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EDITORIAL

Frontiers in natural killer cell immunology

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Natural killer (NK) cells were first observed in 1975, 20 years after the discovery of T and B lymphocytes.[1,2] Despite almost 40 years passing, our understanding of NK cell immunology in general lags far behind that of T and B lymphocytes. However, during the past 5 years, significant progress has been made in understanding NK cell biology. In this issue, there are five reviews highlighting recent progress in studying the education of memory NK cells in the liver,[3] the roles of NK cells in immune tolerance,[4] the interactions of NK cells with other immune cells[5,6] and NK cell immunotherapy for tumors.[7]

Jiang *et al.* 's[3] review recent advances showing that NK cells can mediate memory responses in both mice and humans. They summarize the phenotypic and functional features of memory NK cells, which specifically express surface Thy-1, Ly49C-I, CXCR6 and CD49a, but lack DX5 and can mediate T cell- and B cell-independent adaptive immunity in a contact hypersensitivity model. They also highlight the finding that these memory NK cells are liver-resident in some models. They discuss how the liver functions as an environment in which memory is generated, including the initiation phase and the recall phase, and they consider whether the liver is necessary for the memory function of NK cells. Based on this discussion, Jiang *et al.* propose a liver-resident precursor of memory NK cells, which are developmentally distinct from NK cells derived from the bone marrow.

In the review by Sun et al, the distribution, differentiation, phenotypic features, and functional features of NK cells in immunotolerant organs, such as the liver, uterus and lungs, are outlined.[4] These organs are clearly immunotolerant for sustaining self-homeostasis given the presence of relatively large numbers of negative regulatory immune cells, a huge proportion of which are NK cells (a noticeable feature of NK cell distribution). Sun *et al.*[4] consider that more attention needs to be paid to the possible roles of NK cells in maintaining tolerance and to the special subsets of NK cells with regulatory functions, similar to the studies of the mother/fetus interface by interferon-γ-producing uterine NK cells. Moreover, they consider that, for controlling disease, it will be important to identify the mechanism by which factors in the local microenvironment contribute to NK cell-mediated organ tolerance.

Hedi Harizi reviews interactions between dendritic cell (DCs) and NK cells. The author describes how almost all DC functions are influenced by activated NK cells and, conversely, how NK cell function requires close interactions with activated DCs, through membrane-associated molecules and mediators, among which prostaglandins (PGs), particularly PGE2, contribute to this crosstalk.[5] NK cells cannot produce PGE2 but respond to this molecule, and this review highlights the effects of PGE2 on DC–NK cell crosstalk and the subsequent impact on preventive and pathological immune responses. By contrast, Pedroza-Pacheco *et al.*[6] review the interactions between regulatory T (Treg) cells and NK cells. In tumors, Treg cells may suppress NK cells and, in particular, impair NK cell effector functions. Studies on how NK cells affect Treg cells are rare, and this topic needs to be explored further.

Cheng *et al.*[7] comprehensively summarize recent progress in NK cell-based immunotherapeutic approaches aimed at overcoming NK cell paralysis in patients with tumors. One approach is to expand a pool of allogeneic NK cells, but not autologous NK cells, which have escaped inhibition by self-MHC I molecules and to use these for adoptive cellular immunotherapy. Another approach is to use stable allogeneic NK cell lines, an approach that is now practical in terms of quality control and large-scale production. Alternatively, freshly isolated NK cells or NK cell lines can be genetically modified to express cytokines at a high-level, F*c* receptors, and/or chimeric tumor-antigen receptors. Expandable NK cells for therapeutic applications can be derived from peripheral blood or cord blood cells, stem cells or even induced pluripotent stem cells for large-scale production in GMP facilities. Importantly, Chen *et al.*[7] list NK cell approaches that are in clinical trials. They also discuss predetermining the efficacy of NK cell therapy by laboratory experiments, monitoring NK cell therapy by non-invasive imaging, and clinically evaluating NK cell therapy.

In view of the rapidly evolving field of NK cell biology, many critical questions need to be addressed. The past 10 years of NK cell research show that NK cells play important roles in homeostasis, surveillance and defense, the three major functions of the immune system. NK cells reside in large numbers in several immunotolerant organs (the uterine decidua, the lungs and the liver). They function in a regulatory role at the mother/fetus interface, but an understanding of their roles in immunotolerance in the liver and lungs awaits further study. The roles of NK cells in tumor immunosurveillance were recognized at the time

of discovery; however, NK cell immunotherapy is only now coming of age because recent knowledge allows the power of NK cells to be harnessed. NK cells play a critical role in early control of viral infection, not only through directly killing virus-infected host cells, but also through mounting a systemic immune response by interacting with other immune cells such as DCs and Treg cells. We can speculate that it will soon become practical to generate NK cells by hematopoietic stem cell transplantation (improving grafting and reducing GVHD and GVT) and to administer NK cells to relieve organ transplant rejection, parasitic and HIV infections, autoimmunity and asthma.

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