Göteborg, 2024

Humoral Immune Response with Focus on IgG Glycosylation
In Murine Models

Akademisk avhandling

för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Föreläsningssalen våning 3 Guldhedsgatan 10A, Göteborg, den 11 april 2024, klockan 09.00

av **Priti Gupta**

Fakultetsopponent:

Professor Manfred Wuhrer

Leiden University, Netherlands

Avhandlingen baseras på följande delarbeten

I. **Priti Gupta**, Karin Horkeby, Hans Carlsten, Petra Henning, Cecilia Engdahl. **Bazedoxifene does not share estrogen effects on IgG sialylation.** *PLoS One. 2023 May 18;18(5):e0285755*

II. **Priti Gupta**, Tibor Sághy, Jauquline Nordqvist, Jonas Nilsson, Hans Carlsten Karin Horkeby, Petra Henning, Cecilia Engdahl. **Impact of Estrogen on IgG Glycosylation and Serum Protein Glycosylation in a Murine Model of Healthy Postmenopause.** *Front Endocrinol. 2023 Sep 11:14:1243942*

III. **Priti Gupta**, Zhicheng Hu, Pradeep Kumar Kopparapu, Meghshree Deshmukh, Tibor Sághy, Majd Mohammad, Tao Jin*, Cecilia Engdahl*. **The impact of TLR2 and aging on the humoral immune response to *Staphylococcus. aureus* bacteremia in mice.** *Sci Rep. 2023 May 31;13(1):8850*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

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Abstract

The humoral immune system orchestrates a vital defense mechanism through the secretion of antibodies, especially Immunoglobulin G (IgG), which actively targets and neutralizes foreign particles and pathogens. Glycosylation is a post-translational modification of proteins that affects their size, shape, and folding. IgG glycosylation, plays a pivotal role in mediating both pro- and anti-inflammatory effects in diseases, thereby regulating pathogenicity through alterations in interaction with fragment crystallizable gamma receptors (FcγRs). Despite the recognized importance of IgG glycosylation, the influence of various factors such as estrogen, inflammation, and aging on the humoral immune response remains unexplored in functional models. Therefore, the primary objective of this Ph.D. thesis is to unravel the impact of these factors, with a particular focus on IgG glycosylation, in murine models. First, we investigated whether Bazedoxifene, a 3rd generation selective estrogen receptor modulator (SERM) exhibits estrogenic characteristics in IgG glycosylation under immune-induced postmenopausal conditions. Results demonstrated that Bazedoxifene did not mimic estrogenic effects on IgG glycosylation during pathogenic immune responses. Second, we investigated estrogen's effects on IgG glycosylation in healthy postmenopausal mice. The findings revealed that estrogen treatment in healthy postmenopausal states increased IgG glycosylation, thereby mitigating IgG pathogenicity. Finally, we investigated the impact of aging and toll like receptor 2 (TLR2) on the humoral immune response to bacteremia. Utilizing young and old wild-type (WT) and TLR2$^{-/-}$ mice under both healthy and bacteremia conditions, the study showed that TLR2 and aging significantly altered immunoglobulin levels. Additionally, bacteremia induced a limited response in aged mice, with increased IgG glycosylation observed in healthy and infected conditions in wild type old mice. In summary, this thesis demonstrated the regulation of humoral immune response and the factors including age, sex hormones, and the presence of TLR2, can markedly influence the humoral immune response and IgG glycosylation, leading to a shift from pro- to anti-inflammatory states or vice versa beyond diseased environments.

Keywords: Humoral immunity, Antibodies, IgG-glycosylation, Estrogen, Inflammaging.

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