The role of natural killer cells in pathogenesis of autoimmune diseases

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Abstract

There is growing evidence that NK cell-mediated immunoregulation plays an important role in the control of autoimmunity. NK cells are a subset of lymphocytes that generally contribute to innate immunity but have also a great impact on the function of T and B lymphocytes. The major role of NK cells is cytotoxic reaction against neoplastic, infected and autoreactive cells, but they regulatory function seems to play more important role in the pathogenesis of autoimmune diseases. Numerous studies suggested the involvement of NK cells in pathogenesis of such a common autoimmune diseases as juvenile rheumatoid arthritis, type I diabetes and autoimmune thyroid diseases. The defects of NK cells regulatory function as well as cytotoxic abilities are common in patients with autoimmune diseases with serious consequences including HLH hemophagocytic lymphocytosis (HLH) and macrophage activation syndrome (MAS). The early diagnosis of NK cells defect responsible for the loss of the protective abilities is crucial for the prevention of life-threatening complications and implementation of necessary treatment.

Key words: NK cells, autoimmune reaction, Hashimoto thyroiditis, type 1 diabetes, juvenile rheumatoid arthritis.

Natural killer cells function

Natural killer cells are a subset of lymphocytes that contribute to innate immunity. They are developed in the bone marrow, but there is also evidence suggesting that NK cells can also develop in lymph nodes and liver [1, 2]. There are many factors involved in the regulation of NK cells development and maturation. Amongst them IL-15 seems to play the most essential role in homeostasis and survival [3].

The major role of NK cells is cytotoxic reaction against neoplastic, infected or autoreactive cells. They exert this function mainly through antibody-independent cytotoxicity. Direct cytotoxic effect depends on the balance of stimulatory and inhibitory signals, acting through numerous NK receptors. Killer cell immunoglobulin-like receptors (KIR) play the most important role in NK activation. There are 14 receptors in the KIR family: seven responsible for inhibition (KIR3DL1, 3DL2, 3DL3, 2DL1, 2DL2, 2DL3, and 2DL5), six for activation (KIR3DS1, 2DS1, 2DS2, 2DS3, 2DS4, and 2DS5), and one (KIR2DL4) combining both inhibitory and activating functions [4, 5].

In addition to that, NK cells express also inhibiting receptors including: C-type lectin receptors (CD94-NK-G2A) and leukocyte inhibitory receptors (LIR-1, LAIR-1). Natural cytotoxicity receptors (NKp46, NKp44), C type lectin receptors (NKG2D, CD94-NKG2C) and IgG-like

receptors (2B4) play activating roles [6-8]. The inhibition of NK cell activation depends on the presence of MHC class I molecules. The vast diversity of interactions between polymorphic HLA-A, -B, and -C molecules and the KIR receptors play a crucial role in expansion and individualization of the human immune system. Loss of MHC I antigens e.g. on the surface of malignant or infected cells, leads to the prevalence of the activating over inhibitory signals, what in consequence leads to NK cell activation. In steady-state conditions, NK cells lacking inhibitory receptors might simply be anergized by chronic stimulation through ligands present on normal cells and tissues. However, NK cells can be activated by cytokines or infection and mediate potent effector functions. In addition to inhibitory receptors recognizing MHC class I, NK cells express several other inhibitory receptors that recognize ligands not encoded by MHC genes. The role of these inhibitory receptors in shaping NK cell tolerance and functionality is largely unexplored. It is speculated that these inhibitory receptors might prevent NK cell-driven autoimmunity.

The predominance of activating signals starts cytotoxic mechanisms. Cytolytic effect is mediated through two major pathways. One of them is associated with the activity of membrane-disrupting protein, perforin, that is functionally related to granzymes, serine proteases secreted from cyto-

lytic granules. In this pathway, the first stage of the cell cytotoxicity is target cell recognition by effector NK cells. The next stage is the formation of a lytic synapse between the effector and target cells. The contact with target cells induces changes in ultrastructure of the effector cell. Cell organelles, like microtubules, Golgi apparatus and cytolytic granules become polarized and are translocated to the target contact site. Next, the granules containing perforin and granzymes B involved in cytotoxic effect on target cell are released [9-11]. The other pathway is based on the induction of caspase-dependent apoptosis and acts through the activation of death receptors (e.g. Fas/FasL). Impaired action of perforin, disturbed degranulation process or defects in Fas/FasL-dependent apoptosis pathway may lead to the loss of NK cells function and to development of autoimmune disease.

