ANALYTICAL REVIEWS

UDC 617.741-004.1-053.9
DOI: 10.21668/health.risk/2019.1.16.eng

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NK-CELLS THAT IDENTIFY GLYCOPATTERNS AND THEIR ANTI-TUMOR POTENTIAL AGAINST A BACKGROUND OF EPIDEMICALLY SIGNIFICANT VIRAL INFECTIONS

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Risks related to tumors development against a background of viral infections as well as factors that determine such risks or reduce them have not been examined profoundly so far. Our research goal was to accomplish a scientific review of research on a potential possessed by populations of lectin NK-cells (natural killers) in a body; such populations can have variable sets of lectin and other functionally significant cell surface receptors against tumors in a situation when viruses, including epidemically significant ones, penetrate a body. It is shown that co-functioning of various receptors and their ligands that redistribute cytokines (glycopattern-identifying lectin (basis) receptors, Ig-similar receptors, cytotoxic receptors, and other effector (adjusting) receptors) plays a significant role in intercellular communications and effects produced by NK-populations. NK-populations network is a promising resource for body protection and it should be taken into account when developing new anti-tumor and anti-viral preventive and medical strategies. When certain NK-populations with protective functions are absent in a body, it can be considered a new multi-factor risk of viral and oncologic diseases in an individual or a contingent living in a specific region. The reviewed data can be applied to develop new anti-tumor and anti-viral medications and vaccines as well as medical strategies. Probiotic lectins are promising ligands of intercellular communications associated with immune surveillance.

Key words: *viral infections, tumors, multi-factor disease, risk factors, receptor lectins, NK-cells, anti-tumor strategies.*

Over recent years researchers have detected high prevalence of oncologic morbidity and mortality all over the world. According to data provided by GLOBOCAN-2018 and IARC (International Agency for Research on Cancer) in 2018 Russia occupied the fifth place in the world as per number of death cases among oncologic patients. There are data on oncologic diseases in patients influenced by virus infections and co-infections; for example, up to 2% neoplasms in the world are related to *Epstein-Barr* virus (EBV) [28]. Overall, risks related to tumor development against the background of occurring virus infections as well as factors that determine such risks or reduce them have not been studied to the extent they should be.

But at the same time researchers are paying greater attention to cell populations of in-

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born immunity [1, 15, 19, 27]. Thus, NK (*natural killers*)-cell populations (hereinafter called NK-populations) play a significant role as regards developing anti-body immunity in children [6, 26]. Intercellular communications with NK-populations participation are given special attention due to their anti-microbe, anti-virus, and anti-tumor potential. Receptors that can recognize patterns play an important role in immunity; among them there are receptor lectins (RL) that recognize and bind carbohydrates and glycoconjugates (GC) [1, 2]. However, so far there has been little research on a role played by NK-populations in relation to tumor development against the background of occurring virus infections.

Our research goal was to perform a scientific review of research that focused on assessing anti-tumor potential possessed by lectin NK-populations with variable set of lectin and other functionally significant cell surface receptors in situations when viruses, including epidemically significant ones, penetrated a body.

Viruses and tumors considered in relation to them. Viruses that are examined in the aspect under consideration include the following: arenaviruses (lymphocytic choriomeningitis virus, LCMV), herpes viruses (cytomegalovirus, CMV), in relation to acute leukemia and B-cell lymphomas; co-infections with other viruses; Epstein-Barr virus, EBV, in relation to mononucleosis, Burkitt lymphomas; vaginal herpes viruses [7, 28, 34]); papovaviruses (human papillomavirus, HPV, in relation to cervical cancer); pox viruses (cattle pox virus, mice pox virus, vaccinavirus or orthopoxvirus, VACV) [19, 27]; retroviruses (human immunodeficiency virus, HIV, including co-infection with CMV; in relation to lymphomas); flaviviruses (hepatitis-C virus, HCV; in relation to hepatocellular carcinomas HCC); hepatitis-B virus [HBV] and hepatitis delta virus [HDV]) [25]; togaviruses (chikungunya virus; in relation to sarcomas) [24].

