Göteborg, 2023

Endogenous and microbial modulators of inflammation

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats Aula, Blå stråket 5, mellan målpunkt H och L, den 21 december, klockan 9:00

av Jamie D. Kraft

Fakultetsopponent:
Professor Yolanda Sanz
Spanish National Research Council, Spain

Avhandlingen baseras på följande delarbeten

I. Kraft JD, Blomgran R, Bergström I, Soták M, Clark M, Rani A, Rohini Rajan M, Dalli J, Nyström S, Quiding-Järbrink M, Bromberg J, Skoog P, Börgeson E. Lipoxins modulate neutrophil oxidative burst, integrin expression and lymphatic transmigration differentially in human health and atherosclerosis. *The FASEB Journal* 2022; **36** (3) e22173.

II. Khan MT, Dwibedi C, Sundh D, Pradhan M, Kraft JD, Caesar R, Tremaroli V, Lorentzon M, Bäckhed F. Synergy and oxygen adaptation for development of next-generation probiotics. *Nature* 2023; **620**, 381-385.

III. Kraft JD, Dwibedi C, Makki K, Florén A, Hempenstall E, Bäckhed F, Khan MT, Tremaroli V, Caesar R. Phenotypic variation of novel *Desulfovibrio piger* stains isolated from human faeces. *Manuscript*

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INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Endogenous and microbial modulators of inflammation

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Abstract

Cardiometabolic disease is characterized by dysregulated, chronic inflammation, that may result from impaired resolution pathways or alterations in the gut microbiota. Thus, restoring specialized pro-resolving mediators (SPMs) or intestinal bacteria with immunomodulatory properties represent potential therapeutic strategies for patients.

First, we investigated the ability of the SPMs, lipoxins, to modulate neutrophils from individuals with atherosclerosis. Treatment of neutrophils from patients with atherosclerosis with lipoxins attenuated elevated reactive oxygen species production and expression of the high-affinity conformation of CD11b/18 integrin, and enhanced lymphatic migration. The potential therapeutic effect of lipoxins in atherosclerosis was demonstrated, along with the need to tailor treatment to the requirements of the individual.

Second, for the development of a next-generation probiotic supplementation, we co-isolated *Faecalibacterium prausnitzii* with *Desulfovibrio piger* and demonstrated a cross-feeding mechanism that enhanced growth and butyrate production. *F. prausnitzii* is a highly prevalent and abundant human gut bacteria with immuno-modulatory properties and associations with health. For development into a next-generation probiotic, *F. prausnitzii* was adapted to tolerate exposure to oxygen. *F. prausnitzii* and *D. piger* formulation was well tolerated by mice and humans. We demonstrated a method by which strict anaerobic bacteria can be adapted to tolerate oxygen without impacting potential beneficial properties.

Finally, *D. piger* has been found to be both ubiquitous among individuals but has also been associated with disease. To identify if the discrepancies lie in inter-strain variation, we isolated a *D. piger* strain with genomic similarity to FI11049, previously isolated from a patient with colitis, to compare with the strain co-isolated with *F. prausnitzii*. Anti-inflammatory properties and phenotypic differences were found between the strains. Further studies are required to investigate inter-strain variation to understand disease associations.

Keywords: Inflammation, resolution, specialized pro-resolving mediators, lipoxins, neutrophils, cardiometabolic disease, next-generation probiotic, oxygen-tolerance, *Faecalibacterium prausnitzii*, *Desulfovibrio piger*, inter-strain variation

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