Project title: Computational modelling of causal regulators of immune dysfunction in ageing

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Aim of the Project

Ageing affects multiple organs and systems, but dysfunction of the immune system is likely to be causal for many age-associated conditions including impaired regeneration and wound healing. Understanding how these changes occur and evaluating their impacts in a systematic manner is critical for identifying appropriate therapeutic interventions to promote healthy immune function. Current models for the ageing immune system rely on profiling of immune cells to extrapolate potential molecular regulators that are altered in ageing. Although informative, these models do not represent the highly specialised environment immune cells are exposed to during tissue repair. We propose to generate a model for ageing-related changes to monocytes and macrophages, the immune cells critical for tissue regeneration. This model will be of the multi scale differential equation type, as these approaches permit robust fitting of model parameters to biological data. Using the model we will aim to identify molecules that we predict are causally important for monocyte/ macrophage function in aged people.

Project Description

Immune system changes are likely to be causally important for many of the frailties and diseases that occur in ageing. Monocytes and macrophages are phagocytic cells essential for protection against disease and for repairing body tissues. In ageing and a number of chronic diseases, these cells show altered programs that impair their effectiveness, resulting in muscle weakness and infection. Although a number of changes have been documented, the plasticity and complex behaviour of these cells has prohibited the generation of a comprehensive model that can explain how they are affected by ageing. Monocytes are circulatory cells derived from stem cells in the bone marrow. They are recruited to sites of tissue injury, such as infections, where they often differentiate into macrophages. Both monocytes and macrophages can engulf pathogens and damaged tissues as well as secrete cytokines and chemokines to regulate other immune and resident cells. They are crucial for both promoting inflammation, by activating key signalling pathways such as NF-kB and TLR receptors, but also for resolving inflammation at later stages. Dysregulation of this switch has profound consequences for repair of injured tissue or clearance of pathogens and a common feature of chronic disease and ageing.

Despite the importance of monocytes and macrophages in regulating organismal health, there is little understanding of the molecular changes that affect their function during tissue repair. Specifically, there is no predictive model that can explain the consequences of the molecular changes occurring in these cells as a consequence of ageing or disease. This project therefore aims to generate a digital twin of ageing monocytes and macrophages for predicting how ageing associated changes can affect their function during muscle regeneration.

In this project we will leverage ageing datasets to build multi scale computational models of immune dysfunction in ageing, parametrise the models and then use the modelling framework to produce a digital twin of ageing monocytes. This will then permit us to identify molecules that we predict are causally important for monocyte/ macrophage function in aged people.