Variety of NK-populations typed by receptor lectins

RL subfamily of NKG2 type consists of type II transmembrane glycoproteins which are coded in the 12th human chromosome. CD94 and NKG2 genes are clustered in NK-gene complex (NKC) in the 12th chromosome (in 12p12-p13 chromosome gene cluster related to functioning of heterodimeric CD94NKG2-receptors). They code lectin outer domain and cytoplasmic domain to initiate further communications between NK-cells and some T-cells populations. Lectins from a subfamily that includes NGG2D activating receptors are expressed on NK-cells, NK-T-cells (NKT), subpopulations of gamma-delta-T-cells, T-cells activated by CD8+ (which are in synergy with the human complement system [21]), certain self-reactive CD4+ T-cells [41]. Populations of myeloid cells, monocytes, and NK-cells regulated by MHC-class-I-molecules and cells initiate body responses against tumors and virus infections. NK-cells belonging to RL subfamily NKG2 are lectins and their derivatives within NKG2A/B/C/D/E/H structure: A/B, D are inhibitors of some intercellular pathways (including those via ITIM-motives in RL that influence SHP1-Tyr-phosphatase); C, F, E/H activate other intercellular pathways (including involvement of ITAM-bearing DAP12 and DAP10 adapter proteins, as well as signaling via metabolic ways that depend on protein-Tyr-kinase) [2, 11, 12, 15, 27].

Lectin NK-populations variability occurs not only due to combinational co-expression of NKG2, KIR genes (killer Ig-like receptors), NKp genes (NCR or natural cytotoxic receptors) and CD genes on cells but also due to varying phenotypes of interacting molecules (including those which are part of di- and oligomeric homo-and hetero-structures similar to CD94NKG, or tetrameric HLA-E) and genetic RL variants (multi-allele ones belonging to NKG2C1/2/3 type; NKG2E phenotype as two alternative splicing forms NKG2E and

NKG2H [27=24]). They gradually become apparent under post-genome changes when genetic chimeric products are constructed (shortened ones [belonging to NKG2Ce type – C-end shortened form – NKG2C3]; outer, transmembrane, and cytoplasmic / intracellular RL domains [belonging to NKG2F type that is expressed as an intracellular form only], products of genetic maps obtained for CD94–NKG2 contacts, and others) [12, 27, 39, 40].

Ontogenesis of NK-cells, in its turn, makes its contribution into NK-populations variety. NK-cells usually develop from a common lymphoid predecessor and undergo several stages in the process. CD122 (beta-chain of IL15 receptor) occurrence means that a predecessor has started to differentiate and NK-cells will start to form soon. When NK-cells are developing, one can observe progressive exposure of CD161; CD56, CD94/NKG2A, NKp46 (NCR1, CD335), NKp44 (NCR2, CD336); NKG2D (exposed on all the human NK-cells and participates in Cross-Talk between lymphoid and myeloid cells of anti-viral immunity [36]); and, finally, CD16 and KIR [24]. Stages 4 and 5 are the most significant among all the stages in NK-cells development when it comes to peripheral blood cells; they are characterized with occurrence of CD56bright and CD56dim, respectively. CD56bright in an NK-population is characterized with high expression of CD94. CD56dim of an NK-cell correspond to KIR- and CD16-populaiton as the most mature ones that transform into cytotoxic cells which, in their turn, become maximum and ultimately differentiated and express CD57.

NKG2-receptors can also be met among greatly varying T-lymphocytes subpopulations and it implies there is coherent co-functioning of NK subpopulations and cytotoxic T-lymphocytes subpopulations [12]. NKG2H is expressed in a small number of monocytes in peripheral blood but it is to a greater extent detected in T-cells stimulated by anti-CD3-antibodies [12].

Adaptive RL expression and distribution of RL types between cells populations is influenced by an overall state of a body (heredity, age, sex, immune system state, other factors), pathologies, types of viruses and tumors [8, 10, 35].

Predominantly, NKG2 and KIR and their ligands participate in HLA-class-I modulation [27, 41]. Signals that arise due to interaction between $CD94^{+}NKG2^{+}/KIR^{+}$ receptors and MHC-class-I-glycoproteins as a response to occurrence of abnormal pattern ligands redistribute NK-populations activities. Mobile memory of NK-cells is implemented due to genetic predetermination. Genome of a human body is characterized with moderate variety of NKG2 genes against elevated varying in KIR genes [39]. NKG2D gene polymorphism supports modulation of NK-cellular cytotoxicity. It is significant, for example, in relation to a body being susceptible to HPV-induced cancer [13]. Limited immunologic functions performed by MHC-E/NKG2 system develop in a human body when functions of MHC-I/KIR system expand [39]. Expression of HLA-class-I drops drastically with KIR participation in cells infected with viruses, while expression of HLA-E (is usually detected on tumor cells; is a section where RL are bound) is more stable and is supported by activating NKG2-receptors [10, 12, 27, 39].

