NKT10 cells: a novel iNKT cell subset

Gerhard Wingender, Duygu Sag and Mitchell Kronenberg

Invariant Natural Killer T (iNKT) cells are a unique subset of T cells that combine features of innate NK cells and of adaptive memory T cells [1, 2]. This hybrid character of iNKT cells, combined with the fact that they express an invariant TCR α-chain, led to their naming. In contrast to conventional T cells, iNKT cells recognize glycolipid antigens presented to them by the non-polymorphic MHC class I-homologue CD1d. The best-studied antigen for iNKT cells is α-galactosylceramide (αGalCer), which is the chemically optimized version of a naturally occurring antigen, presumably from bacteria. Following TCR stimulation iNKT cells rapidly produce copious amounts of various cytokines, including Th1-, Th2-, and Th17 cytokines. Through these cytokines iNKT cells can have a pronounced effect on the immune system, impacting an impressive variety of different immune reactions. They are involved in a range of chronic and acute inflammatory processes, including responses to pathogens and tumors, as well as in autoimmune responses. Furthermore, the antigenic response of iNKT cells is highly conserved in evolution, with mouse iNKT cells able to recognize human CD1d and vice versa. As basically all human iNKT cells share the same invariant TCR and respond to the same CD1d/antigen complexes in a comparable fashion, their therapeutic potential is great. Therefore, it is not surprising that αGalCer and other iNKT cell antigens are under continuing development as therapeutic agents [1, 2].

Although essentially all iNKT cells recognize αGalCer bound to CD1d via their invariant TCR, it became clear in recent years that iNKT cells are not uniform [1, 2]. Based on preference in the production of particular cytokines and the expression of specific transcription factors, iNKT cells can be subdivided into subsets that are reminiscent to CD4+ T helper cell subsets. In particular, NKT1, NKT2 and NKT17 cells are biased to the production of Th1, Th2 and Th17 cytokines, respectively. These subsets develop naturally and can be detected in the thymus. Additional subsets were found to differentiate following antigenic exposure: T\textsuperscript{\textth{1}}-like NKT\textsuperscript{\textth{1}} cells and iNKT cells expressing FoxP3 [1, 2].

Recently, we described a novel iNKT cell subset with IL-10-dependent regulatory function, which we termed NKT10 cells [3]. Interestingly, NKT10 cells express several markers commonly associated with regulatory T cells, including CD152 (CTLA4), CD279 (PD1) and CD304 (Neuropilin-1). Following antigenic stimulation the production of pro-inflammatory cytokines by NKT10 cells was greatly reduced compared to other iNKT cell subsets. Importantly, however, NKT10 cells were able to produce IL-10. Through this IL-10 production, NKT10 cells could impair anti-tumor immune responses and protect mice against experimental autoimmune encephalomyelitis (EAE), a mouse model of autoimmune disease [3]. Although, production of IL-10 by iNKT cells had been reported previously (see [3] for full discussion and references), a separate population dedicated to producing IL-10 with a distinct phenotype had not been described. In mice NKT10 cells were found in the thymus, spleen and other organs, but they were particularly frequent in white adipose tissue, where up to 13.5% of the iNKT cells produced IL-10 following activation [3]. Furthermore, we could detect NKT10 cells in human peripheral blood mononuclear cells, albeit at a low frequency (0.5%) [3]. Subsequently, others demonstrated that adipose NKT10 cells are important in maintaining the anti-inflammatory environment in the adipose tissue. In a mouse model, the presence of NKT10 cells supported the expansion of regulatory T cells and anti-inflammatory M2 macrophages [4].

Importantly, we also noted that NKT10 cells could be expanded greatly by in vivo treatment of mice with αGalCer [3]. The reduced production of pro-inflammatory cytokines by αGalCer-expanded NKT10 cells has previously led researchers to the erroneous conclusion that αGalCer stimulation of iNKT cells would induce an inactive state resembling anergy. Interestingly, the expansion of NKT10 cells by αGalCer was not a default response to strong antigenic stimulation. Although presentation of αGalCer by a bone marrow derived cell type could induce expansion of NKT10 cells, presentation by either DCs or B cells was not required [5], suggesting either redundancy or that this requires so far unknown properties of the cell presenting αGalCer.

The stimulation of iNKT cells with αGalCer is characterized by a mixed Th0-response, with both IFNγ and IL-4 being produced. Some other iNKT cells can also be induced to produce IL-4. This ability allows iNKT cells to orchestrate the ensuing global immune response towards either a Th1- or Th2-type. Importantly, the Th1/Th2-biasing nature of the antigen depends on the trans-activation of NK cells downstream of iNKT cell activation, as the immediate response
of iNKT cells towards antigenic stimulation is always a mixed Th0-response [6]. We have found that the ability of αGalCer to expand NKT10 cells in vivo was shared with four Th1-biasing antigens with related structures (C-Gly, EF77, SMC124 and DB06-1) [5, 7]. In contrast, a Th2-biasing iNKT cell antigen (OCH), or cytokine-driven iNKT cell activation due to TLR engagement or infections, did not induce NKT10 cell expansion [5].

NKT10 cells represent the first iNKT cell subset with a regulatory function under resting, steady-state conditions in mice and humans. We expect that this knowledge and the selective activation of particular iNKT cell functional subsets will help to resolve current controversies about the dichotomous nature of iNKT cells observed in various studies, namely their ability to exert either pro- or anti-inflammatory effects. Together with our data on the antigenic requirements for NKT10 cell expansion in vivo, such knowledge will likely help to understand the functional consequences of glycolipid antigens in therapy and how to deliberately tailor iNKT cell responses for therapeutic applications.

Gerhard Wingender: Izmir Biomedicine and Genome Center (iBG-izmir), Dokuz Eylul University Health Campus, Balcova/Izmir, Turkey, and La Jolla Institute for Allergy and Immunology (LJI), La Jolla, CA, USA
Correspondence to: Gerhard Wingender, email gerhard.wingender@deu.edu.tr

Keywords: iNKT cells, innate T cells, NKT10 cells, IL-10
Received: August 10, 2015
Published: August 26, 2015

REFERENCES

1. Buechel HM, et al. Cytokine. 2015; 72: 204-209.
2. Wingender G, et al. The Autoimmune Diseases (5th edition), 2014; 103-129.
3. Sag D, et al. J Clin Invest. 2014; 124: 3725-3740.
4. Lynch L, et al. Nat Immunol. 2015; 16: 85-95.
5. Wingender G, et al. J. Immunol. 2015; 195: 924-33. doi:10.4049/jimmunol.1500203. [Epub 2015 Jun 15].
6. Sullivan BA, et al. J. Immunol. 2010; 184: 141-153.
7. Birkholz A, et al. J. Immunol. 2015; 195: 924-933.