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ЗАВИСИМОЕ ОТ ЛЕКТИНОВ РАЗНООБРАЗИЕ ПОПУЛЯЦИЙ ПРИРОДНЫХ КИЛЛЕРНЫХ КЛЕТОК В КОММУНИКАЦИЯХ ПРОТИВ ОПУХОЛЕЙ И ВИРУСОВ

Лахтин М.В., Лахтин В.М., Алёшкин В.А., Афанасьев С.С.

ФБУН «Московский научно-исследовательский институт эпидемиологии и микробиологии имени Г.Н. Габричевского» Роспотребнадзора, Москва, Россия

Резюме. Популяции природных киллерных клеток человека (ППККЧ) против опухолей в присутствии вирусов оценены как сильно варьирующие и рано адаптированные к патологическим сигналам в организме, мобильные и избирательно действующие, способные к комбинированию агенты. ППККЧ осуществляют различные действия в результате кофункционирования рецепторных лектинов (РЛ), распознающих гликопаттерны (РЛ как триггеры, инициаторы и базисные агенты для надстроечных реакций), и Ig-подобных, цитотоксических и прочих вспомогательных коммуникативных и эффекторных рецепторов (роль РЛ как инструментов тонкой настройки мозаики поверхностноклеточных рецепторов в направлении необходимой функциональной ориентации ППККЧ), а также их лигандов (модуляторов созданных конечных рецепторных мозаик). Такие наученные и переобученные ППККЧ играют важную роль в перераспределении ППККЧ-индуцированных противоопухолевых и антивирусных цитокиновых наборов в организме. Межклеточный коммуникативный потенциал ППККЧ также учитывает другие клетки врожденного иммунитета и адаптированные для врожденного иммунитета клетки, что может служить перспективным и универсальным ресурсом защиты человека. ППККЧ должны учитываться при разработке новых маневренных и надежных, сбалансированных профилактических и иммунотерапевтических, противоопухолевых/антивирусных систем и вакцинных стратегий. Открыты пути к алгоритмам тонкой настройки (RL-KIR/NCR/CD/ их комбинации) РЛ-базисного конструирования веера противоопухолевых/антивирусных ППККЧ с дальнейшим потенциалом инициирования. Ключевую важность приобретает скрининг спектра ППККЧ у индивидуума и потенциального пациента для дополнительной оценки защитного статуса и выработки персонизированных коммуникативных противоопухолевых/антивирусных стратегий. Установленный статус NK (natural killers)-компартмента будет характеризовать резистентность индивидуума/контингента индивидуумов против вирусных инфекаций эпидемиологической значимости, играть важную роль при оценке противоэпидемической защиты региона.

Ключевые слова: популяции киллерных клеток, рецепторные лектины, гликоконъюгаты, цитокины, врожденный иммунитет, мукозальный иммунитет, дисбиозы, пробиотические лектины, противоопухолевые стратегии, антивирусные стратегии

Адрес для переписки:
Лахтин Михаил Владимирович
ФБУН «Московский научно-исследовательский институт эпидемиологии и микробиологии имени Г.Н. Габричевского» Роспотребнадзора
125212, Россия, Москва, ул. Адмирала Макарова, 10.
Тел.: 8 (495) 452-18-16.
E-mail: info@gabrich.com

Address for correspondence:
Lakhtin Mikhail V.
G. Gabrichevsky Research Institute for Epidemiology and Microbiology
125212, Russian Federation, Moscow, Adm. Makarov str., 10.
Phone: 7 (495) 452-18-16.
E-mail: info@gabrich.com

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LECTIN-DEPENDENT DIVERSITY OF NATURAL KILLER POPULATIONS AND COMMUNICATIONS AGAINST TUMORS AND VIRUSES

Lakhtin M.V., Lakhtin V.M., Alyoshkin V.A., Afanasiev S.S.

G. Gabrichevsky Research Institute for Epidemiology and Microbiology, Moscow, Russian Federation

Abstract. Response of human natural killer (NK) cell populations (NKP) against tumors in the presence of viruses was evaluated as a quite variable, early adapting for the pathological signals in organism, mobile and selective combination agents. NKP act as a result of co-functioning between the receptor lectins (RL) recognizing glycopatterns (RL as triggers, initiators and basic agents for coupled activities), and Ig-like, cytotoxic and other additional communicative and effector receptors (superstructural, tuning for achievement of final effector-type NKP constructions required), and their ligands (modulators of final cell surface receptor mosaics). Such NKP created play important role in redistribution of NKP-induced antitumor/antiviral cytokines in organism. Intercellular communicative potential of NKP also involves other innate and innate-like cells. Such extended communications of NKP provide a prospective and universal resource of human protection. NKP must be under consideration upon development of new maneuvre and relilable prophylactic and immunotherapeutic antitumor/antiviral systems and vaccine strategies. The ways for the fine tuning (RL-KIR/NCR/CD/their combinations) algorithms of RL-based creation of antitumor/antiviral NKP are revealed. Key role is given to screening spectrum of patient NKP for development of communicative anticancer/antiviral strategies. The status of NK compartment will characterize resistance of individuum/contingent of individuums to viral infections of epidemiological significance, will play important role in anti-epidemic protection of regional population.

