Regulation of immune response by natural killer (NK)T cells

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NKT cells are T cells that recognize lipid antigens presented by a class Ib MHC molecule, CD1d. Although NKT cells comprise a small T-cell population, they play critical roles regulating immune responses in infections, autoimmune diseases and cancer. NKT cells have at least two subsets based on T cell receptors expressed. Type I expresses a semi-invariant TCRα chain utilizing Vα14Jα18 (Vα24Jα18 in humans). Type II is defined as those that do not express the Vα14Jα18 TCRα chain. Type I NKT cells frequently facilitate and type II NKT cells usually suppress immune responses. The two types of NKT cells not only have opposing roles in immune regulation but also counteract each other, defining a new immunoregulatory axis. Changing the balance along this axis is a key to manipulate immune responses. One way of tipping the balance is to activate one NKT cell type with an exogenous agonist. In fact the type I NKT-cell agonist , α-galactosylceramide (KRN7000), has been shown to induce strong tumor immunity in mice. However, it has drawbacks that may be reasons for limited success of KRN7000 in clinical trials. We recently discovered a new type agonist, β-mannosylceramide (β-ManCer), which induces tumor immunity by activating type I NKT cells but through a different mechanism from that of KRN7000. Moreover, KRN7000 and β-ManCer synergized to induce tumor immunity. All together, despite being a small T cell population, NKT cells are attractive targets to manipulate the immune system to skew the response in a favorable direction.