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COOPERATION OF INNATE AND ACQUIRED IMMUNE SYSTEM DERIVED SIGNALS INDUCES STROMAL CELL ACTIVATION IN CHRONIC INFLAMMATION AND ECTOPIC LYMPHONEOGENESIS

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Background Acquisition of lymphoid-like features is a hallmark of ectopic lymphoneogenesis. In lymph nodes, gp38+ fibroblastic reticular cells (FRC) are responsible for lymphoid chemokines/cytokine production and lymphocyte compartmentalisation. gp38 up-regulation on stromal cells has been observed in cancer and inflammation, suggesting that stroma can acquire lymphoid like features in these conditions. IL-22 and IL-4 are produced by a novel population of innate lymphoid cells (ILCs), similar to lymphoid tissue inducer cells, which have been shown to be critical regulators of stromal cell activation in lymphoneogenesis. The role of ILCs as well as other innate immune cells, in the context of stromal cell activation in inflammation is unknown. The authors designed a novel inducible model of ectopic lymphoneogenesis, in adenoviral infected murine salivary glands to evaluate the dynamics of gp38 expression and the signals regulating stromal cell activation in different phases of inflammation.

Materials and methods Flow cytometry on disaggregated tissue, qRT-PCR and immunofluorescence was performed at different time points post cannulation (pc) in WT and knockout mice (IL-4R^{-/-}, IL-22^{-/-}, Rag^{-/-}, Ltα^{-/-}, LTβR^{-/-}) in order to investigate the role of these molecules in stromal cell activation.

Results FACS analysis showed that in WT mice stromal cell activation occurs with significant increase in the percentage of FRC (CD45-GP38+CD31⁻ cells) at day 2 pc. with peak of activation between day 5–8 pc. The full acquisition of lymphoid stromal features with high levels of lymphoid chemokine and cytokine expression was attained by day15 pc. This correlates with acquisition of lymphoid features by the inflammatory aggregates. In absence of innate immune system signals (IL-22, IL-4) lack of gp38 up-regulation at day 2 pc, 5 pc and 8 pc was observed suggesting their role in the initial stromal cell activation. Interestingly, RAG, LTβR, LTα KO mice did not show this defect instead there was a normal degree of stromal cell activation in the early phases (2–8 days pc) but a dramatic decrease in the number of FRCs by day 15 pc. This decrease associated with a significant decrease in lymphoid chemokine/cytokine expression and disorganisation of the inflammatory aggregates.

Conclusions Overall, these data suggest that stromal cell activation in ectopic sites results from the coordinated actions of signals derived by both the innate and acquired immune system. While innate immune cell signals are likely to be responsible for early activation of local stroma and gp38 acquisition, but maturation into lymphoid stroma requires lymphocyte derived signals and is dependent on LTβR signalling.