

Regulatory Interactions of the N-formyl Peptide Chemoattractant Receptor with Membrane Skeletal Proteins of Human Neutrophils

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Control of formyl peptide chemoattractant receptors (FPR) is a process of central importance to chemotaxis of phagocytes towards sites of bacterial infection. The membrane skeleton meshwork (MSK) underlying the plasma membrane of human neutrophils has been implicated in the regulation of these receptors. The association of FPR with the MSK, measured by pelletability of FPR in Triton X-100 extracts of membranes, depends on the stimulation state of the cell, showing minimal association in membranes from unstimulated cells and nearly complete association in membranes from homologously desensitized cells (see figure, next page). If membranes are more completely solubilized in octyl glucoside and then exchanged into Triton X-100, FPR is found in tight association with a protein immunologically related to actin. Receptor also binds to immobilized rabbit actin or free neutrophil cytosolic actin.

Most recently, we have identified two proteins of molecular weight 45 and 40 kDa that appear to crosslink to the agonist occupied FPR, forming complexes of 110 and 150 kDa. The 110 kDa species appears when receptor is not associated with G protein, but is more efficiently crosslinked in the presence of Gi2. The 150 kDa species is found only in the presence of Gi2 when the FPR forms a hydrodynamically stable 7S complex with FPR. We surmise that the 45 and 40 kDa species may be actin and Gia, respectively. Studies are underway to confirm the identity of these species and a function for the FPR actin complexes.

Recent Publications

Jesaitis, A.J., Erickson, R.W., **Klotz, K.-N.**, Bommakanti, R.K., Siemsen, D.W., Functional interaction of human N-formyl peptide chemoattractant receptors with actin. *J.Immunol.* **151**: 5653-5665, 1993.

Jesaitis, A.J. and **Klotz, K.-N.**, Cytoskeletal regulation of chemotactic receptors: Molecular complexation of N-formyl peptide receptors with G proteins and actin. *Eur. J. Haematol.* **51**: 288-293, 1993.

Klotz, K.-N., Krotec, K.L., Gripenrog, J., and **Jesaitis, A.J.** Regulatory interaction of N-formyl peptide chemoattractant receptors with the membrane skeleton in human neutrophils. *J. Immunol.* **152**: 801-810, 1994.

Klotz, K.-N. and **Jesaitis, A.J.** Regulatory interactions of N-formyl peptide chemoattractant receptors with the membrane skeleton in human neutrophils. *Bioessays* **16**: 193-198, 1994..



Model of regulatory interactions of FPR with G proteins and actin. In responsive human neutrophils (left), most of the FPR are found in the light fraction of the plasma membrane (PM-L) which also contains most of the G proteins. A shift of FPR to the heavy plasma membrane fraction (PM-H) with a characteristic enrichment of cytoskeletal proteins, is observed as desensitization occurs. Rodbell's finding of polydisperse G protein structures provides an attractive basis for membrane compartmentalization, with domains with G proteins allowing for signal transduction ("G domain") and domains with actin where receptors cannot access signal transduction partners ("A domain"). The polymeric structure of G proteins and actin would exclude mixing of these proteins by diffusion. The FPR, however, could diffuse between the different domains until agonist binding would permit interaction with G proteins or actin.