Pools of lectin NK-populations differ significantly as regards their functions as they are aimed at different virus and cellular targets in such a way that there is correspondence of NK-populations (to relevant sets of lectin and other receptors) within a species. One can observe interspecific correspondence of interactions performed by mice lectin Ly49H+ NK-populations against mice CMV [27], or lectin NK-populations in a human body or a macaque, depending on HIV1 or SIV, respectively [39]. NK-cells differentiation is age-dependent [24]. Expression of CD94+NKG2C-/NKG2A+, NKG2D, NKp30(NCR3, CD337) and NKp46 on NK-

cells falls with age [32, 35]. Discrepancies in NK-populations phenotypes occur in relation to a sex [32]. Systems of RL and NK-cells or other myeloid cells (monocytes and macrophages) that expose them vary depending on age [6, 8, 24, 27, 32, 35]. NK-populations are determined not only by sets of lectin, Ig-like, cytotoxic, and other receptor markers (NKG2, KIR, NKp, CD), but also ratios of their expressions quantities, stages in their development, their maturity (how differentiated they are and how apparent their cytotoxicity is).

CD - indicators of NK-populations

CD co-function with RL both in individual NK-cells and within co-functioning NK-populations. RL together with CD are identified as combined markers of cells populations [1, 2]. Several key CD are given below.

*CD3 and CD20 (T- and B-cells markers) are absent in NK-cells.

*CD11b-CD27+; CD11b-CD27+ are markers that show a weakened differentiation (immaturity) of NK-cells [19].

*CD56brightNKG2C+-population that is able to expand in CMV-individuals; cells show inhibiting Ig-like RL (KIR and leukocyte Ig-like receptor [LILRB1]), specific to HLA-class-I-molecules against low levels of activating receptors NKp46 and NKp30 [27]; CD56bright is a marker of immature NK-cells (more than 90% NK-cells which are able to adapt further and turn into mature ones [11]).

*CD56dim/CD57+NKG2C+-populations are detected in patients with lymphoma [11, 29]; elevated frequency of CD56dim and CD57+ in NK-cells were detected in men [32]; CD57 is a marker that shows terminal differentiation of NK-cells [31]; CD56dim-populations express either CD94NKG2A+ or co-express CD94NKG2C+ and KIR+ [11].

*CD69 is a marker showing activation of NK-cells differentiation [19].

*CD94+NKG2+ are markers with synergetic functioning of CD94/NKG2A and CD94/NKG2C [11, 24, 27], CD94 is a significant factor in protection against viruses [11, 27, 31, 39].

*CD94+NKG2A+, NKG2D+ and NKp46+ function in synergy [24, 36].

*CD158a, CD158b are markers showing recovery and strengthening of NK-population that produces perforin and granzymes [23].

Cytokines and NK-populations

Anti-tumor effects produced by inborn immunity become apparent via modulating production of cytokines sets and, as a result, factors that are cytotoxic in relation to tumor cells are produced (or delivered) there where a tumor is localized in a body. Anti-tumor NK-production of interferon (IFN-gamma) [6, 15, 17, 20, 22, 23, 24, 29] and tumor necrosis factor (TNF) is induced [15, 24, 29]. NK-cells are controlled with interleukins (IL-2, 5, 12, 13, 15, 18) [15, 24, 30] and with participation of colony stimulating factor (CSF1) [37]. IL15 is a key interleukin here and crucial for NK-cells maturation, differentiation and survival; it potentiates cytotoxicity of NKG2-populations [6, 24, 30]. Suppression of NK-cells functions is influenced by transforming growth factor (TGF- beta1) of tumor nature [8, 40]. CSF1 induces occurrence of RAE-1-delta on macrophages that infiltrate a tumor, and RAE-1-delta is a specific ligand that regulates NKG2D-populations [37].

NK-cells ability to produce cytokines is associated with specific stages in NK-cells development. CD56bright NK-population efficiently produces cytokines as a response to stimuli, however, CD56dim NK-cells can be more efficient in producing cytokines [24]. TNF-alpha is produced by NK-cells in the process of their differentiation, and only later, when competing with CD56 expression and against a decrease in IL5 and IL13 production, NK-populations become able to produce IFN-gamma [24].

Cytotoxic factors of NK-populations

As phenotypes are transformed into relevant cytotoxic cells populations, granzymes A, B, and K, perforin, and other anti-tumor agents are released in the process [6, 19, 23]. These factors are in systemic contrast with scattered

tumor factors (lactate dehydrogenase, TGF-beta, CSF1, some others) [8, 37, 40].