Keywords: NK cells, NK cell populations, receptor lectins, glycoconjugates, cytokines, innate immunity, mucosal immunity, dysbioses, probiotic lectins, antitumor strategies, antiviral strategies

During last few years the interest of investigators with respect of innate immunity cell populations was significantly increased [2, 13, 16, 30]. NK (natural killers) compartment of innate immunity plays important role especially in childhood when formation of antibody immunity takes plays [4, 28]. Receptor lectins (RL) recognizing carbohydrates, glycoconjugates (GC) or glycopatterns play important roles in immunity [1, 2]. There are notable cases of tumors which are influencing by viral infections. Up to 2% of world tumor diseases involve the presence of Epstein–Barr virus (EBV), functionally coupled to EBV infection [31]. However, the role of cell NK-populations (NKP) in connection to tumor processes accompanied with viral infections is still scantily explored.

The present overview evaluates key potential of lectin NKP against tumors which are under influence by infectious viruses (also viruses of epidemiological significance).

Viruses and tumors (which are functionally coupled to viruses; tumors under influencing by viruses)

There are limited number of examples of viral infections studied in accepted in review aspect: arenaviruses (lymphocyte virus of choriomeningitis, LCMV), herpesviruses (cytomegalovirus, CMV, in connection to acute leukemiya and B cell lymphomas; EBV, in connection to mononucleoses and Burkitt lymphomas [6, 31], papovaviruses (human papilloma virus, HPV; in connection to cervical cancer), poxviruses (the viruses of smallpox cows and mice, orthopoxvirus of smallpox, VACV) [16, 30], retroviruses (human immunodeficiency virus, HIV-1); in connection to lymphomas), flaviviruses (hepatitis-C-virus, HCV; in connection to hepatocellular carcinomas, HCC); hepatitis-B-virus [HBV] and hepatitis-δ-virus [HDV]) [26].

Diversity of NK cells and NKP

Subfamily of lectin NKG2-receptors reveals transmambrane glycoproteins of type II which are encoded in human chromosome 12. Genes CD94 and NKG2 are observed within gene cluster 12p12-p13 participating in functioning heterodimeric CD94NKG2-receptors and coding lectin ectracellular and cytoplasmic domains for initiation of communications of NK cells and sets of T cell populations. NKG2D-receptors are expressed on protective human cells including NK cells, NK-T cells (NKT), subpopulations of γδ-T cells, activated $CD8^+$ T cells (the latter as cofunctioning to human complement system), some autoreactive $CD4^+$ T cells [18, 24, 49]. Initiation of organism responses against tumors and viruses involves MHC-class-I-molecules of myeloid cells, monocytes and NK cells. NK cells possessing NKG2-receptors are represented by lectin cell populations $NKG2A^+/B^+/C^+/D^+/E^+/H^+$: A^+/B^+, D^+ – inhibitors of intercellular pathways (also through ITIM-motifs in RL influencing SHP-1-Tyr-phosphatase); C^+, F^+, E^+/H^+-activators of other intercellular pathways (also through ITAM-carrying adaptor proteins DAP-12 or

DAP-10, also signaling through protein-Tyr-kinase depending pathways) [1, 8, 10, 13, 30].

Diversity of lectin NKP is influenced by not only combinations of co-expression of genes NKG2, KIR (killer Ig-like receptors), NKp (natural cytotoxic receptors, NCR) and CD on cells, but also by varying phenotypes of interacted molecules (also within di- and oligomeric homo/heterostructures such as CD94NKG, tetrameric HLA-E) and genetic variants of RL (multiallelic like NKG2C1/2/3; phenotype NKG2E as two alternatively splicing forms NKG2E and NKG2H [30]); upon constructing genetic chimeric products (truncated [like NKG2Ce – C-terminal limited form – NKG2C3]; extracellular, transmembrane and cytoplasmic/intracellular domains of RL [like NKG2F expressing as intracerllular form], products of genetic map contacts like $CD94^{-}$NKG2, others) [10, 30, 46, 47].

Ontogenesis of NKP contributes to their diversity. Development of NK cells from common lymphoid ancestor passes few steps. Appearance of CD122 (β-chain of receptor of IL-15) indicates the beginning of differentiation of ancestor in direction of NK cell forming. NK cell development is accompanied with progressive exhibition of CD161; CD56, CD94/NKG2A, NKp46 (NCR1, CD335), NKp44 (NCR2, CD336); NKG2D (expressed on all human NK cells, participate in Cross-Talk between innate immunity lymphoid and myeloid cells [41, 48]); and finally CD16 and KIR [24]. An increase of $CD56^{dim}$ NK cells (mainly observed in the $CD16^{+}$ subsets) was registered when synbiotic induces response of human to viral infection (on example of influenza virus) [37]. Among aforementioned steps of NK cell development, the last steps are characterized with appearance of $CD56^{bright}$ or $CD56^{dim}$. $CD56^{bright}$ NKP is characterized with high level of expression of CD94. $CD56^{dim}$ NK cells represent KIR and CD16 populations as mostly mature ones and transforming into cytotoxic cells whicn are become terminally differentiated and express CD57.

