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Mammary Epithelial Stat3 Expression Modulates the Inflammatory Signature of the Gland During Regression Post-weaning

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Post-lactational regression of the mammary gland (involution) is characterised by significant cell death and the acquisition of an inflammatory transcriptional signature. We have previously demonstrated a fundamental role for Stat3 in the coordination of cell death during involution. In the present study, we investigate whether epithelial expression of Stat3 impacts the innate immune environment of the gland, and the number of inflammatory cells present, by examining mice in which Stat3 is conditionally deleted only in the mammary epithelium.

There is a marked Stat3-dependent increase in expression of genes associated with the acute phase response and innate immunity during first phase involution. From 48 hours onwards, chitinase 3-like 1, which has been associated with chronic inflammatory conditions, is dramatically upregulated by Stat3. Concurrently, the number of mammary macrophages and mast cells increases per unit area. Interestingly, this increase is reduced in the absence of epithelial Stat3, and expression of arginase-1 and YM1, markers of alternatively activated macrophages, is significantly decreased in the Stat3 deleted glands. Furthermore, iNOS, associated with a classically activated macrophage phenoptype, shows markedly elevated expression in the absence of epithelial Stat3. The increase in expression of matrix metalloproteinase enzymes normally observed during second phase involution is significantly reduced in the absence of Stat3.

Thus we demonstrate that Stat3 is a key transcriptional regulator of genes associated with innate immunity and wound healing, and epithelial Stat3 modulates numbers of macrophages and mast cells present per unit area during involution. These findings have relevance to investigation of the pathogenesis of pregnancy associated breast cancer and the role of Stat3 signalling in neoplastic mammary epithelium.