Göteborg, 2017

Functional Modulation of the Pattern Recognition Formyl Peptide Receptors in Neutrophils

Lipopeptides – allosteric modulators of G-protein-coupled receptors

Akademisk avhandling

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

Fredagen den 10 februari 2017 klockan 9:00

av

Malene Winther

Fakultetsopponent:

Professor Attila Mócsai

Semmelweis University, Hungary

Avhandlingen baseras på följande delarbeten

I. Winther M, Gabl M, Oprea TI, Jönsson B, Boulay F, Bylund J, Dahlgren C, Forsman H. Antibacterial activity of pepducins, allosterical modulators of formyl peptide receptor signaling. *Antimicrobial Agents and Chemotherapy (2014) 58:2985-2988*

II. Winther M, Gabl M, Welin A, Dahlgren C, Forsman H. A neutrophil inhibitory pepducin derived from FPR1 expected to target FPR1 signaling hijacks the closely related FPR2 instead. *FEBS Letters (2015) 589:1832-1839*

III. Skovbakke SL, Winther M, Gabl M, Holdfeldt A, Linden S, Wang JM, Dahlgren C, Franzyk H, Forsman H. The peptidomimetic Lau-(Lys-βNSpe)$_6$-NH_2 antagonizes formyl peptide receptor 2 expressed in mouse neutrophils *Biochemical Pharmacology (2016) 119:56-65*

IV. Winther M, Rajabkhani Z, Holdfeldt A, Gabl M, Bylund J, Dahlgren C, Forsman H. Pepducins from formyl peptide receptors allosterically modulate the function of the same receptor in human and murine neutrophils, but with an outcome (positive or negative) that is not dependent upon the origin of their receptors. *In manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICINE

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Functional Modulation of the Pattern Recognition Formyl Peptide Receptors in Neutrophils

Lipopeptides – allosteric modulators of G-protein-coupled receptors

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Abstract

G-protein-coupled receptors (GPCRs), which are the largest class of cell-surface receptors, are involved in a range of physiologic processes and pathologies, making this a highly interesting group of proteins as targets for drug development. Studies of these receptors have uncovered novel receptor biology concepts, including biased signaling, functional selectivity, and allosteric modulation. "Tailor-made" lipopeptides (pepducins and lipopeptoids) represent novel and promising classes of receptor-specific allosteric modulators. In this thesis, immunomodulating lipopeptides that interact with a group of pattern recognition receptors, formyl peptide receptors (FPRs), which play key roles in host defense against microbial infections, tissue homeostasis, and the initiation and resolution of inflammation, are generated and functionally characterized. The FPRs are expressed in both human and murine white blood cells, and novel allosteric lipopeptide modulators that selectively interact with human and murine receptors are described. We show that the targeted receptor is not always the one that might be expected. This receptor hijacking process raises questions about the precise mechanisms of action of these lipopeptides and of these types of molecules acting as a molecular pattern that is recognized by the receptor group studied. Fundamental differences are also revealed by the receptor-ligand recognition profiles, between mice and men. This represents important knowledge needed for the development and use of animal models for human diseases.

In summary, the results presented in this thesis not only highlight the value of the different lipopeptides as tools for modulating receptor activities in human and murine immune cells, but also provide new insights into the allosteric modulation concept.

Keywords: Human, mouse, neutrophil, reactive oxygen species, formyl peptide receptor, pepducin, G-protein-coupled receptor, lipopeptoid, pattern recognition receptor

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