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Potential biomarkers for acute and chronic rejection after lung transplantation

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Förmaket, Vita Stråket 12, Sahlgrenska, fredagen den 18 november, klockan 09.00

av Petrea Ericson

Fakultetsopponent:
Professor Arne Egesten
Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Ericson P, Lindén A, Riise GC
BAL levels of IL-18 do not change before or during acute rejection in lung transplant recipients Respir Med 2004; 98 (2):159-63.

II. Riise GC, Ericson P, Bozinovski S, Yoshihara S, Anderson GP, Lindén A.
Increased net gelatinase but not serine protease activity in bronchiolitis obliterans syndrome J Heart Lung Transplant 2010; 29 (7):800-7.

III. Ericson P, Tengvall S, Stockfelt M, Levänen B, Lindén A, Riise GC.
Involvement of IL-26 in bronchiolitis obliterans syndrome but not in acute rejection among lung transplant recipients Submitted

IV. Ericson P, Mirgorodskaya E, Hammar O, Viklund E, Almstrand AC, Larsson P, Riise GC, Olin A-C. **Low levels of exhaled surfactant protein A associated with BOS after lung transplantation** Transplantation Direct 2016;2: e103.

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Potential biomarkers for acute and chronic rejection after lung transplantation

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Abstract

Chronic rejection in the form of bronchiolitis obliterans syndrome (BOS) is the main hindrance for long-term survival after lung transplantation. Repeated acute rejections (AR) constitute a major risk factor for developing BOS. The aim of this thesis was to expand the knowledge of the biological processes underlying AR and BOS and to identify potential immunological biomarkers for these conditions. The following specific research questions were posed: Are alterations in IL-18 concentration associated with AR (paper I)? Are there local pulmonary changes in the protease/anti-protease balance in BOS (paper II)? Is the neutrophil mobilizing cytokine IL-26 involved in AR and BOS development (paper III)? Does composition of particles in exhaled air (PEx) differ between BOS/non-BOS (paper IV)?

Methods: In a biobank of collected bronchoalveolar lavage (BAL) samples from lung transplant recipients (LTRs), we identified patients, with or without AR and BOS respectively, who were carefully matched. The matching procedure included preoperative diagnosis, age, gender, type of and time after transplantation to avoid the influence of confounding clinical factors. Inflammatory cells and soluble mediators involved in the inflammatory process were analyzed in BAL samples (paper I-III). In paper IV, particles in exhaled air (PEx) in LTRs and healthy controls was investigated with a novel method that enables non-invasive sampling from the distal airways.

Results: There were no changes in IL-18 concentration or correlation between IL-18 and lymphocyte percentages in BAL samples from patients with AR (paper I). Increased net gelatinase activity and a clear correlation between activity and concentration of the gelatinase MMP-9 (but not MMP-2) as well as a correlation between activity and neutrophil percentages were found in BAL samples from BOS patients (paper II). It was also found that the concentration of IL-26 in BAL samples from patients with BOS (but not AR) was increased and intracellular IL-26 was detected in alveolar macrophages and lymphocytes (paper III). Finally, surfactant protein A was lower in PEx from BOS patients compared to stable LTRs and LTRs exhaled a higher amount of PEx than healthy controls (paper IV).

Conclusions: These findings forward evidence that local unopposed gelatinase activity, likely to be accounted for by the gelatinase MMP-9 from neutrophils, and the neutrophil mobilizing cytokine IL-26 from macrophages and lymphocytes, are involved in BOS development. The results also show that PEx composition differs between stable LTRs and patients that develop BOS. The clinical utility of PEx as a non-invasive diagnostic tool in the follow up after lung transplantation and the possibility of targeting MMP-9 and IL-26 for early detection, monitoring and possibly even treatment of BOS warrant further study.

Key words: lung transplantation, graft rejection, bronchiolitis obliterans syndrome, IL-18, MMP-9, IL-26, surfactant protein

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