IMMUNOLOGICAL RISK STRATIFICATION OF THE BRONCHIOLITIS OBLITERANS SYNDROME AFTER LUNG TRANSPLANTATION

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September 13th, 2011

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The development of chronic allograft rejection after lung transplantation (LTx) is the most common cause of poor long-term survival in lung transplant recipients. This rejection leads to obliteration of the bronchioli, resulting in the bronchiolitis obliterans syndrome (BOS). Since this obliteration has a patchy distribution and normal lung tissue obtained by a transbronchial biopsy does not exclude rejection, a surrogate marker based on lung function decline is currently the gold standard for the diagnosis of BOS. The exact mechanism of BOS is unknown. Repetitive damage of (sub) epithelial cells seems to play an important role, leading to activation of the immune system and eventually chronic inflammation. Due to this response immune markers may be elevated or decreased. This thesis examines several biomarkers in blood that may be helpful in the identification of patients who are at risk for developing BOS.

The first biomarker we examined is CD30 in the soluble form. CD30 is expressed on Th2 cells and a soluble form (sCD30) is shed into the blood if Th2 cells are activated. In this study concentrations of sCD30 prior to LTx and after LTx were evaluated. We demonstrated that sCD30 values prior to LTx discriminated patients developing BOS while sCD30 values after LTx did not. It is remarkable that the high sCD30 values before LTx were decreased after surgery. We suppose that immunosuppressive drugs may have suppressed the sCD30 values. A study in atopic dermatitis (AD) patients, a mainly Th2 associated disease, confirmed this assumption: the immunosuppressive drug enteric coated mycophenolate sodium (EC-MPS) but not cyclosporine (CsA) indeed showed suppression of sCD30 values.

The second biomarker that was evaluated was TARC. The chemokine TARC binds to CCR4 expressed on Th2 cells. We demonstrated that TARC levels in patients developing BOS were lower compared to non-BOS patients. If TARC values were below the 325 pg/ml at the first month after LTx, an increased risk of developing BOS was identified. In our cohort of AD patients we demonstrated a correlation between TARC levels and parameters to evaluate disease activity not only during EC-MPS treatment but also during CsA.

Furthermore, the mannose binding lectin (MBL) was examined as potential biomarker in BOS. MBL plays an important role in the innate immunity and the elimination of viruses and bacteria. We demonstrated a correlation between low MBL values before and CMV reactivation after LTx. There was a trend between low MBL levels before transplantation and a superior survival rate after transplantation. No association was found between MBL values and the development of BOS.

Lastly, natural killer (NK) cells were assessed. NK cells are one of the main cellular components of the innate immunity and play a role in the lysis of viral infected cells. The action of NK cells is controlled by activating and inhitory killer immunoglobulin-like receptors (KIRs). We demonstrated that KIR gene content of recipients, especially activating KIRs, is associated with BOS but not with the reactivation of CMV.

In conclusion, this thesis demonstrates that MBL values, KIR genotype and TARC values are associated with the development of BOS and that the type of immune suppressive regimen applied after LTx may influence the applicability of possible biomarkers.