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Molecular insights into the specificity and potency of metabolite-mediated T-cell immunity

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Mucosal associated invariant T (MAIT) cells are an abundant human T cells subset that are variably activated by small-molecule metabolites presented by the MHC class 1 related molecule, MR1. During infection with riboflavin-producing microorganisms, the microbial metabolite 5-amino-6-D-ribitylaminouracil (5-A-RU) reacts with glycolysis byproducts of glyoxal/methylglyoxal forming highly potent ribityl pyrimidine ligands. These pyrimidine intermediates are trapped by MR1 and presented on the surface of the antigen-presenting cells encountering the MAIT T cell receptor (TCR) leading to the activation of the MAIT cells. These riboflavin-based MAIT cell agonists are unique for a wide range of microbes and accordingly represent a molecular signature of microbial infection. The most potent MAIT agonist is 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), but the mechanism that underpins this potency remains unclear.

To explore the molecular basis for the high potency of 5-OP-RU as a MAIT agonist, we chemically synthesized and characterized a large panel of 5-OP-RU analogues, termed "altered metabolite ligands" (AMLs), and investigated functionally and structurally their impact on MAIT TCR recognition. Here, modification of the 5-OP-RU ribityl moiety impacted differentially on MAIT TCR binding affinity, consistent with the ability of AMLs to stimulate MAIT cells. Through an analysis of 13 high-resolution (~ 1.9 Å) MAIT TCR-MR1-AML crystal structures, we show that the propensity of MR1 upregulation on the cell surface was related to the nature of MR1-AML interactions. Further, MR1-AML adaptability and a dynamic compensatory interplay at the MAIT TCR-AML-MR1 interface impacted on the affinity of the MAIT 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 specificity and potency.

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2. Salio, M.#, Awad, W.# et al. (2020). Ligand-dependent downregulation of MR1 cell surface expression. *PNAS*, 202003136.
3. Awad W., et al. (2020). Atypical TRAV1-2- T cell receptor recognition of the antigen-presenting molecule MR1. *J. Biol. Chem.*, in press.

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