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Title: LSC 2013 abstract - Prominence of MMP-12 and MMP-13 in dendritic cells and the impact on a murine model of bronchiolitis obliterans

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Body: Rationale: Long-term success of lung transplantation is largely limited by the occurrence of bronchchiolitis obliterans (BO) which may result in extensive fibrosis and obliteration of the small airways. The underlying mechanisms entailing BO remain unclear, however, evidence suggest the involvement of pulmonary dendritic cells (DCs) and matrix metalloproteinases (MMPs). We hypothesize that MMP-12/-13 are important for the function of DCs, and that their inhibition will diminish airway obliteration in a murine heterotopic trachea transplant model (HTT). Methods and results: For in vitro analysis of DC function, bone marrow derived DCs (BMDCs) were generated. The expression of MMP-12 and -13 was confirmed on mRNA and protein level. Activity of MMP-12 was detected and quantified by FRET. To confirm the requirement of specific MMPs for BMDC invasion, we used MMP-12/-13 inhibitors in a 3D transwell collagen invasion assay. Importantly, BMDCs treated with MMP-12 inhibitor demonstrated decreased migration. Interestingly inhibition of MMPs showed no impact on the phagocytic potential of BMDCs using labeled OVA and flow cytometry analysis. To address the in vivo relevance of these findings, a murine HTT model was established which revealed the typical BO phenotype. The expression of MMP-12/-13 in these transplanted trachea was confirmed on mRNA level whereas the localization was assessed using IF staining. Conclusion: Inhibition of MMP-12 decreases the migration potential of BMDCs while preserving their phagocytosis capacity. Moreover, MMP-12 and -13 are expressed in tracheal grafts in the HTT model. Thus, MMP-12 and-13 may be a promising target for therapeutic intervention.