Sex and age determine the heterogeneity, transcriptional identity and function of peritoneal macrophages

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Introduction
Macrophages reside in the body cavities to maintain serosal homeostasis and provide immune surveillance. We have previously shown that turnover of F4/80hi CD102+ peritoneal macrophages from the bone marrow is sexually dimorphic, with high rates in males and very low rates in females. Here, we investigate the factors controlling the dimorphic lifespan of peritoneal macrophages and the impact that differential turnover has on the function and composition of the peritoneal population.

Materials, Methods and Results
Using a combination of fate mapping techniques we show that dimorphic turnover of resident peritoneal macrophages is driven by changes in the local environment that arise upon sexual maturation. Population and single cell RNAseq revealed striking dimorphisms in gene expression between male and female peritoneal macrophages that was in part explained by differential heterogeneity between these populations. By assessing the development of dimorphisms with age, using tissue-protected bone marrow chimeric mice to estimate the time of residency of cells in the tissue, and by analysing dimorphisms in monocytopenic Ccr2-/- mice, we demonstrate that certain sex-dependent features of peritoneal macrophages appear dependent upon differences in cell longevity. By blocking one of these features, we provide evidence that dimorphic heterogeneity and turnover of peritoneal macrophages results in differences in the ability to protect against pneumococcal peritonitis between the sexes.

Conclusion
Sex dimorphisms in gene expression and function of peritoneal macrophages arise in part from the sexually dimorphic lifespan of these cells. Hence, time of residence within the tissue appears to contribute to the transcriptional identity and function of peritoneal macrophages. These findings have important implications for understanding the functional heterogeneity of resident macrophages across tissues.

Keywords : resident, macrophage, sex, peritoneal, lifespan
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