学位論文抄録

Ligand-guided different responses via the neutrophil C5a receptor

（同じC5aレセプターを介しながらリガンド誘導性に異なる好中球の反応）

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Abstract of The Thesis

Background and Purpose: Leukocyte chemoattractants are divided into the pure chemotactic factor and the classical chemoattractant. The former induces only leukocyte chemotaxis, while the latter induces not only cell migration but also release of granular components and generation of radical oxygen species. The difference between these ligand-induced outcomes has been thought to depend on characters of their receptors. Recently, two new ligands of the C5a receptor were identified in addition to C5a. I found that Skp, one of the new ligands, behaved as a pure chemoattractant, while the others are classical factors, indicating the ligand but not the receptor guides the leukocyte responses at least in the case of C5a receptor-mediated phenomena. The major purpose of my research is to reveal the molecular structural characteristics of the C5a receptor ligands which results in the different leukocyte responses.

Experiments: We identified the sub-molecular region of Skp that binds and activates the C5a receptor to be -Gln103-Asp104-Arg105- utilizing synthetic peptide fragments and site-directed mutants of Skp. Because the C5a amino acid residue equivalent to Gln103 of Skp is Leu72, we prepared a Gln103Leu-Skp mutant as a recombinant protein. With this mutation, Skp gained secretagogue functions including induction of the respiratory burst and granule release reactions and leukotriene generation, in addition to the chemoattraction, as displayed by C5a.On the other hand, when we substituted Leu72 with Gln in C5a, the Leu72Gln-C5a mutant lost its secretagogue function. These functional conversions were reproduced using synthetic peptides mimicking the receptor-binding/activating regions of the recombinant proteins. Receptor binding assays utilizing the mimicking peptides demonstrated only a small difference between the Leu72-C5a and Gln72-C5a peptides. Consistently, Leu72Gln-C5a apparently antagonized C5a secretagogue function.

Conclusion: Our experimental results indicate that the difference between a chemotactic response and a combined chemotactic/secretory response can be attributed not to the nature of the receptor but to guidance by the ligand, at least in the case of C5a receptor-mediated leukocyte responses. It must be of interest to compare intracellular signal transduction pathways between the pure chemotactic ligand and the classical chemotactic ligand of the C5a receptor in future.