Universität Basel

Research Project

The multiverse of MR1-restricted T cells and of their stimulatory metabolite antigens

Third-party funded project

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The multiverse of MR1-restricted T cells and of their stimulatory metabolite antigens1. Summary of the research planA central mechanism of immune response is antigen recognition. The dogma that only peptides stimulate T cells has become obsolete after the evidence that structurally different molecules, including lipids and small metabolites, are immunogenic for T cells. Ongoing studies are revealing the relevance of non-peptide-specific T cells in microbial and tumor immunity and in co-ordinating immune response.Non-peptidic antigen recognition by T cells is the subject of our scientific interest. Recently, we focused on T cells recognizing metabolite antigens presented by the MR1 restriction molecule. The immunological functions of this novel population of T cells are still poorly characterized and their role in diseases remains to be investigated. Unexpectedly, these studies are unravelling a new world of antigens consisting of small metabolites that may accumulate within bacterial cells, tumor cells and activated B cells. The coordinated regulation of cellular metabolism and its alteration in bacteria and host cells are novel perspectives for understanding how metabolite-specific T cells participate in host defences and immune homeostasis. We plan to address three aspects:1.The repertoire of metabolite antigens stimulating MR1-restricted T cells.2.The metabolome regulation and the mechanisms of metabolite-presentation by MR1.3.The role of MR1-restricted T cells in the immune response.These studies will take advantage of a combination of state-of-the-art methodologies: cellular techniques to isolate and characterize MR1-restricted T cells, single cell transcriptomics and multidimensional flow-cytometry to investigate the presence of distinct MR1-restricted T cell populations, knock-out cells by CRISPR/Cas9 technique to identify key genes involved in MR1 antigen-presentation, and biochemical tools (HPLC separation and mass spectrometry) to identify novel stimulatory metabolites. Finally, two novel models of TCR retrogenic mice will be generated to investigate the regulatory role of MR1-restricted T cells in antibody responses and in tumor immunosurveillance.Overall, these studies aim at understanding the physiological implications of metabolite antigen recognition by T lymphocytes. Targeting metabolite-specific responses may represent a so far unforeseen immune strategy for inducing more efficient responses to microbial and tumor antigens.

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