NUR77 HAS A CELL INTRINSIC ROLE IN NATURAL KILLER T CELL DEVELOPMENT AND FUNCTION

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Abstract

Natural killer T (NKT) cells are innate-like lymphocytes that respond to self and foreign glycolipids under inflammatory conditions. NKT cells have constitutively high levels of Nur77, an orphan nuclear receptor family transcription factor that is induced very early during their ontogeny. Nur77 function in NKT cells has not been explored, however. Nur77 is known to transcriptionally control negative selection of conventional T cells, development of regulatory T cells and differentiation of effector $CD8^+$ T cells. Thus, we hypothesized that Nur77 controls a lineage-specific gene expression program essential for the proper development of functional NKT cells. We found that, akin to conventional T cells, NKT cells poorly developed in transgenic mice that overexpressed wild type Nur77 ($wtNur77^{tg}$) in T lineage only. Introgression of the rearranged Va14i a-chain gene into $wtNur77^{tg}$ mice ($wtNur77^{tg}$; $Va14^{tg}$ mice) rescued NKT cell development but was arrested at the precursor stage 0. NKT cells in $wtNur77^{tg}$; $Va14^{tg}$ mice expressed lower levels of PLZF when compared to NKT cells in non-transgenic mice. So also, NKT cells in $wtNur77^{tg}$; $Va14^{tg}$ mice do not respond to glycolipid agonists. These findings are consistent with differences in the transcripomes of stage 0 NKT cells isolated from $Va14^{tg}$ versus $wtNur77^{tg}$; $Va14^{tg}$ mice. Collectively, our data suggest that Nur77 induction initiates a gene expression program in developing NKT cells that are critical for developmental progression and function of NKT cells.