Subpopulations of natural killer cells

Natural killer cells population is heterogenic. Several subpopulations may be recognized, differing in phenotype, cytokine profile and cytotoxic abilities. In a healthy person five populations are found: CD56^{bright} CD16$^-$, CD-56^{bright} CD16^{dim}, CD56^{dim} CD16$^-$, CD56^{dim} CD16^{bright}, CD56$^-$ CD16^{bright}. In normal conditions CD56^{dim} CD16$^-$ and CD56$^-$ CD16^{bright} subpopulations are in minority (10%) and CD-56^{bright} CD16- and CD56^{bright} CD16^{dim} dominate (90%). Among many important differences between NK cells subpopulations some deserve special attention: CD56^{bright} cells lack KIR and ILT2 (immunoglobulin-like transcript 2) while in CD56^{dim} subpopulation expression of these molecules is high. On the other hand, inhibitory receptors CD94/NK2A could be found on the surface of the majority of CD56^{bright} cells and only on low number of CD56^{dim} cells. So many differences in expression of biologically relevant surface molecules within the different subpopulations of NK cells may indicate their multiple functions. It was shown that CD56^{dim} cells exert higher cytotoxic activity in comparison with CD56^{bright} cells [12, 13]. Their cytoplasmic granules contain more perforins and granzymes. Furthermore, they are also able to form more conjugates with K562 target cells. High expression of CD16 molecules on their surface increases the efficacy of antibody dependent cytotoxicity (ADCC). On the other hand, CD56^{bright} cells are the most effective in cytokine production (interferon γ – IFN-γ, tumor necrosis factor α – TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 10 – IL-10, interleukin 13 – IL-13) what suggest their immunoregulatory function [14].

Natural killer cells located in secondary lymphatic tissue (e.g. tonsils, lymph nodes or spleen) differ from the circulating NK cells. They are activated by dendritic cells and secrete large amount of cytokines, especially interferons, which stimulate immune response trough T lymphocytes activation [6].

Natural killer cells and autoimmunization

The role of the NK cells in the development of autoimmune diseases seems to be very plausible. They are capable of destroying autoreactive cells directly in their target organs or play an indirect role by the regulation of adaptive immune response. Natural killer cells may interfere with antigen presenting cells (dendritic cells) in the priming of autoimmune response inducing T and B autoreactive lymphocyte proliferation [15]. It is also well known that NK cells might prevent autoimmune response by the inhibition of the presentation of self-antigens by dendritic cells. On the other hand, NK cells secrete various cytokines that suppress B and T cell function or even destroy them [16].

It has been shown that NK cells can kill autologous cells [17]. Under normal conditions, molecules on the surface of the autologous cells (MHC I) engage inhibitory receptors on the surface of NK cells preventing them from delivering lytic signal and making them self-tolerant. Loss of self-tolerance can occur if an autologous cell loses the expression of MHC I [18].

Natural killer cells have been identified in target organs of patients suffering from autoimmune diseases [19, 17]. In the course of several autoimmune diseases NK cells are recruited as a first line of defense to the place of autoimmune reaction. Moreover, in infection-related autoimmune processes, NK cells might suppress autoimmunity by rapid clearing of the pathogen and inhibition of the immune-mediated tissue damage [20]. On the other hand, a vigorous attack towards infected autologous tissues could result in destruction of the target cells and release of autoantigens [18]. This situation supported by inflammatory milieu might lead to activation of quiescent autoreactive lymphocytes responding to the spread of autoantigens. In addition, NK cells secrete cytokines such as IFN-γ, which activate macrophages and direct the immune response toward Th1. It is likely that triggering an NK cell response in first line of defence may lead to inflammation and autoimmune disease [4]. In this context, it is possible that the presence of greater number of activating NK receptors may translate into enhanced activating signals allowing loss of self-tolerance. This hypothesis was confirmed to be true in various autoimmune diseases [4, 21-23].

Another potential mechanism of NK cells involvement in autoimmunization may be connected with a presence of various KIR haplotypes. There are many studies indicating potential role of KIR type in the development of autoimmune disease. *KIR2DS1* gene was suggested to be less common in patients with atopic dermatitis compared to healthy controls [24]. On the other hand *KIR2DS1* was more frequent in patients with systemic lupus erythematous [25]. *KIR3DS1* was more often found in patients with multiple sclerosis (MS) [26]. The positive correlation was also suggested for *KIR2DS1* and HLA-Cw6 in patients with psoriasis [27].

