Interleukin-1 Signaling and CD4+T Cells Control B Cell Recruitment To The Lungs In Chronic Beryllium Disease

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Introduction & Aims

Chronic Beryllium Disease (CBD) is a lung disorder caused by beryllium exposure, leading to chronic inflammation and granuloma formation. The disease is linked to *HLA-DPB1* alleles, which present beryllium as a neoantigen, activating CD4+ T cells and driving inflammation.

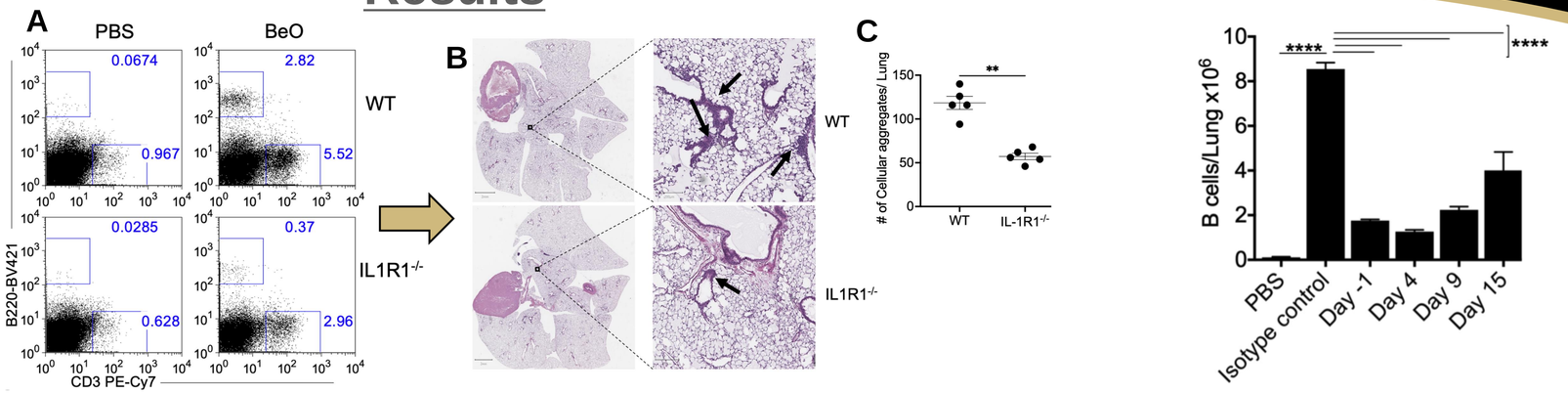
While T cells are well studied in CBD, the role of B cells and innate immune signaling is less clear. IL-1 signaling plays a key role in immune activation, while the CXCL13-CXCR5 axis is known to regulate B cell migration. The aim of this study was to examine how IL-1, CD4+ T cells, and CXCR5 control B cell recruitment and immune responses in CBD using murine models and gene expression analysis.

Methodology

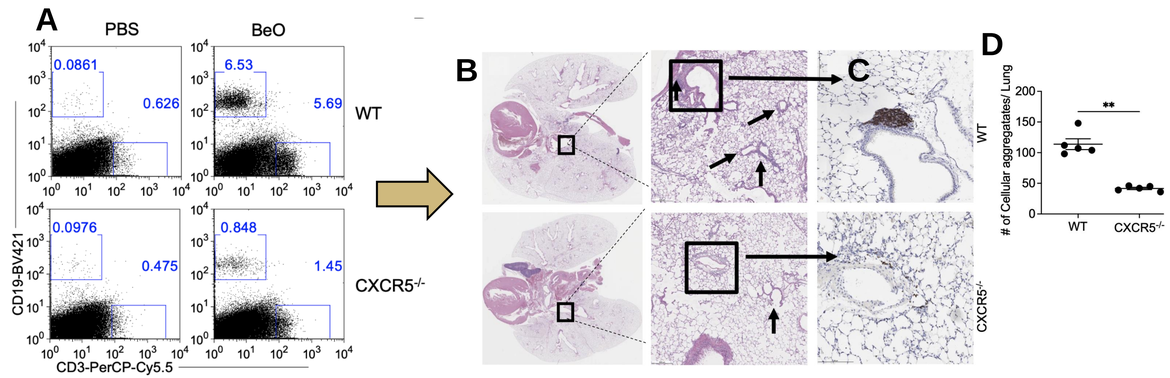
To study B cell recruitment in CBD, we used wildtype (WT), Interleukin-1 Receptor 1 knockout (IL-1R1 KO), CXCR5 knockout (CXCR5 KO), and HLA-DP2 transgenic mice, which predispose mice to developing CBD.