NK-populations with anti-tumor / anti-viral activities (the order: NK-populations; tumor targets linked to viruses; effects produced by NK-populations)

*NKG2A+CD56bright; "humanized" mice B-cell lymphoma; IFN-gamma release by the population, cooperation with NKp44-receptors in order to inhibit B-cell transformation linked to EBV [22].

*NKG2A+; when VACV is present, populations are expressed more strongly [19].

*NKG2A+KIR−; set a limit to lytic EBV-replication [28].

*NKG2A+ against EBV [11].

*NKG2A+KIR+, NKG2A+NKG2C-KIR-, NKG2C+KIR+; CMV-infected derivatives of human monocytes; KIR+NKG2C+ doesn't influence a response by KIR-NKG2C-

*NKG2C+; U266 (cells of human multiple myeloma) from CMV-seropositive donors, K562 (leukemic human cells); expansion of the population in a body is stimulated [6, 10], occurrence of latent CMV in healthy donors becomes apparent via stronger NK-cytotoxicity [6].

*NKG2C+CD57+; lymphomas; the population expands as a response to CMV [31].

*NKG2C+ (predominantly); mice lymphomas; action performed by the population and caused by CMV occurrence takes place after allogenic transplantation [30].

* NKG2C+; anti-tumor application of ligands for NKG2C [33].

* NKG2C+; CMV-infected endothelial cells of the aorta; character of population modulation depends on a type of CMV-infected cells [10].

*NKG2C+NKG2A-; 221.AEH (transfected HLA-E+-cells of human lymphoma); NK-cytotoxicity is three times higher than in non-transfected ones, 221.AEH и ИЛ15 make for expansion of the population in a body [6, 33].

*NKG2C+CD94+; Burkitt lymphoma; the population participates in protection of cooperation together with gamma-delta-T-cells [11].

*NKG2C+NKG2A−KIR+; co-infection caused by EBV and CMV; stimulation of NK-population [11].

*NKG2C+CD56dim/CD57+ (mature and cytotoxic); leukemic T-cell lymphoma; after blood was transplanted, and CMV reactivated, 2 years later the population increases up to 33% of all lymphocytes; produces TNF-alpha and IFN-gamma against cells of leukemic T-cell lymphoma [29].

*NKG2D+; patients with HCV-induced HCC; increased NKG2D expression on monocytes together with anti-tumor effects produced with NKG2D-ligands [8].

*NKG2D+; patients with anogenital cancer (HPV is detected); NKG2D-determined cytotoxicity is enhanced, susceptibility to cancer falls [13].

*NKG2D + (NK92: chimeric TN-cells); xenografts of HCV-induced HCC; the population is with expression of NKG2D, produces IFN-gamma, and is efficient against TGF-beta-producing tumor cells [40].

*NKG2D-4-1BB-CD3z-CAR+-redirected T-cells CD45RA- of the memory (CD45RA-NKG2D-CAR+) were cytotoxic for osteosarcomic cells 531MII which expressed ligands to NKG2D (lysed them) in vitro and in mice bodies [16].

As we can see from all the data given above, multifunctional NKG2A+-, NKG2C+- и NKG2D+-populations with RL from NKG2-subfamily have been examined most profoundly. They act as glycopatterns identifiers, inducers (in modulating intercellular communications pathways), and basic ones (to increase selectivity of an effect, additional superstructural / adjusting / tuning receptors are required). Some other combinations of receptors in NK-populations are also known [11, 12, 35, 39]. So, a set of NK-populations acts as "network-within-network".

Strategies of NK-population use

Protective NK-populations are synergetic with other cellular (CD8+ T-cells, blood cells,

macrophages, and dendritic cells) and complicated immunity systems. A significant contribution is made by accumulation of anti-tumor / antiviral circulating monocytes in a body and their consequent transportation to a tumor; infiltration expansion by cells of network NK-compartment into microenvironment around a tumor is also very important.

Multi-functionality of genetic inclusions in the human genome has not been studied enough as it is the case with apparent endogenous retrovirus-like inclusions which account for about 8% repeats in the human genome [18]. Such inclusions are co-localized with protection genes (lectin-like components in C4B и C4A [3] complement) and it should provide their co-functioning in protective activities [18]). Such protection could possibly result in initiation and longer persistence of protector NK-populations in a body that prevent viruses from expansion. There are a lot of example cases when seropositive people (with latent CMV-infection) are healthy (not patients). Besides, more than 90% adult population (not necessarily patients) "undergo" EBV occurrence in their bodies without any symptoms [7]. Therefore, an adaptive set of preventive and therapeutic NK-populations that exists in a human body offers a lot of prospects for their application against active epidemically significant viral infections as well as against tumors initiation and development.

