Altered pIgR/IgA mucosal immunity in bronchiolitis obliterans syndrome

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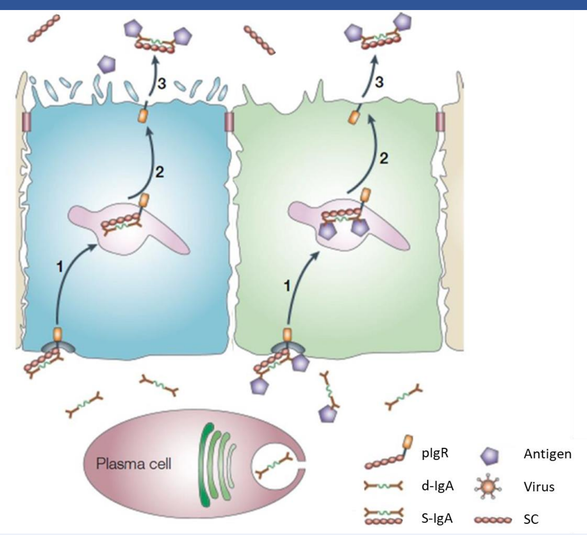
Introduction

Lung transplantation (LTx) is the standard therapy for selected patients with end-stage lung diseases. Its long-term prognosis is hampered by the occurrence of chronic allograft rejection (CLAD). Bronchiolitis obliterans syndrome, an obstructive form of CLAD, is favored by several factors, including recurrent post-LTx infections.

Secretory immunoglobulin A (S-IgA), resulting from the transcytosis of d-IgA (see Figure) ensures active defense at mucosal surfaces against pathogens, pollutants and antigens. The function of its epithelial transporter, the polymeric immunoglobulin receptor (pIgR), is reduced in several chronic respiratory diseases, including COPD and asthma.

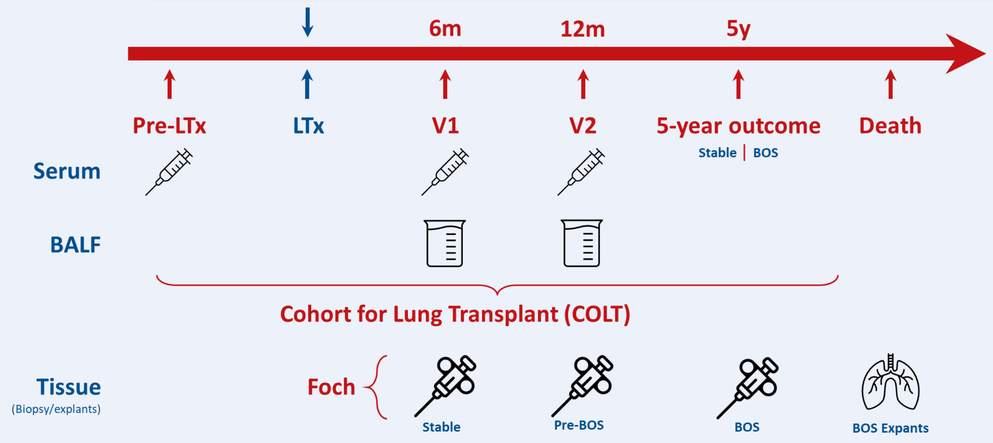


Objectives

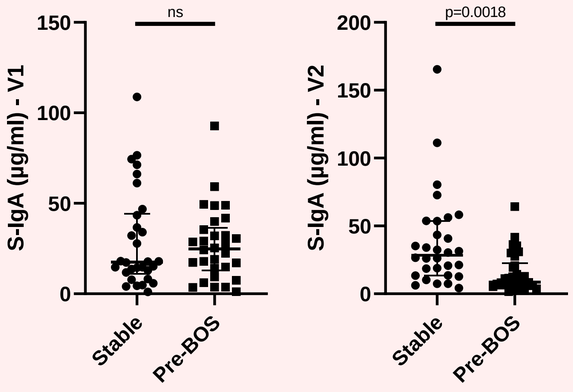
To explored whether the pIgR/S-IgA system is altered in a subset of LTx recipients (LTRs), and whether this defect could favor/correlate with BOS development.