Overall, several reports support the idea that the presence of particular disturbances of NK cells frequency and activity may lead to the development of some autoimmune conditions. It is well known that patients suffering from autoimmune disorders are highly predisposed to the development of severe complications like macrophage activation syndrome (MAS) and hemophagocytic syndrome (HLH). Macrophage activation syndrome is caused by hyperactivation of immune response as a consequence of impaired NK cells function. In population of patients with autoimmune disorders, systemic juvenile idiopathic arthritis (SJIA) patients and type 1 diabetic patients are extremely predisposed to this syndrome. Hemophagocytic syndromes were also described as a complication of several autoimmune disorders, e.g. systemic lupus erythematosus (SLE), juvenile dermatomyositis and Kawasaki disease. The majority of MAS and HLH cases remain undiagnosed and appropriate treatment is not applied.

Autoimmune diseases

Currently about 5% of the population of the developed countries is affected by various types of autoimmune diseases [18]. The background of autoimmune diseases is multifactorial and remains unclear. However, the existence of a strong genetic component determining susceptibility to these diseases is well known. Moreover, environmental factors are necessary to trigger their development. Under normal conditions, self-tolerance mechanisms prevent intra-thymic maturation and activation of autoreactive lymphocytes due to the mechanism of central tolerance. Nonetheless, small pool of autoreactive cells escapes from the selection to peripheral circulation. There are also peripheral mechanisms (peripheral self-tolerance) aimed at destroying autoreactive lymphocytes. If central or peripheral tolerance mechanisms fail, immune reaction to self-antigens can initiate autoimmunity [28, 29].

Juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis (JRA), a syndrome of heterogeneous clinical features, is the most common rheumatoid disease in children. Juvenile rheumatoid arthritis is characterized by the presence of chronic synovitis in the absence of other identifiable diseases known to be associated with arthritis. There are at least three major types: pauciarticular (four or fewer joints involved), polyarticular (five or more joints) and systemic. The systemic form with markedly febrile presentation is certainly the most distinct clinical subtype of this disease. Arthritis affects approximately one per 1000 children in a given year. Fortunately, most of these cases are mild. However, approximately one per 10,000 children will develop more severe arthritis. Typically, the onset of an acute inflammatory arthritis follows a viral or bacterial infec-

tion. This type of arthritis usually disappears within a few weeks or months. JRA is the most common type of arthritis that persists for months or years.

In patients suffering from rheumatoid arthritis elevated concentration of inflammatory cytokines were observed in the affected joints that were infiltrated by T lymphocytes, B lymphocytes, macrophages and NK cells. The majority of synovial NK cells are CD56^{bright} (60%) with elevated expression of inhibition-related CD94/NKG2A receptors and decreased expression of KIR and CD16 receptors [30, 31]. This population of NK cells showed also upregulated expression of several chemokines and adhesion molecules. It may explain their selective recruitment to the synovium [31]. The other authors indicates the increased expression of activation-related receptors (CD69 and NKp44) on the surface of synovial NK^{bright} cells as well as higher production of IFN-γ and TNF-α in comparison to circulating NK cells [32]. It was also suggested that synovial NK cells may stimulate macrophages differentiation into dendritic cells [33] and may lead to increased proliferation of synovial fibroblasts through the secretion of IL-22 [34]. Dendritic cells may play a pathogenic role in autoimmunity by presenting self-antigens to T cells in an immunogenic fashion and by collaborating in the activation of autoreactive B cells. To do so, DCs have to be activated and express immunogenic costimulatory molecules and pro-inflammatory cytokines. Abnormal expression of MHC I on synovial cells in the course of inflammation may result in activation of NK^{bright} cells, directed into proinflammatory cytokines secretion and the loss of their regulatory function [35, 36].

In contrast with the increased number and activity of NK cells in synovial fluid, the population of circulating NK cells seems to be negatively affected. Various studies showed the reduced number and cytotoxic activity of NK cells in blood of patients with JRA [37-39]. Moreover it was found that the great number of patients with JIA had almost complete absence of NK^{bright} cells in circulation [40]. Simultaneous presence of the increased number of pathologically activated NK^{bright} cells in synovial fluid as well as reduced number and activity of NK in circulation confirms important role of natural killers in pathogenesis of autoimmune arthritis. About 7% of patients with systemic juvenile idiopathic arthritis develop MAS in the course of their disease. Pathogenesis of MAS is not fully elucidated. Although it is suggested that SJIA may be one of the early symptoms of MAS which only in some patients, transforms into severe form. This hypothesis could be confirmed by the observation that both disorders seem to have similar clinical picture (fever, hepatomegaly, splenomegaly, lymphadenopathy, extremely high serum ferritin level, elevated D-dimer level, leukopenia). Clinical data shows that up to 50% of SJIA patients exhibit hyperactivation of macrophages and/ or hemophagocytosis in bone marrow. Nevertheless, the majority of those patients never develop fully symptomatic

MAS [41]. The pathogenesis of MAS may be related to the decrease of NK cell's activity. The most consistent immunologic abnormality reported in these patients is involved the impairment of cytotoxic functions, however, the detailed mechanism of this condition including the clear role of NK cell dysfunction still requires elucidation.

