

Preface

Natural killer T (NKT) cells discussed in this book are CD1d-restricted T cells, not to be confused with NK cells. Unlike conventional T cells restricted by conventional class I or II major histocompatibility complex (MHC) antigens, they respond to antigens presented by CD1d, which is a non-classical MHC class I-like molecule. It has been two decades since NKT cells were first identified as NK1.1 expressing T cells. One of the highlights of the early discoveries on NKT cells is the identification of their unique TCR gene segment usage, namely V α 14J α 281 (now called V α 14J α 18), forming an invariant TCR alpha chain (now these NKT cells are called type I NKT cells or iNKT cells) and its prototypic agonistic antigen alpha-galactosylceramide (KRN7000). This stunning finding shed light on some important characteristics of this relatively small but pivotal T cell population. First, NKT cells recognize lipid, not protein, antigens, indicating that this T cell subset surveys a range of antigens distinct from that of conventional T cells. Given that lipids are major components of any cells or viruses, it makes sense the immune system has a T cell repertoire that surveys lipids. Second, despite the fact that NKT cells are only approximately 1% of mouse spleen cells, they can strongly regulate tumor immunity. Third, because of the expression of the invariant TCR alpha chain, one can stimulate most type I NKT cells with a single antigen such as KRN7000.

Overall, NKT cells bridge the gap between the innate and adaptive immune systems. Like innate immune cells, they can respond quickly to be among the first responders on the scene, and rapidly produce cytokine. As adaptive immune cells, they provide the T cell arm of the immune system the capacity to recognize lipid antigens, as mentioned. They also play a regulatory role as well as an effector one, with the ability to activate T and B cells, NK cells, and dendritic cells, but also the ability to downregulate these under certain conditions.

An important technical break though made for NKT cell research was the invention of CD1d-tetramer and CD1d-dimer by which we can stain and identify NKT cells with flow cytometry. With this now widely used tool, we learned that NK1.1 can no longer be used as a marker for this T cell population, but the only way to define NKT cells is as “CD1d restricted T cells.” Now we understand that there are many subsets of NKT cells that can be defined by their TCR gene segment usage

(e.g., V β 2, 7, or 8) or surface molecule expression pattern (such as CD4⁺ or CD4⁻8⁻, or NK1.1⁺ or NK1.1⁻) or cytokine profile. Among the subsets of CD1d-restricted T cells, ones that lack the semi-invariant TCR and use more diverse TCRs, but still recognize lipids presented by CD1d, were discovered and are now called type II NKT cells. These seem to play more of a regulatory role, especially in tumor immunity, but can have effector functions as well.

With the fact that KRN7000 is a strong inducer of tumor immunity through activating NKT cells as well as for a long time the only tool available to specifically activate NKT cells, knowledge of NKT cells has been accumulated through functional studies in the context of tumor immunology including clinical trials of KRN7000 in cancer patients. Although the main focus of this book is to review what we have learned about NKT cells with studies in cancer immunology and to examine their clinical utility, the knowledge should be informative to understand this underappreciated T cell population in many other fields outside of tumor immunology.

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