Systems Biology Based Approaches to Identify Biomarkers in Seasonal Allergic Rhinitis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i Föreläsningssal 1, Drottning Silvias barn- och ungdomssjukhus,Göteborg, Fredagen den 21 Sep 2012, kl 13.00

av

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Avhandlingen baseras på följande delarbeten:

I. **Wang H.**, Barrenäs F., Bruhn S., Mobini R. & Benson M.
Increased IFN-γ activity in seasonal allergic rhinitis is decreased by corticosteroid treatment.
J Allergy Clin Immunol (2009); 124(6):1360-2. (Joint first co-author)

II. **Wang H.**, Chavali S., Mobini R., Muraro A., Barbon F., Boldrin D., Åberg N. & Benson M.
A pathway-based approach to find novel markers of local glucocorticoid treatment in intermittent allergic rhinitis.
Allergy (2011); 66(1):132-40.

III. **Wang H.**, Gottfries J., Barrenäs F. & Benson M.
Identification of Novel Biomarkers in Seasonal Allergic Rhinitis by Combining Proteomic, Multivariate and Pathway Analysis.
PLoS One (2011); 6(8):e23563.

IV. Zhao Y., **Wang H.**, Gustafsson M., Muraro A., Bruhn S. & Benson M.
Combined Multivariate and Pathway Analyses Show That Allergen-Induced Gene Expression Changes in CD4+ T Cells Are Reversed by Glucocorticoids.
PLoS One (2012); 7(6):e39016. (Joint first co-author)

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Abstract:

Glucocorticoids (GC) are the most effective anti-inflammatory treatment for seasonal allergic rhinitis (SAR). However, a few patients with SAR show poor response to GC treatment. Hence, there is a clinical need to find biomarkers to predict and monitor treatment response. Given that GC may affect the expression of a large amount of genes and proteins in different cells and tissues from SAR, it is a formidable challenge to understand these complex changes and to identify candidate biomarkers by studying individual genes. The aim of the study was to develop systems biology based approaches to identify biomarkers for GC treatment response in SAR.

To achieve this goal, clinical investigations, experimental studies and bioinformatics analyses were combined. We profiled gene- and/or protein expression in nasal mucosa, nasal fluids and *in vitro* allergen-challenged CD4+ T cells from patients with SAR by gene expression microarray- and quantitative proteomics analysis. Ingenuity pathway analysis (IPA) and/or multivariate analysis were employed to prioritize candidate biomarkers and genes of importance to allergy. We further validated candidate biomarkers by ELISA.

We showed that several pathways, such as the *acute phase response pathway,* were enriched with genes-coding proteins that may be candidate biomarkers. We identified several novel biomarkers for GC treatment response in SAR including orosomucoid (ORM), apoliprotein H (ApoH) and fibrinogen alpha chain (FGA). With integrated multivariate and pathway analyses we also demonstrated that the expression of allergen-induced genes in CD4+ T cells from patients with SAR was reversed by GC treatment. We indentified that increased IFN-γ activity in allergen-challenged CD4+ T cells was decreased by GC treatment.

In conclusion, we developed systems biology based approaches for the identification of novel biomarkers in SAR. These approaches may be generally applicable to identify biomarkers in clinical studies of complex diseases.

Keywords: seasonal allergic rhinitis; glucocorticoids; gene expression microarray analysis; proteomics; multivariate analysis; pathway analysis; biomarkers

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