Project Title: "Aged immune failure and reversal"

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Research Group: Skin Cancer and Ageing

Immune decline is one of the defining problems of an ageing population. Elderly people have reduced responses to vaccines, failure of tumour surveillance and chronic inflammation, defined as low-grade immune activation (inflammaging). This immune decline drives multimorbidity and premature mortality. Research has focused primarily on cell-intrinsic T cell decline, such as thymic atrophy reducing naive T cell output and clonal exhaustion contracting the repertoire. Recent work shows mitochondrial T cell dysfunction is both a consequence of T cell ageing and drives multiorgan ageing[1], which reframes immunosenescence as a metabolic disease.

The metabolic determinants of T cell ageing extend to the extracellular environment, where lipids are active instructors of immune cell fate across both innate and adaptive arms of immunity. For T cells specifically, extrinsic lipid regulation demonstrates that chylomicrons in circulating blood are taken up by naive CD8+ T cells via LDLR, delivering cholesterol to the lysosomal compartment where it activates mTORC1, driving translational priming of mitochondrial and effector programmes that persist durably through activation and expansion. Notably T cells have greater effector function when they are primed postprandially[2].

Our lab investigates how organ-specific lipid milieus impact cancer invasion, organ tropism and immunity[3-5], and the lipid species and ratios that organise the plasma membrane into functional nanodomains to control receptor clustering and modulate signalling thresholds across immune lineages. We want to study how ageing modifies the lipid composition of the extracellular milieu and how this impacts immune competence.

We will map how ageing sculpts the systemic and organ lipidome using lipidomics, lipoprotein fractionation, spatial approaches including superresolution microscopy across tissues (co-supervision: Dr Jonathan Worboys, Lydia Becker Institute, University of Manchester). We will focus particularly on lipid species and classes known to determine T cell activation quality. Beyond T cells, we will interrogate how the aged lipid environment shapes innate and adaptive immunity more broadly and contributes to tumour immunosurveillance. We will use in vivo approaches to modify the lipidome and test restoration of immune competence in antitumour immunity.

References

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