Targeted Project / AY 2023 -2024

Defining the molecular mechanisms of TCR-independent T cell function

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Department/Institute: Babraham Institute

Research area: Immunology

Project outline:

Cytotoxic T lymphocytes are critical for immunological defence against viruses and cancer. Stimulation of these cells induces both cytokine secretion and directed lysis of target cells. While the process by which CTLs recognize specific antigens through their T cell receptors (TCRs) has been extensively studied, it is increasingly clear that CTLs can also respond to other signals such as cytokines and danger signals. CTLs whose TCRs do not bind relevant antigens infiltrate inflammatory lesions in infection, autoimmune diseases and cancer. Although often called "bystander T cells", emerging evidence indicates that these cells make important contributions to the immune response by secreting inflammatory cytokines and engaging in cytolytic activity upon activation of NKG2D, a receptor commonly used by NK cells. However, the molecular mechanisms of TCR-independent CTL responses remain unclear.

This project will address the question: How do CTLs respond to TCR-independent signals and how does this compare with TCR-induced responses? We will approach this by examining signalling pathways, transcriptional changes, and effector molecule secretion by stimulated cells. Techniques will include high-dimensional single-cell assays of signalling mediators, RNA-sequencing, flow cytometry, secretion assays and live-imaging cytotoxicity assays. This work will shed light on an under-studied facet of T cell biology with implications for host defence and self tolerance. The project will provide interdisciplinary training in both experimental cellular immunology and high-dimensional data analysis, including coding in R and applied statistics.

For more information about the lab, please see the lab website and selected publications:

- https://www.babraham.ac.uk/our-research/immunology/arianne-richard

- Ma CY, Marioni JC, Griffiths GM, Richard AC. Stimulation strength controls the rate of initiation but not the molecular organisation of TCR-induced signalling. Elife (2020) 9:e53948. doi: 10.7554/eLife.53948

- Richard AC, Lun ATL, Lau WWY, Gottgens B, Marioni JC, Griffiths GM. T cell cytolytic capacity is independent of initial stimulation strength. Nat Immunol (2018) 19(8):849–58. doi: 10.1038/s41590-018-0160-9

BBSRC DTP main strategic theme: Understanding the rules of life

BBSRC DTP secondary strategic theme: Bioscience for an integrated understanding of health