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Title: Aberrant metalloprotease expression and activity in bronchoalveolar lavage fluid of bronchiolitis obliterans patients

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Body: Long-term success of lung transplantation (LT) is hindered by the development of bronchiolitis obliterans syndrome (BOS). Increased expression of matrix metalloproteases (MMPs) and tissue inhibitors of metallopreoteases (TIMPs) have been observed in BOS patients suggesting a role for proteases and tissue remodeling. However, little is known about the activity state of MMPs and their actual binding to TIMPs. Therefore, we investigated the levels of different molecular forms of MMPs in lung transplant recipients with unimpaired pulmonary function and early clinically diagnosed BOS. Cell differentials, cytokine levels (IL-6, IL-8), TIMP (1 – 4), total MMP-1, -2, -3, -7, -8, -9, -12 and -13 levels and activity of these MMPs using an MMP activity assay were measured in bronchoalveolar lavage (BAL) fluid from stable LT patients (n=20) and LT patients with BOS (n=20). The patient's rejection status was assessed by patho-histology. The number of BAL lymphocytes and neutrophils as well as the levels of IL-8, TIMP1 and 2 and total MMP-2, -3, -7, -8 and -9 were significantly higher in patients with BOS compared to stable LT patients. Interestingly, while active MMP-7 was significantly lower in BAL of BOS patients compared to stable LT patients, levels of TIMP1- and TIMP2-bound MMP-7, -8 and -9 were significantly increased in patients with BOS. In conclusion, we demonstrate that development of BOS after lung transplantation is associated with increased levels of TIMP 1 and 2 and total MMP-2, -3, -7, -8 and -9. Furthermore, we show for the first time that levels of TIMP-bound MMPs are associated with BOS which indicates that these enzymes have been active previously.