Type 1 diabetes

Type 1 diabetes (T1D) is an autoimmune disease caused by the destruction of pancreatic β cells. It accounts for only about 5-10% of all cases of diabetes; however, its incidence continues to increase worldwide and it has serious short-term and long-term complications. The disorder has a strong genetic background, involving HLA complex [42], but the factors that trigger the onset of clinical disease remain largely unknown. Two forms of type 1 diabetes are identified: type 1A resulting from a cell-mediated autoimmune attack on cells, and type 1B, far less frequent, has not known cause, and occurs mostly in individuals of Asian or African descent, who have varying degrees of insulin deficiency between sporadic episodes of ketoacidosis [13]. Besides genetic background some environmental factors are considered as triggers that alter immune function, thereby initiating cell destruction leading to type 1 diabetes. Putative triggers include viruses (e.g. enteroviruses, Coxsackie, congenital rubella) [43], environmental toxins (e.g. nitrosamines) [44], or food (e.g. early exposure to cow's milk proteins, cereals, or gluten) [45]. The abnormal activation of the T-cell-mediated immune response in susceptible individuals leads to an inflammatory response within the islets (insulitis) as well as to a humoral (B cell) response with production of antibodies to cell antigens. A link between diabetes and NK cells was suggested for the first time in animal models. The potential of NK cells to destroy islet cells was demonstrated in NOD mice [18]. It is also suggested that pancreatic cells of T1D susceptible individuals could have an abnormal response to IFN, which would render them susceptible to viral infections and subsequent cell death induced by NK cells. This could trigger T1D not only directly, causing beta cell lysis, but also indirectly. NK mediated damage could contribute to the release of autoantigens that could prime autoreactive T cells and trigger the disease [18, 28]. Systemic abnormalities of NK cells have also been described in animal models for T1D but results were not clear. The studies on NK cells in human type 1 diabetes are also ambiguous. In a few studies a reduction of the number of peripheral blood NK cells in T1D patients has been found. Some authors suggested that this abnormality could be persistent and possibly genetically determined [46]. Functional abnormalities in lytic activity and expression of activating receptors have also been reported in NK cells of patients with T1D. However it might be connected with the disease state and progression. Either a direct effect of the NK cells or an abnormality that could interfere with their function could be potentially implicated, such as an impaired secretion of cytokines capable of interfering with NK cells receptors [16].

Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT) is one of the most common human autoimmune diseases responsible for considerable morbidity in women [47]. The disorder affects up to 2% of the general population [48]. It leads to hormonal hypofunction of thyroid galand.The overt disease is defined by the dramatic loss of thyroid follicular cells (thyrocytes), hypothyroidism, goitre, circulating autoantibodies to two primary thyroid-specific antigens, thyreoglobulin (Tg), thyroid peroxidase (TPO), and lowered concentrations of serum T3 and T4 [49]. HT often coexists with other autoimmune diseases such as type 1 diabetes (T1D), celiac disease, rheumatoid arthritis, multiple sclerosis, vitiligo etc. [50]. The development of the autoimmune failure of the thyroid is a multistep process, requiring several genetic and environmental abnormalities to converge before full-blown disease develops. At the onset of the disease, MHC class II-positive antigen-presenting cells (APC), particularly dendritic cells, and different subclasses of macrophages, accumulate in the thyroid [51]. APC present thyroid-specific autoantigens to the naïve T cells, leading to activation and clonal expansion. Thus, the initial stage of the disease is followed by a clonal expansion and maturation of autoreactive T and B lymphocytes in the draining lymph nodes. Breakdown of the immune tolerance might occur in several ways including interrupting central tolerance (e.g. deletion of autoreactive T cells in the thymus), defects in maintaining peripheral tolerance (e.g. activation-induced T-cell death and suppressing activity of regulatory T lymphocytes) and anergy (e.g. the expression of MHC class II molecules on non-professional APC). Immune response abnormalities caused by defective response of suppressor T cells play a key role in etiopathogenesis of this disease. This autoimmune reaction is organ specific. Excessive stimulation of T helper cells leads to increased activation of B cells and their maturation to plasmocytes able to produce anti-thyroid antibodies. High titer of anti-TPO (thyroid peroxidase) and anti-Tg (thyroglobulin) antibodies are found in more than 90% of patients with chronic autoimmune thyroiditis. In addition, stimulation of cytotoxic T cells is observed, which results in the destruction of thyroid follicular cells.

