Differenciation and migration of cytotoxic lymphocytes

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The dissection of the role of Natural Killer (NK) cells in immunity has been hampered by the lack of genetic models where the function of these cells can be assessed unambiguously and by the lack of NK cell markers. Our goal was to address both issues. To this aim, we combined genetics and microarray studies to demonstrate that the activating NK cell receptor NKp46 was expressed in a quasi-selective fashion by mammalian NK cells. We generated several transgenic and knockin mice expressing genes under the control of the NKp46 promoter that can be used as relevant models for the study of NK cells. For example, NKDTR-EGFP mice express both EGFP and the diphteria toxin receptor under the control of the NKp46 promoter. NK cells of these mice can be depleted by a single dose of diphteria toxin, which provides the first opportunity to clearly assess the role of NK cells in various systems. We also generated a microarray database that allows identifying and annotating the set of genes expressed by NK cells. By comparison with other leukocyte populations, the NK cell transcriptional signature has been identified. Bio-informatic analyses are performed to predict the function of these genes and to assign them to known molecular pathways. Gene knockdown and knockout are also used to test the function of novel genes identified using this screen. S1P5, a novel gene involved in NK cell trafficking, has been identified using this strategy. S1P5 is a sphingosine-1 phosphate receptor that regulates NK cell homing to peripheral organs. We followed up this initial finding and started to dissect the mechanisms of NK cell trafficking in vivo. Moreover, we have identified several genes that could be involved in NK cell degranulation. Studies in a human NK cell line are ongoing to address their function.