

Receptor Cross-Talk and Neutrophil Function

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen, våning 3 i Mikrobiologihuset, Guldhedsgatan 10A, Göteborg

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av

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Avhandlingen baseras på följande arbeten:

- I Önnheim K, Bylund J, Boulay F, Dahlgren C, Forsman H.
Tumour necrosis factor (TNF)-alpha primes murine neutrophils when triggered via formyl peptide receptor-related sequence 2, the murine orthologue of human formyl peptide receptor-like 1, through a process involving the type I TNF receptor and subcellular granule mobilization.
Immunology. 2008 Dec;125(4):591-600
- II Forsman H, Salomonsson E, Önnheim K, Karlsson J, Björstad A, Leffler H, Bylund J, Karlsson A, Dahlgren C.
The beta-galactoside binding immunomodulatory lectin galectin-3 reverses the desensitized state induced in neutrophils by the chemotactic peptide f-Met-Leu-Phe: role of reactive oxygen species generated by the NADPH-oxidase and inactivation of the agonist.
Glycobiology. 2008 Nov;18(11):905-12.
- III Forsman H*, Önnheim K*, Andréasson E, Christenson K, Karlsson A, Bylund J, Dahlgren C
Reactivation of desensitized formyl peptide receptors by platelet activating factor: a novel receptor cross talk mechanism regulating neutrophil superoxide anion production.
PLoS One. 2013;8(3):e60169 *= *Joint first authors*
- IV Önnheim K, Christenson K, Amirbeagi F, Martner A, Bylund J, Dahlgren C, Forsman H
ATP triggers reactivation of desensitized formyl peptide receptors: A novel receptor cross talk mechanism regulates phagocyte superoxide anion production
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Abstract:

The chemotactic recruitment of neutrophils, the most abundant white blood cell in human circulation, to sites of infection and inflammation, is dependent upon a gradient of chemoattractants released from cells at the inflamed area. The chemoattractants, including formyl peptides, are recognized by G-protein coupled chemoattractant receptors (GPCRs) present on the neutrophil surface. Activation of GPCRs in neutrophils mediates chemotaxis, but also granule mobilization and the generation of reactive oxygen species (ROS). ROS and granule constituents are not only essential for effective microbial killing, but may also account for unwanted tissue destruction. Stringent activation and termination of neutrophil GPCR signaling is therefore crucial for fine-tuning of inflammatory reactions. Two well-known control mechanisms are 1) receptor desensitization, a non-signaling state reached after termination of the agonist-induced GPCR signal, and 2) priming, a hyper-responsive state involving upregulation of surface receptors.

The data presented in this thesis explore both of these control mechanisms, and in addition provide evidence for the existence of a novel receptor cross-talk mechanism whereby already desensitized receptors can be reactivated.

We first show that in analogy to what is known for human neutrophils, TNF- α is able to prime mouse neutrophils for FPR stimulation. Next we show that FPR desensitization can be broken by treatment with the b-galactoside binding human lectin galectin-3. This process is dependent upon ROS-mediated inactivation of the FPR agonist, which in turn relies on the carbohydrate-binding domain of the lectin and on the presence of the neutrophil peroxidase MPO. Most importantly, this thesis also discovers a novel cross talk mechanism whereby desensitized FPRs can be reactivated and turned into active signaling. We show that stimulation of FPR desensitized neutrophils with 1) extracellular ATP (a damage-associated molecular pattern; DAMP) and 2) the platelet activating factor (PAF) transmit signals leading to reactivation of FPRs. This could be an important mechanism for amplification of cellular responsiveness during contact with multiple inflammatory mediators simultaneously. The signals leading to FPR reactivation were shown to be independent of intracellular calcium signaling, and an intact actin cytoskeleton, but required calyculinA-sensitive phosphatases. The data presented challenge the current view of actin-dependent FPR desensitization and the view of the desensitization process as a stable point-of-no-return.

Key words: neutrophils, FPR, receptor cross-talk, phagocytes

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