Experimental Immunology

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MR1-restricted T cell recognition of metabolite antigens in cancer, infections and autoimmune diseases

T lymphocytes recognize a variety of antigens and exert important functions in immune response. The activation of T cells is mediated by engagement of the T cell receptor (TCR) that recognizes antigens on the surface of antigen-presenting cells. T cells may recognize antigens of different chemical composition, including short peptides, lipids, and small metabolites. Upon interaction of complexes formed by antigen-presenting molecules and antigens with TCR, T cells become activated and exert their effector functions.

We study the nature of the antigens that stimulate T cells. Recently, we have focused on a new population of T cells that we identified and called MR1T cells and that recognize endogenous metabolites presented by the antigen-presenting molecule MR1. We found that MR1T cells use a polyclonal TCR gene repertoire, they have different functional capabilities, including killer and helper functions, and are present in healthy individuals with frequencies similar to those of peptide-specific T cells. They also show different gene regulatory mechanisms, thus indicating that they are a functionally heterogeneous population of T cells, resembling adaptive T cells specific for peptide or lipid antigens. An important characteristic of MR1T cells is that they mostly recognize tumor cells and not healthy cells. This unexpected tumor recognition bias is due to the preferential accumulation of unique metabolite antigens within tumor cells. Our laboratory has started a multi-disciplinary approach to identify the nature of these novel tumor antigens using molecular approaches to reveal genes relevant to metabolite accumulation. We also have established tools to perform HPLC separation of metabolites from tumor cells, which are then tested for their stimulatory capacity and structure by mass spectrometry and NMR. We have generated a large number of MR1T cell clones that have been tested against >50 tumor cell lines. These studies revealed that MR1T cells recognize patterns of tumor cells. Transfer of TCR genes confirmed TCR specificity. Furthermore, tumor cells were also grouped according to their capacity to stimulate most or only some of tested MR1T cells. We interpret these findings with the presence of MR1T TCR that recognize metabolite antigens shared among many tumors, and with the presence of multiple types of metabolic alterations that occur in tumor cells. The combination of both induces a pattern-type recognition of tumor cells by MR1T cells.

These findings have raised major interest in using MR1T cells in novel types of anti-tumor cell therapy. This is justified by several reasons as follows, i) the metabolites stimulating individual MR1T cells accumulate in many tumor types, independently of their tissue origin; ii) metabolite antigens cannot be readily modified by tumor cells, limiting recognition escape associated with antigen modification as the case with peptide antigens; iii) MR1 is ubiquitously expressed and even tumor cells expressing very low levels of MR1 on their membrane may efficiently stimulate specific MR1T cells; iv) the MR1 gene is not polymorphic and thus the same MR1T TCR recognizes tumors from different individuals; v) MR1T cells show killer and helper functions, which are both required for optimal anti-tumor cell therapy.

Current studies are addressing the nature of the stimulatory antigens, the regulation of metabolic pathways relevant to generation and accumulation of MR1T-stumulatory metabolites, the identification of the cellular compartments where metabolites are generated and how they are transported to those where they can meet MR1 protein, and the nature of the co-stimulatory/inhibitory molecules that control the activation of MR1T cells. Ad hoc animal models are being exploited to investigate their capacity to recognize and control tumor expansion *in vivo*.

MR1T cells have the function of surveying the metabolic integrity of other cells and may prevent accumulation of metabolic alterations leading to dysregulated cell proliferation. Their use in novel tumor cell therapy approaches may represent a natural outcome of future translational applications.

Selected Publications

Mori L and De Libero G (2020). "Bohemian Rhapsody" of MR1T cells. Nat Immunol 21, 108–110.

Di Blasi D, Boldanova T, Mori L, Terracciano L, Heim MH and De Libero G (2020). Unique T-Cell Populations Define Immune-Inflamed Hepatocellular Carcinoma. Cell Mol Gastroenterol Hepatol 9, 195–218.

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Lepore M, Kalinichenko A, Calogero S, Kumar P, Paleja B, Schmaler M, Narang V, Zolezzi F, Poidinger M, Mori L et al. (2017). Functionally diverse human T cells recognize non-microbial antigens presented by MR1. Elife 6.

Mori L, Lepore M and De Libero, G (2016). The Immunology of CD1- and MR1-Restricted T Cells. Annu Rev Immunol 34, 479–510.