Structural Biology of Innate Immunity

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【Outline of survey】

Innate immunity is a defense system that detects invasion of pathogens by recognizing pathogens associated molecular patterns such as LPS for gram-nagtive microbials or double stranded RNA for viruses. Innate immunity is a sole immune system for non-vertebrates such as insects that lack acquired immunity. It is regarded as a front-line of our defense system. In the present project we will elucidate the molecular mechanism for activation of innate immunity on a structural basis. For the first target we will study phagocytic NADPH oxidase. Upon phagocytosis of invasive microbials, neutrophils generate superoxide anion into the phagosome, which is then converted to reactive oxygen species to kill microbials. Since reactive oxygen species are hazardous to our system, superoxide generation should be tightly regulated. NADPH oxidase comprises membrane bound flavocytochrome b558 and cytosolic factors. In the resting state the membrane and cytosolic components are separated from each other, but in the activated state the conformation change of cytosolic components occurs, inducing relocation of cytosolic components to bind to flavocytochrome b558. For the second target we study the activation mechanism of IRF-3, a transcription factor for IFN α/β production. Upon virus invasion, IRF-3 is phosphorylated to form a dimer, which is then relocated to the nucleus to bind CBP/p300 and the IFN responsive element. IRF-3 is regarded as the initial switch for burst of IFN α/β production. We will elucidate the activation mechanism of both NADPH oxidase and IRF-3 on a structural basis.

【Expected results】

Infectious diseases caused by microbials and viruses are still the most hazardous to human beings and are some of the most serious causes of death in the Third World. In the present project we elucidate the activation mechanism of the proteins responsible for defense against infectious diseases on a structural basis, leading to the development of anti-inflammatory and anti-viral drugs.

【References by the principal researcher】

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② Takahasi K, Suzuki NN, Horiuchi M, Mori M, Suhara W, Okabe Y, Fukuhara Y, Terasawa H, Akira S, Fujita T, Inagaki F. X-ray crystal structure of IRF-3 and its functional implications. *Nat Struct Biol.* 2003 Nov; 10(11): 922-7.

【Term of project】 FY 2005 - 2009 | 【Budget allocation】 87,900,000 yen

【Homepage address】 http://protein.pharm.hokudai.ac.jp/