Methods

Serum (n=178) and bronchoalveolar fluid (BALF, n=120) were retrospectively collected from 60 LTRs from the COLT cohort. Among them, 30 LTRs did not develop BOS during the 5-years follow-up ('stable' group), and 30 did ('pre-BOS' group). Two and three time-periods were assessed for BALF and serum, respectively (see picture beside). In addition, tissue from 72 LTRs was collected at Foch hospital : trans-bronchial biopsies (TBBs) from stable (n=22), pre-BOS (n=20) and BOS (n=14) LTRs, along with BOS explants (n=16). BALF were assessed for S-IgA, while serum were assessed for total IgA, IgA_1, IgA_2 (not discussed here) and the secretory component (SC). Tissues were assessed for pIgR expression and IgA-producing plasma cells, stained for CD79a, CD138 and IgA.

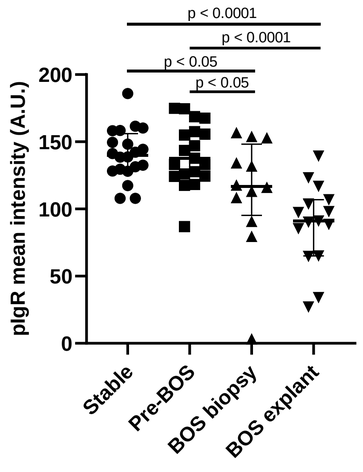


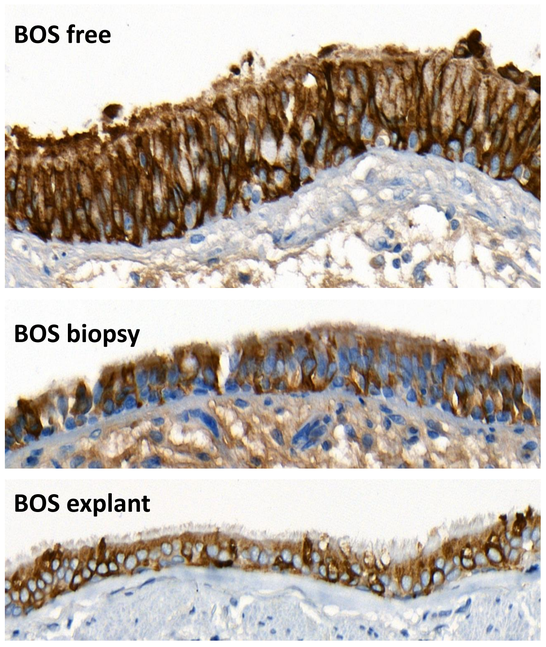
Results

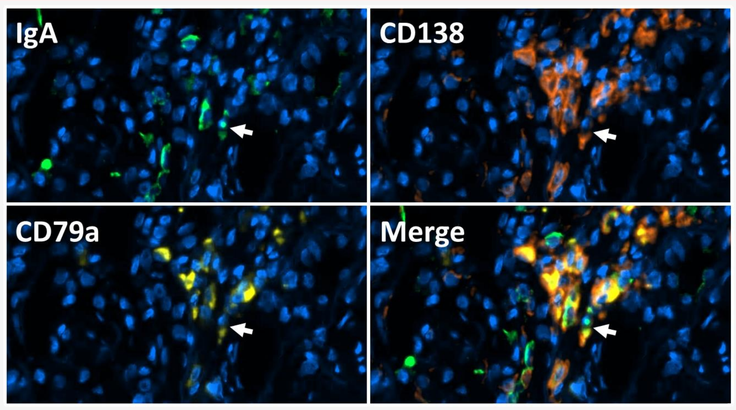


Decreased S-IgA in pre-BOS BALF
We observed increased S-IgA levels in BALF from pre-BOS patients as compared with stable patients, but only at the second time point (V2).
V1 : 6 months post-LTx
V2 : 12 months post-LTx

Decreased pIgR expression in BOS
TBBs and explants were stained for pIgR, and pIgR epithelial expression in the small airways was quantified using Visiopharm®. We observed reduced pIgR expression in BOS biopsies, that was further aggravated in BOS explants. No difference was observed between stable and pre-BOS samples.