Some authors indicate that NK cell activation modifies antibody responses against autoantigens confirming a role for NK cells in B cell mediated autoimmunity.

Besides these mechanisms several abnormalities of cytotoxic cell activity have been described [52]. The defect in spontaneous cytotoxicity as well as in NK cytokines production in HT patients was reported [9, 53, 54]. The

impairment of NK functions can be explained by the expansion of B/T cell subsets and activity by means of enhancing Th1 autoimmune cell-mediated responses and by increasing some Th2-associated cytokines, such as IL-5 and IL-13 what may indirectly suppress the Th1 autoimmune mechanism [55]. Nevertheless the measurement of NK activity in blood from HT patients by cytolytic assay or phenotypic analysis has produced variable and contradictory results [55, 56]. However, Ashouri et al. suggested that the activating KIR genes may have an influence on susceptibility to HD [4]. This hypothesis was also confirmed by the other author who showed that that KIR genotypes containing six inhibitory KIR genes occurred less frequently in HT patients indicating less inhibition and probably more activating signals predispose individuals to HD susceptibility [21].

It is possible that NK cells may be involved in various stages of Hashimoto thyroiditis development. Secretion of cytokines e.g. interferon-γ may lead to excessive T cell activation with resultant recruitment and activation of macrophages and damage to follicles. Likewise they are able to play the role of effectors in antibody-dependent cell–mediated cytotoxicity, through the binding of antithyroid. The mechanism and the intensity of spontaneous cytotoxic activity of NK cells should be also taken under consideration as the element of Hashimoto thyroiditis pathogenesis.

Severe defects in natural killer cells function

One of the most severe disorders related to NK cell impairment is hemophagocytic lymphohistiocytosis (HLH). This disease may lead to uncontrolled hyperactivation of T lymphocytes and macrophages which phagocyte erythrocytes, leukocytes, platelets and their precursors within bone marrow, liver, and lymph nodes. As a consequence, patients suffer from fever, advanced pancytopenia, and hepatosplenomegaly. This disorder is life-threatening and the affected patient may require bone marrow transplantation [57-59]. In the majority of cases of genetically determined familial form of HLH mutations impairing perforins production or degranulation process occurs thus lytic action of NK cells is diminished. As a consequence, elimination of pathogen is impaired and immunological system is constantly stimulated. Finally defective clearance results in overproduction of inflammatory cytokines and growth factors and subsequent hyperactivation of macrophages. Activated macrophages infiltrate internal organs, including: bone marrow, liver, spleen, lymph nodes, CNS and the heart. Hypercytokinemia acts directly on macrophages and provokes blood cell uptake (hemophagocytosis) [60, 61].

Macrophage activation syndrome clinically resembles familial HLH. MAS is a sepsis-like clinical syndrome caused by hypercytokinemia due to a highly stimulated but ineffective immune response. Coagulopathy and hemorrhages, hemophagocytosis, decreased white cell count, fever, rash, hepatosplenomegaly and central nervous system dysfunction are among diagnostic criteria of MAS, but it is very difficult to diagnose due to the lack of specific clinical signs.

In both cases viral infection is the most common factor that triggers hemophagocytic syndrome (particularly EBV or CMV). MAS is related to lower frequency of NK cells or perforins secreting cells in bloodstream. Impaired perforins release could be detected in CD8 lymphocytes as well. Defect in cytotoxic process in NK cells and CD8 lymphocytes may be common for both MAS and HLH, although for MAS it was not clearly identified [40, 62].

Disorders affecting the function and/or the number of NK cells may lead to instability of immune system and uncontrolled proliferation of pathologically changed cells. As a consequence, it may lead to development of autoimmunization. Taking all the above under consideration, the assessment of NK cell repertoire seems to be important, because relevant imbalance in NK cell subsets and activity has commonly been found in various different autoimmune conditions. Moreover significant abnormalities may lead to the development of severe clinical implications.

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