NKG2-receptors and their ligands create a metabolic supervisory communication channel between lymphoid and myeloid immunity cells; they co-stimulate cytotoxic responses via NKp46-receptors of NK-cells and cytotoxic receptors of T-cells; induce sets of antitumor and antiviral cytokines; support proliferation and survival of effector cells [36]. It can be applied to work out strategies aimed at fighting against tumors including those incorporating antiviral effects. As a result, essential NK-cell types and populations grow in number and their expansion inside a tumor takes place [11, 14, 15, 27]. Effects produced by NK-populations are coordinated with the complement system [21].

Below there are some promising ways how to apply NK-populations.

*NKG2+-populations for creating new antiviral strategies (as it is the case with HIV1) [31, 39].

*Targeted application of NKG2D+-populations against tumors with the use of NKG2D-receptors belonging to supervisory effector NK-cells which act in a stand-by mode and monitor occurrence / initiation of tumor ligands on stress cells as such ligands are tumor precursors [8, 14]. And here cells that express NKG2D-ligands (as it happens in case of super-expression of sets in stress cells insides the intestines) are recognized and eliminated by supervisory cells and it is aimed at preventing carcinogenesis, for example, rectum cancer [14].

*CD56brightNKG2A+-population applied in adjusting EBV-associated lymphomas [22].

*Treatment provided for patients with acute lymphoblastic leukemia via recovery and growth of NK-populations with expression of CD158a, CD158b, perforin, and granzyme K among NK-populations with different granzymes types expression [23].

*Transplantation of blood with therapeutic NK-populations against hematologic tumors [30].

*Targeted regulation of interactions with adapter proteins DAP12 and DAP10 that involves NK-populations [12, 27, 33].

*Application of NK-populations based on orthologs and paralogs of mammals RL for treatment [39].

*Application of antitumor genetically modified chimeric NK-populations of CAR [chimeric antigen receptor]-T-cells (for example, with expressed chimeric receptor TN that includes outer and transmembrane domains of TGF-beta-type-II-receptor and intracellular domain of NK-cellular activating receptor NKG2D [40]).

There are also promising preventive and therapeutic possibilities to prevent dysbiotic states of mucosal biotopes in open cavities from transforming into tumor ones, including participation of NKG2D/ NKG2D-ligands NK-populations system that activates DDR-pathway (DNA damage response) as well as effects produced by probiotic lectins with cytokine-like activities [5, 13, 14]. Since probiotic lectins, in case of microbe-virus dysbiosis, can be selectively aimed at opportunistic pathogens (including those changed under inflammation) and can also act as probiotics when probiotic cellular microflora is absent in mucosal biotopes against HPV occurrence in them which is a potential inducer of vaginal cancer, one can predict that there can be anti-cancer / antiviral synergy of probiotic lectins and NKG2D-caused cytotoxicity that reduces susceptibility to cancer [5, 13, 38].

Conclusion. Influence exerted on NK-populations networks by lectin receptors (that initiate cascades of identifying communications), Ig-like, cytotoxic, CD- and some other receptors as well as their ligands (including glycoconjugates that modulate RL) is very promising for creating and regulating long-term antitumor and antiviral processes in a body. When key oriented NK-populations with protective functions are absent in a body, it can be considered an additional multi-factor risk criterion that possibly indicates elevated risks of viral and oncologic diseases in an individual or population living on a specific territory or in a specific region. It is advisable to diagnose which NK-populations are present in a body to strategically assess antitumor and antiviral state of a donor and a patient, to work out optimized personified treatment, as well as to construct preventive-therapeutic cellular-cytokine combinations with participation of chimeric gene-modified NK-populations belonging to CAR-T type, for example, to perform highly efficient targeted/selective CAR-T anticancer therapy [9, 16, 40]. The given data can be applied to develop new antitumor and antiviral medications, vaccines, and medical strategies. Probiotic lectins are promising ligands participating in intercellular communications in the process of immune surveillance [3, 4].

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors state there is no any conflict of interests.

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Received: 18.10.2018
Accepted: 26.01.2019
Published: 30.03.2019