Editorial

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Natural Killer Cells: Biology, Physiology and Medicine – Part 1

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In the beginning of the 1970s, a number of groups observed unexpected spontaneous cytotoxic activities among lymphocytes. While at first considered as 'annoying' background phenomena, subsequent studies led to the realization that a new subpopulation of lymphocytes could be linked to this activity [1, 2]. The cells were termed 'natural killer' or, briefly, 'NK' cells [2]. Studies of these cells initially engaged a rather small community of scientists, who often had to fight for their existence among other fellow immunologist, many of whom were studying the more 'sophisticated' adaptive immune cells – the T cells and B cells. However, growing insights into the molecular specificity of NK cells [3–5], and insights into their role in controlling virus and intracellular bacteria infections, certain tumors and their ability to regulate other immune cells, hence affecting complex diseases such as autoimmune and hypersensitivity conditions, have put NK cells in the front seat of modern immunology [6]. New insights are rapidly attributing new features to the cells, e.g. a possible role in controlling T-cell and macrophage homeostasis [7] and possibilities to use them in therapeutic settings of cancer [8]. Furthermore, the recent identification of adaptive immune cell features of NK cells is a 'hot topic' at the moment [9]. Studies of NK cells now engage a large community of scientists, working in diverse areas of NK cell research, in experimental model systems as well as in humans [10].

In this issue, as well as in the next issue of the *Journal of Innate Immunity*, a series of review articles on NK cells is published, summarizing some of the recent research activities within this growing field of research. Several leading scientists have made seminal contributions to the two issues. In the first issue (Vol. 3, Issue 3, 2011), a series of reviews relating to the molecular specificity of NK cells, including studies of their receptors and receptor signaling, is presented. These are followed by a series of reviews that discuss NK cell interactions with other immune cells and NK cell responses to infections. In the second issue (Vol. 3, Issue 4, 2011), we will publish reviews relating to the life span of NK cells, their development, differentiation and senescence. NK cell interactions with tumor cells will also be reviewed, as well as new insights into hematopoietic stem cell transplantations where NK cells may contribute to tumor eradication. Finally, two reviews will cover the role of NK cells in organ transplant rejection and in an inflammatory disease setting.

The first review in this series of articles is an update on the molecular mechanisms for NK cell activation. With an array of activating and inhibitory receptors, Bryceson et al. [11] describe how NK cells upon target cell engagement can specifically get activated to eradicate infected and transformed cells. Likewise, it is described how similar receptors control the production of chemokines and cytokines, fulfilling important tasks in con-

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trolling immune responses. Continuing on the same theme, Vogler and Steinle [12] provide a 'snapshot' of the current knowledge on receptors of the NKRP1 and their genetically linked CLEC2 ligands in mouse and man. As is nicely reviewed, recent research efforts have begun to systematically elucidate the expression and function of numerous NKRP1 and CLEC2 members in rodents and corresponding receptor/ligand pairs in humans. While most studies on NK cells are being conducted in mice and humans, non-human primates are used as important experimental models for diseases that cannot easily be studied in e.g. mice. Hence, it is of importance to characterize NK cells and their receptors also in this group of animals. In this context, Walter [13] provides a review on our current knowledge of non-human primate NK cell receptors interacting with major histocompatibility complex (MHC) class I proteins, which also provides an interesting perspective on the evolution of these rapidly evolving receptor families. Among NK cell receptors, the killer cell immunoglobulin-like receptors (KIRs) that recognize class I MHC molecules have attracted significant interest since their discovery in the early 1990s. These molecules display variegated expression patterns on NK cell populations and regulate the activation thresholds of NK cells. Control of KIR expression is currently a hot topic. Expression frequencies of individual KIRs are independent on MHC class I and instead established and maintained by a dynamic, yet not very well defined, transcriptional program. Cichocki et al. [14], in a comprehensive way, review recent advances in our understanding of the architecture of the regulatory regions within KIR genes and discuss a potential role for non-coding RNA in KIR transcriptional regulation during NK cell development. A substantial body of evidence has demonstrated that a family of PI3K isoenzymes, which mediate the interchange of phosphates on inositol phospholipid species at the plasma membrane, have a prominent role in NK cell biology, affecting cell growth, survival, proliferation and motility of the cells. Kerr and Colucci [15] nicely cover this topic. An extensively studied feature of NK cells is their interactions with other immune cells including cells of the myeloid linage. Wehner et al. [16] summarize recent studies on the bidirectional crosstalk between human dendritic cells (DCs) and NK cells. They discuss how the reciprocal activation of DCs and NK cells, upon contact between the two cells, may play a pivotal role in the immune defense against viruses and tumors. On a similar theme, Seya et al. [17] discuss recent advances related to DC-mediated NK cell activation. In particular, they discuss how DCs, in response to 'microbial patterns', by virtue of cytokine production and other cytokine-independent means participate in driving NK cell activation. As alluded to, one of the hallmarks of NK cells is their ability to respond to viral infections. Brandstadter and Yang [18] provide an overview of how NK cells are activated in response to viral infections and continue to discuss the recruitment of activated NK cells to the site of infection, and then discuss NK cell effector mechanisms against virally infected cells. Covering an area that has not so often been reviewed in the past, Guilmot et al. [19] discuss NK cell responses to infections in early life. They summarize the phenotype and functional abilities of NK cells from healthy infants, and NK cell responses against viral, bacterial and protozoan infections early in life. In a final paper in this first issue on NK cells, Naper et al. [20] discuss the role of NK cells in controlling a bacterial infection. They take the discussion from the point of view of their own studies in the rat as an experimental model and compare results with others in the mouse model.

