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Editorial Note

Natural killer T cells

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This issue of Biomedical Journal includes two review articles on natural killer T cells. The first review article has been written by Drs. Birkholz and M. Kronenberg: « Antigen Specificity of Invariant Natural Killer T Cells » [1]. The second review is from Dr Agnès Lehuen and her colleagues on « Regulatory Role of Natural Killer T Cells in Diabetes » [2].

Dr Kronenberg's review principally describes the ligands of natural killer T-cells (iNKT) bearing a T cell receptor (TCR) comprising an invariant TCR alpha-chain associated with a limited number of V-beta chains. It analyzes in depth the lipid antigens which are presented by the weakly polymorphic CD1d molecule, structurally similar to MHC class I molecules. The mode of interactions of alpha-galactosylceramide (alphaGalCer) with CD1d and the invariant TCR are described. Several head group modifications of the alpha-GalCer sugar moiety have been shown to alter TCR binding and iNKT responses. Indeed, some synthetic compounds related to alphaGalCer were inactive while others were shown to preferentially trigger Th1 or Th2 iNKT responses. Modifications of lipid chains of CD1d agonists lead to the synthesis of new antigens with Th2 or Th1 profiles. Stronger interactions of these modified agonists with CD1d and/or prolonged presentation of them by dendritic cells triggered higher IFN-gamma production *in vivo*. This resulted in a stronger adjuvant effect when compared to regular alphaGalCer. Other parts of this review are devoted to the structural analyses of endogenous ligands and foreign antigens from bacteria, fungi and parasites. Isoglobotrihexosylceramide, the first self-ligand to be identified, is shown complexed to mouse CD1d and mouse iNKT TCR in a crystal structure. Numerous microbial antigens recognized by iNKT TCRs are glycolipids capable of stimulating protective immune responses against pathogens. This very interesting review clearly shows that deciphering the biochemical rules of interactions in the various tri-molecular CD1d-antigen-INKT TCR complexes, is likely to lead to the synthesis of agonists with therapeutic values.

The second article by Dr Lehuen and her colleagues presents evidence demonstrating that iNKT cells are implicated in the control of type 1 diabetes in NOD mice. The number of iNKT cells is decreased in NOD mice and while these cells secrete IFN-gamma, their IL-4 production is much lower than in control animals. The authors describe their own experiments which show that iNKT lymphocytes are able to induce anergy of autoreactive T cells and/or inhibit the production of IFN-gamma by the remaining pathogenic T lymphocytes. Interestingly, they showed that iNKT cells are able to stimulate the expansion of regulatory T lymphocytes by converting naive diabetogenic T cells into regulatory T cells. The authors describe the complex interactions between various cell populations and the secretion of multiple cytokines involved simultaneously in the control of viral infection and the induction of tolerance to pancreatic beta-cells. Interestingly, the authors present results from the literature showing that a subpopulation of iNKT lymphocytes ($CD4^{-}$, $NK1.1^{-}$) synthesizes high levels of IL-17 and small amounts of IL-4 and IFN-gamma. These iNKT 17 lymphocytes increase the incidence of diabetes in NOD mice. Finally, the impact of microbiota on type 1 diabetes and host metabolisms is discussed in the context of iNKT cells and lipid antigens. In the last paragraph, the authors analyze recent data suggesting that iNKT are also involved in protection against type 2 diabetes, restore insulin sensitivity and decrease body fat. This stimulating review summarizes our present knowledge on iNKT cell role in protection against diabetes and shows the complexity of the protective mechanisms involved.

REFERENCES

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