Göteborg, 2022

Free Fatty Acid Receptor 2 - A G protein coupled receptor with unique signaling properties in neutrophils

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, Göteborg, den 9 september, klockan 09.00

av **Simon Lind**

Fakultetsopponent:

PhD Dorothee Kretschmer

University of Tübingen, Institute of Microbiology and Infection Medicine, Tübingen, Tyskland

Avhandlingen baseras på följande delarbeten

I. **Simon Lind**, André Holdfeldt, Jonas Mårtensson, Martina Sundqvist, Lena Björkman, Huamei Forsman, Claes Dahlgren. Functional selective ATP receptor signaling controlled by the free fatty acid receptor 2 through a novel allosteric modulation mechanism. FASEB J. 2019; 33: 6887-6903

II. **Simon Lind**, André Holdfeldt, Jonas Mårtensson, Martina Sundqvist, Terry P Kenakin, Lena Björkman, Huamei Forsman, Claes Dahlgren. Interdependent allosteric free fatty acid receptor 2 modulators synergistically induce functional selective activation and desensitization in neutrophils. Biochim Biophys Acta Mol Cell Res. 2020; 1867: 118689.

III. **Simon Lind**, André Holdfeldt, Jonas Mårtensson, Kenneth L. Granberg, Huamei Forsman, Claes Dahlgren. Multiple ligand recognition sites in free fatty acid receptor 2 (FFAR2) direct distinct neutrophil activation patterns. Biochemical Pharmacology 2021; 193: 114762

IV. **Simon Lind**, Dagny Olofsson Hoffman, Huamei Forsman, Claes Dahlgren. Allosteric Receptor Modulation uncovers an FFAR2 antagonist as a positive orthosteric modulator/agonist in disguise. Cellular Signalling 2022; 90: 110208

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Simon Lind

Avdelningen för reumatologi och inflammationsforskning, Institutionen för medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 22.

Abstract

The overall aim of the PhD thesis was to determine the role of neutrophil pattern recognition receptors in the initiation and resolution of inflammatory processes. Neutrophil pattern recognition receptors such as the formyl peptide receptors (FPRs) and the short free fatty acid receptors (FFARs) belong to the family of G protein coupled receptors (GPCR). The FPRs recognize danger peptides having a formylated methionyl group in the N-terminus, peptides generated not only by bacteria but also during synthesis of proteins encoded for by the mitochondrial DNA. FFARs recognize metabolites generated during fiber fermentation by gut microbes. The thesis work has been focused on the coupling between ligand recognition by these receptors and the down-stream intracellular signals transduced. The work started with studies on the FPRs, receptors that have been implicated to trigger both pro- and anti-inflammatory responses. However, the work on one of the FFARs (FFA2R) expanded rapidly to become the mainstage. Receptor recognition of orthosteric ligands and allosteric modulators and the subsequent novel receptor down-stream signaling induced by newly developed tool compounds have been studied. The neutrophil pattern recognition receptors are regarded as promising therapeutic targets for the treatment of diseases in which the inflammatory response needs to be properly controlled. The results presented in the thesis have increase our knowledge about the regulatory roles not only of the FFARs but also of the FPRs in inflammation. Hopefully, this knowledge will be of help in the efforts to develop pharmaceutical drugs that can be used to modulate inflammatory processes in direct and controlled ways.

Keywords: Neutrophil, G protein coupled receptors, FFA2R, signal transduction, allosteric modulation, reactive oxygen species, biased signaling

ISBN 978-91-8009-855-7 (PRINT)
ISBN 978-91-8009-856-4 (PDF)

http://hdl.handle.net/2077/71517