- **Beryllium exposure** → Mice received multipledoses of BeO (100 µg/mouse) via oropharyngeal aspiration over 21 days.
- **Blocking Experiments** → IL-1 signaling was inhibited using recombinant IL-1 receptor antagonist or an anti-IL-1α mAb. CD4+ T cell cells were blocked with an anti-CD4 mAb, and B cells with an anti-CD20 mAb.
- **Adoptive B Cell Transfer** → B cells from WT spleens were injected into B cell-deficient (mMT) mice to test their protective role.
- **Flow Cytometry** → Used to quantify B and T cells in lungs.
- **ELISA** → Measured CXCL13, IL-1α, and IL-1β levels in lung fluid.
- **Histology & IHC** → H&E staining and B220 IHC for B cell localization in the lungs
- **RNA Sequencing** → Identified genes linked to antigen presentation, interferon signaling, and tight junctions.

Results



IL-1R1 Signaling is Required for B Cell Recruitment in CBD: IL-1R1 KO mice exhibit reduced B cell recruitment and lung inflammation compared to WT controls. (A) Flow cytometry plots show B220+ B cell and CD3+ T cell frequencies in the lungs of BeO-exposed WT and IL-1R1 KO mice. (B) H&E staining of lung sections reveals fewer perivascular immune cell aggregates in IL-1R1 KO mice. (C) Quantification of cellular aggregates confirms a significant reduction in IL-1R1 KO mice, suggesting IL-1 signaling is necessary for B cell accumulation. (n=5 per group, One-way ANOVA $P < 0.01$ (**)).



CXCR5 Expression is Essential for B Cell Homing in CBD: CXCR5 KO mice show impaired B cell recruitment and reduced immune cell aggregates in the lungs. (A) Flow cytometry plots display the frequency of B220+ B cells and CD3+ T cells in BALF of BeO-exposed WT vs. CXCR5 KO mice. (B,D) H&E staining reveals a lack of cellular aggregates in CXCR5 KO lungs. (C) Immunohistochemistry (IHC) for B220+ B cells further confirms the absence of B cell clusters in CXCR5 KO mice. (n=4-5 per group, One-way ANOVA $P < 0.01$ (**)).

CD4+ T Cells Regulate Early B Cell Recruitment to The Lungs in CBD: CD4+ T cell depletion reduces B cell recruitment in a time-dependent manner. (A) Flow cytometry analysis of B220+ B cells in BALF of BeO-exposed WT mice treated with anti-CD4 monoclonal antibody (mAb) at different time points: Day -1 (before BeO exposure), Day 4 (early depletion), Day 9 (mid-phase), and Day 15 (late-phase). Mice receiving anti-CD4 mAb before or early after BeO exposure showed the greatest reduction in B cells, while later depletion had a lesser effect. (n=4 per group, One-way ANOVA, $P < 0.01$ (**), $P < 0.001$ (***), $P < 0.0001$ (****)).

Conclusions

- IL-1 signaling and CD4+ T cells are essential for B cell recruitment in CBD, promoting immune cell accumulation and inflammation in the lungs.
- The CXCL13-CXCR5 axis is critical for B cell migration, as CXCR5 KO mice show significantly reduced B cell infiltration and immune aggregates.
- B cells play a protective role in modulating lung inflammation, and their absence leads to increased lung injury, highlighting their potential as therapeutic targets.