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Editorial

Natural Killer Cells in Healthy and Diseased Subjects

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Natural killer cells or NK cells have been known since the 70s on the basis of their functional properties [1, 2], but essentially no molecular markers existed able to specifically identify them. Still in the early eighties, the few scientists that worked in NK cells field had difficulty convincing about the existence of those cells while, in the same period, immunologists were essentially in the search of the δ-chain of the T-cell receptor.

Nowadays, following the molecular characterization of different surface receptors and the signalling pathways as well as the characterization of the molecules specifically recognized and the analysis of their 3D-structures, the research on NK cells has become a highly competitive field. Researchers studying different functional and molecular aspects have been challenged to understand the function of these cells and the mechanism of the regulation of their function in terms of NK cell licensing or education and NK memory. In addition, it is always more complex the crosstalk with other cell of the immune system either by cell contact or through the release of soluble factors. Briefly, natural killer cells are responsible for the immune responses against tumor or virally infected cells. Their function is tightly regulated by a clonal and stochastic distribution of germline-encoded cell surface receptors, and these molecules are able to deliver either inhibitory or activating signals. Thus, every NK cell is equipped by at least a single inhibitory receptor which is functionally dominant and that senses the level of surface expression of MHC class I molecules on autologous cells mediating self-tolerance [3–15]. This function has been maintained during mammalian evolution by expansion of different multigene families coding for receptors with marked structural divergences that have been evolved in the different species together with appropriate MHC molecules serving as ligand [16]. Any alteration on target cell of the surface expression level of the MHC class I molecules, induced by viral infection or tumor transformation, induces NK-mediated cell killing. NK cell receptors evolved in a highly dynamic fashion, primarily driven by the necessity to deal with a large variety of pathogens and to recognize properties of cells characteristic of tumor transformation.

In this special issue, a series of reviews or articles on natural killer cells are published and summarize information related to NK cells and diseases and the rationale use of these knowledge for clinical applications. In detail we summarize the molecular and structural analysis of NK receptor and their interaction with ligands and how the diversity of KIR genotype and of HLA class I molecules are related with the outcome of a number of key human infections [17, 18]. Other contributions are based on the analysis of the knowledges regarding the molecular interactions between NK cells and myeloid antigen-presenting cells and their role in the regulation/polarization of adaptive immune responses [19, 20]. The ability of distinct species of gut-derived commensal bacterial to differently affect the outcome of DC/NK crosstalk and the Th1 polarization of the adaptive immune response is also discussed [19, 20]. The complex network of interactions involving the immune system is also through the use of cytokines. The functional redundancy and the specific role of the common gamma-chain cytokine family (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) in the regulation of the immune response and in the homeostasis of the lymphoid cells and the acquisition of memory-like functions have been analyzed [21]. In addition, novel strategies to deliver cytokines and the use of immunokine aimed to maximize their therapeutic