Clearly, research on NK cells is expanding in a way not seen in the past. It is our hope that the interested reader will become up to date with some of the very many interesting topics of research that the NK cell field has to offer. Yet more topics will be covered in the next issue of this journal. Enjoy!

References

1 Herberman RB, Nunn ME, Lavrin DH: Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic acid allogeneic tumors. 1. Distribution of reactivity and specificity. Int J Cancer 1975;16:216–229.

2 Kiessling R, Klein E, Wigzell H: 'Natural' killer cells in the mouse. 1. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. Eur J Immunol 1975;5:112–117.

3 Kärre K, Ljunggren HG, Piontek G, Kiessling R: Selective rejection of H-2-deficient lymphoma variants suggests alternative immune defense strategy. Nature 1986;319:675–678.

4 Ljunggren HG, Kärre K: In search of the 'missing self': MHC molecules and NK cell recognition. Immunol Today 1990;11:237–244.

5 Bryceson YT, Ljunggren HG, Long EO: Minimal requirement for induction of natural cytotoxicity and intersection of activation signals by inhibitory receptors. Blood 2009;114:2657–2666.

6 Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S: Functions of natural killer cells. Nat Immunol 2008;9:503–510.

7 Bryceson YT, Rudd E, Zheng C, Edner J, Ma D, Wood SM, Bechensteen AG, Boelens JJ, Celkan T, Farah RA, Hultenby K, Winiarski J, Roche PA, Nordenskjöld M, Henter JI, Long EO, Ljunggren HG: Defective cytotoxic lymphocyte degranulation in syntaxin-11 deficient familial hemophagocytic lymphohistiocytosis 4 (FHL4) patients. Blood 2007; 110:1906–1915.
8 Ljunggren HG, Malmberg KJ: Prospects for the use of NK cells in immunotherapy of human cancer. Nat Rev Immunol 2007;7:329–339.
9 Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, Yokoyama WM, Ugolini S: Innate or adaptive immunity? The example of natural killer cells. Science 2011; 331:44–49.
10 Colonna M, Jonjic S, Watzl C: Natural killer cells: fighting viruses and much more. Nat Immunol 2011;12:107–110.
11 Bryceson YT, Chiang SCC, Darmanin S, Fauriat C, Schlums H, Theorell J, Wood S: Molecular mechanisms of natural killer cell activation. J Innate Immun 2011;3:216–226.
12 Vogler I, Steinle A: Vis-à-vis in the natural killer cell gene complex: genetically linked natural killer cell receptor/ligand pairs in the natural killer cell gene complex. J Innate Immun 2011;3:227–235.
13 Walter L: Major histocompatibility complex class-I-interacting natural killer cell receptors of nonhuman primates. J Innate Immun 2011;3:236–241.
14 Cichocki F, Miller JS, Anderson SK: Killer immunoglobulin-like receptor transcriptional regulation: a fascinating dance of multiple promoters. J Innate Immun 2011;3:242–248.
15 Kerr WG, Colucci F: Inositol phospholipid signaling and the biology of natural killer cells. J Innate Immun 2011;3:249–257.
16 Wehner R, Dietze K, Bachmann M, Schmitz M: The bidirectional crosstalk between human dendritic cells and natural killer cells. J Innate Immun 2011;3:258–263.
17 Seya T, Kasamatsu J, Azuma M, Shime H, Matsumoto M: Natural killer cell activation secondary to innate pattern sensing. J Innate Immun 2011;3:264–273.
18 Brandstadter JD, Yang Y: Natural killer cell responses to viral infection. J Innate Immun 2011;3:274–279.
19 Guilmot A, Hermann E, Braud VM, Carlier Y, Truyens C: Natural killer cell responses to infections in early life. J Innate Immun 2011; 3:280–288.
20 Naper C, Shegarfi H, Inngjerdingen M, Rolstad B: The role of natural killer cells in the defense against *Listeria monocytogenes:* lessons from a rat model. J Innate Immun 2011; 3:289–297.