Molecular basis underpinning metabolite-mediated T-cell immunity

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Metabolite based T cell immunity is emerging as a major player in antimicrobial immunity, autoimmunity and cancer. Here, small molecule metabolites were identified to be captured and presented by the major histocompatibility complex (MHC) class-I related molecule MR1 to T cells, namely Mucosal Associated Invariant T cells (MAIT) and diverse MR1-restricted T cells. Both MR1 and MAIT T cell receptors (TCR) are evolutionarily conserved in many mammals, suggesting important roles in host immunity. Namely, during infection with riboflavin-producing microorganisms, MR1 trapped riboflavin-based metabolites and presented on the surface of the antigen-presenting cells encountering the MAIT TCR leading to the activation of the MAIT cells. How modifications to these small molecule-metabolites affect presentation by MR1 and MAIT cell activation remains unclear.

To dissect the molecular basis underpinning MR1 antigen capture and MAIT recognition, we chemically synthesized and characterized a large panel of these naturally occurring metabolites, termed “altered metabolite ligands” (AMLs), and investigated functionally and structurally their impact on MAIT recognition. Through the generation and detailed analysis of 13 high-resolution MAIT TCR-MR1-AML crystal structures, along with biochemical and functional assays, we show that the propensity of MR1-upregulation on the cell surface was related to the nature of MR1-AML interactions. MR1-AML adaptability and a dynamic compensatory interplay at the TCR-AML-MR1 interface impacted on the affinity of the TCR-MR1-AML interaction, which ultimately underscored the ability of the AMLs to activate MAIT cells. Therefore, we determined the molecular basis underlying MR1 antigen capture, MAIT TCR recognition and thereby provide insights into MAIT cell antigen potency.

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