potential and to costimulate the NK cell activation by enhancing NK cell adhesion to target cells have been described [21, 22]. Several reviews analyze the mechanism of recognition used by NK cells to sense viral pathogens, like HCV, HBV, HIV, CMV, and other infectious diseases [1, 23–25] and the potential role of NK cells during severe sepsis and septic shock [26]. Cytomegaloviruses evolved different mechanisms to hide and survive to immune-related responses. Innate immunity is the first line of defence in the case of CMV infections, and viral particles are known to modulate the expression of ligand molecules specific for NK-triggering receptor on the surface of infected cells. In addition, some viral genes are also known to encode MHC class I-like surface molecules contributing to immunoevasion both in mice and in humans [23, 24]. Since CMVs and their respective hosts coevolved, it is tempting to speculate that the viral MHC class-I-like molecules originate from the host genomes. Revilleza et al. on the bases of nucleotides, proteins, and crystallographic/modelling structural data obtained from human and mice speculate that a single ancient event of partial genome transfer and not multiple phenomena may have evolved the different CMV class I-like molecules [23]. In various mice strains the capture of host-genome has originally allowed the development of MHC class-I-like molecules able to interact with inhibitory Ly49 receptors. Instead B6 and Ma/My have evolved activating Ly49 molecules, which through the interaction with viral class I-like molecules and/or with the presence of additional factors are able to trigger NK cell cytolysis rather than inhibit and probably to contribute to the development of NK cell memory [24]. Thus it appears clear that there is a strict interplay among NK cells, their receptors and the responses toward viral pathogens. To address these issues, we have an depth analysis discussing the different triggering receptors expressed by NK cells, their level of expression and the possible ligands involved in the interaction with cells infected by viruses belonging to different families (Orthomyxo-, Paramyxo-, Flavi-, Lentiviridae) [25]. Thanks to the latest review in which we have found discussed the NK-mediated responses following viral pathogen infection, here we find some recent points of view about how also microbial sepsis and the "systemic inflammatory response syndrome" or peptic shock may be related with NK cell-immune responses [26]. All the information regarding NK receptors and their ligands, as well as the fine regulation of innate/acquired immune-responses orchestrated by NK cells and the cytokines network are the basis for better use in cancer therapy. The NK cell responses toward tumor using specific mAbs and an ADCC mechanism and all attempts to increase anti-tumor cell cytotoxicity using cytokine combinations, TLR agonist and immunokines are also discussed [27, 28]. ADCC is often impaired in PBMC from patients with advanced cancer as a result of NK cell dysfunction probably generated by tumor-produced soluble factor(s) (i.e., TGFβ), thus any approaches aimed to increase the ADCC killing are necessary to obtain an efficient tumor cell readication.

Along this line, IL15, IL2 and the use of Lenalidomide, an analog of thalidomide known to increase FcγR-mediated signalling, adoptive cell transfer and ex-vivo cell expansion, have been successfully used [28]. Although, the firsts attempts in the use of autologous ex vivo expanded cells did not give encouraging results, it is now clear the basis of these failures, making allogeneic cell transfer more attractive. The use of KIR/HLA class I-mismatched cells, selected in order to be not sensitive to inhibitory signals from the recipient HLA ligands, have been proved to be protective against disease relapses [28].

The other face of the coin of NK cells and tumor is shown by Schmitt et al, that focalizes our attention on a rare form of hematolymphoid tumors including the extranodal NK/T-cell lymphoma (NKTCL) that is considered inside the provisional group of chronic NK-cell lymphoproliferative disorder. This lymphoma is apparently associated with EBV-associated malignancy with very poor prognosis, rare in western countries, but it represents at least 10% of non-Hodgkin's lymphomas in Asia and Central/South America [29]. Finally, two reviews are taking care of using the combined analysis of genetic data regarding KIR and HLA class I molecules and their association in autoimmune diseases and the cytokines network below the pathogenesis of chronic inflammation [30, 31]. In both cases, a decrease of the strong inhibitory pathways controlled by HLA-C-specific receptors and thus a reduced activating threshold promote immune responses, and this effect of changing the threshold of immune-suppression/activation may contribute to explain the genetic susceptibility of different autoimmune diseases.

In the last years, we have assisted to an explosion in the research field centered on NK cells. In the near future, we will see the publication of different results in the regulation of receptors and ligands expression by miRNA, as exemplified by the recent published article regarding the control of HLA-C expression in HIV infection [32]. There are different arguments that need a detailed study. Among these, we also know that KIR recognizes HLA class I ligands on the basis of the presence of particular amino acid residues; probably different exceptions exist. In addition, very little information is available about the role of viral peptides, presented by HLA class I able to trigger the activation of Killer Ig-like Receptors (KIR2DS, KIR3DS). The absence of such information might explain the failure, so far, of an experimental identification of ligands specific for different triggering KIR, with a single exception [33]. Finally, a complete characterization of the molecules recognized by all the cloned NK cells receptors is still needed to analyze in detail all the triggering pathways induced by NK cell-mediated recognition.

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