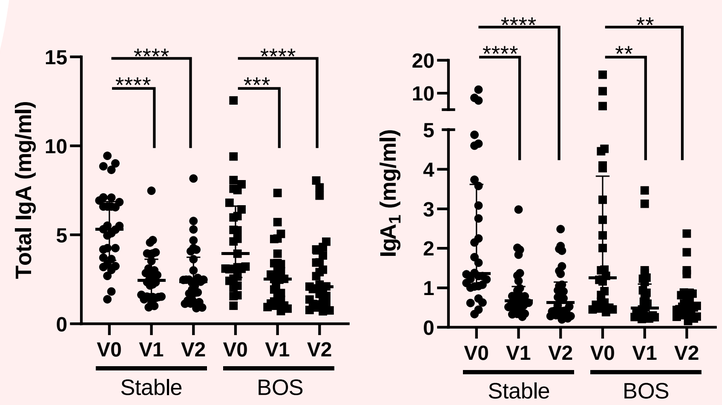


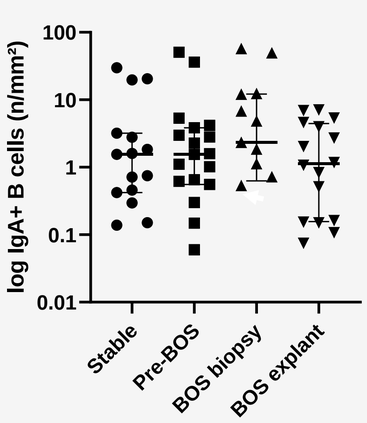
Conclusions

1. IgA mucosal immunity is altered during BOS, with reduced pIgR expression in early disease and reduced S-IgA prior to clinical diagnosis, irrespectively of plasma cell production

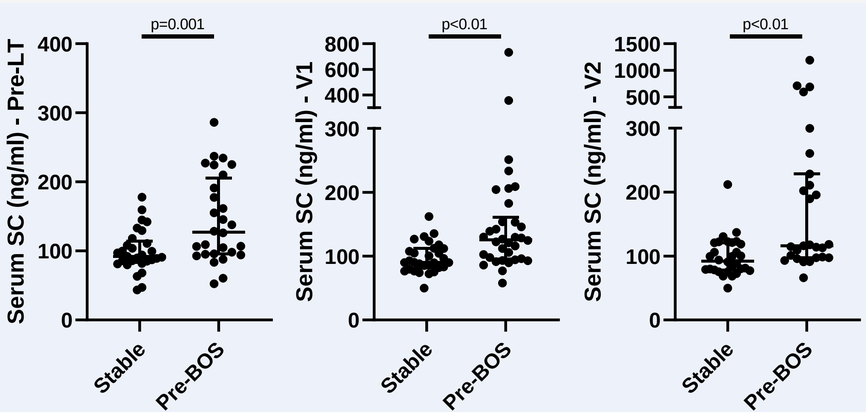
2. Whether impaired S-IgA immunity contributes to BOS development by favoring lung infections requires further studies

Decreased serum IgA after LTx
IgA levels were significantly reduced after LTx, both in stable and in pre-BOS patients, possibly due to immunosuppressive drugs. This decrease was selectively observed for IgA_1 and not for IgA_2 (not shown)





Unchanged subepithelial IgA-producing B cells
Subepithelial IgA plasmocytes were counted after a triple staining (CD138-CD79a-IgA, cf. triple positive cell pointed by the arrow). No difference was observed in absolute (n/mm²) and relative (n/number of total B cells) numbers across the groups.



Increased serum SC levels in pre-BOS LTx candidates and recipients. SC serum concentration was assessed in serial samples from LTx recipients. SC is mainly found in mucosal secretions and its presence in serum could result from a spill-over from the mucosal compartment. In our samples, SC levels were significantly higher not only in pre-BOS LTx recipients, but also in patients awaiting LTx who developed BOS after LTx was performed. *Pre-LTx : sample collection prior to LTx; V1 : 6 months post-LTx; V2 : 12 months post-LTx*

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