

Natural and synthetic antigenic ligands of NKT cells and their role in anti-tumor rejection

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CD1d-restricted NKT cells have been reported to regulate primary as well as transplanted tumors, but the ligand that activates NKT cells in these conditions has remained elusive. An agonist ligand of their TCR, alpha-GalactosylCeramide, was serendipitously identified based on the anti-tumor properties of marine sponge extracts. However, alpha-glycosylated ceramides have not been identified in vertebrates suggesting that they are not the natural ligands. We have used genetic mutations of enzymes controlling key steps of lipid metabolic pathways to zoom in on candidate classes of lipids, and synthetic chemistry to evaluate their ability to stimulate NKT cells. We will present our results suggesting that a single self-glycosphingolipid can function as an agonist ligand of mouse and human NKT cells. Furthermore, we have identified microbial ligands that function as agonist NKT cell ligands. Together, our results suggest that NKT cell dual recognition of self and foreign glycolipids may explain their function in cancer as well as infection.

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