】

Since the comprehensive of genomic or proteomic analyses have revealed the networks of protein complexes, growing attention has been paid to the protein interactions involved in epigenetic regulation or post-translational modification. We have developed a method to generate specific monoclonal antibodies against target proteins and identified protein complexes that play important roles in the regulation of transcription or the cell-cycle. We have also identified pentraxin 3 (PTX3)-associating proteins in the blood of patients with sepsis, and found that PTX3, classified as a soluble pattern-recognition receptor known to bind pathogens or complement proteins, binds to neutrophil extracellular traps (NETs) components (Fig.1). Many proteins have been shown to interact with PTX3, but the molecular pattern of recognition has not yet been elucidated.

The aim of this project is to develop a screening method for a new therapeutic approach for intractable diseases such as cancer and severe sepsis by analyzing the mechanism of protein-protein or protein-RNA interactions.

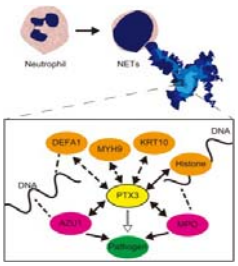

Fig. 1 PTX3 complex in sepsis

【Research Methods】

Proteins undergo conformational changes upon interaction, which is essential in the signal transduction or protein activation. Analysis of the mechanism of interaction and identification of hotspots of interacting surfaces are thus important for designing drugs that acts as inhibitors of protein-protein interactions. In this study, we focus on the interaction of PTX3 with its interacting proteins in order to identify the dynamic mechanism of interaction using structural analysis combined with computer simulation. We attempt to raise antibodies that fix the conformation of such proteins in their active or inactive form for structural study.

We also focus on Wilms' tumor-1-associated protein (WTAP), which we identified as a regulator of the cell-cycle and recently determined its role on the RNA processing in combination with a set of associating proteins. In this study, we analyze the mechanism of this RNA processing in terms of structural aspects using computer simulation technique. From these results, we will attempt to understand how the molecule recognizes its interacting partners.

【Expected Research Achievements and Scientific Significance】

Although the sepsis is the leading cause of death in the ICU in developed countries, there is no efficacious therapy. This study should provide a possible candidate of drug by analyzing the relation between innate immunity and sepsis. The method of structural study with computer simulation should shed light on the mechanism of dynamic molecular interaction and provide a method of screening inhibitors of protein-protein interactions.

【Publications Relevant to the Project】

・Daigo K, Hamakubo T *et al.* The proteomic profile of circulating pentraxin 3 (PTX3) complex in sepsis demonstrates the interaction with azurocidin 1 and other components of neutrophil extracellular traps. *Mol Cell Proteomics*. 11(6): M111.015073, 2012.
・Horiuchi K, Hamakubo T *et al.* Wilms' tumor 1-associating protein regulates G2/M transition through stabilization of cyclin A2 mRNA. *Proc Natl Acad Sci U S A*. 103(46):17278-83. 2006

【Term of Project】 FY2013-2017

【Budget Allocation】 162, 000 Thousand Yen

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