NKG2-receptors also occur among varying populations of T-lymphocytes that simplify communicative Cross-Talk cofunctioning NKP and cytotoxic T lymphocytes in direction NK cells – T cells [10, 23]. NKG2H is expressed on small part of periphery blood monocytes but, in more extent, are revealed on T cells stimulated with anti-CD3-antibodies [10].

Expression of RL and distribution of RL types between NKP are influenced by current status of organism (heredity, age, gender, state of immune system, the presence of pathologic processes, viral infection and tumor types, others) [7, 9, 37, 42].

In modulation of HLA-class-I participate preferencially receptors NKG2 and KIR and their ligands [30, 49]. Signals, induced upon interactions between receptors $CD94^{+}NKG2^{+}/KIR^{+}$ and MHC-class-I-glycoproteins in response of appearance of anormal pattern ligands, redistribute activities of NKP. Realization of NK cell memory is genetically determined. Genome is characterized with moderate diversity of genes NKG2 against the background of increased diversity of genes of KIR [46]. Polymorphism of gene NKG2D provides modulation of NK cell cytotoxicity. It is of importance for example in connection to organism sensitivity to HPV-induced cancer [12]. In whole, in case of human development of limited immunological functions of the system MHC-E/NKG2 progresses against the background of broadening of functions of the system MHC-I/KIR [46]. Elevated HLA-A expression provides enhanced levels of an HLA-A-derived signal peptide that influence expression of HLA-E (the ligand for the inhibitory NKG2A) [39]. HLA-B haplotypes, in their turn, support NKG2A-mediated NK cell licensing/education (NKG2A-mediated inhibition impairing NK cell clearance of HIV-infected targets). As a result, therapeutic blockade of interaction between HLA-E and NKG2A may help in treatment of HIV disease. [39]. In cells infected with viruses (as in case of CMV) expression of HLA-class-I is strongly decreased involving KIR, while expression of HLA-E (can be as a ligand for RL) is more resistant and supported with activator NKG2-receptors [9, 10, 30, 46].

NKP (and their combinations together with other type protective cell populations of Cross-Talk) are functionally and significantly different and directed towards different viral and cell targets. There is mammal intraspecie accordance within NKP (accordance to final tuning panels of lectin and other type receptors). For examples, it is observed a specie adequacy of interaction of murine lectin $Ly49H^{+}$ NKP against murine CMV [30], lectin NKP of human or macaques depending on HIV-1 or SIV (simian immunodeficiency virus), respectively [46]. Age dependent differentiation of NK cells is observed [24]. Expression levels of $CD94^{+}NKG2C^{-}/NKG2A^{+}$, NKG2D, NKp30 (NCR3, CD337) and NKp46 at NK cells are decreased upon age increase [35, 42]. There are differences between phenotypes of NKP in connection to gender [35]. Systems of RL and RL-exposing NK cells and other myeloid cells (monocytes and macrophages) vary depending on age [4, 7, 24, 30, 35, 42]. NKP are determined with not only compositions of lectin, Ig-like, cytotoxic and other receptors markers (NKG2, KIR, NKp and CD), but also by their relative compactness/dencity (on cells and within NKP), developmental stages, maturity states (the level of differentiation and cytotoxicity).

CD – additional indicators within NKP

CD cofunction to RL of both individual NK cells and within compositions of interacting RL of NKP in combinations of CD is identified as combinative markers of NKP [1, 2].

Below some key CD are presented.

*CD3 and CD20 (markers of T and B cells) – their absence on NK cells.

*$CD11b^{-}CD27^{+}$; $CD11b^{-}CD27^{+}$ – markers of decreased level of differentiation of NK cells (the presence of immature forms) [16].

*$CD56^{bright}NKG2C^{+}$ population which is capable to expansion in CMV-seropositive individuals; cells

reveal inhibiting Ig-like RL (KIR and leukocyte Ig-like receptor [LILRB1]) which are specific to HLA-class-I-molecules against the background of low levels of activating receptors NKp46 and NKp30 [30]; $CD56^{bright}$ – marker of immature NK cells (more than 90% NK cells capable for further adaptation to converse into mature forms [8]); $CD56^{bright}$ NKP express chemokine receptors CCR1, CCR5 and CCR6, which are involved in intercellular Cross-Talk depending on inflammation [23].

*$CD56^{dim}/CD57^{+}NKG2C^{+}$ populations were found in limphoma patient [8, 32]; NKP of males are characterized with increased frequences of $CD56^{dim}$ and $CD57^{+}$ [35]; $CD56^{dim}$ populations express $CD94NKG2A^{+}$ or co-express $CD94NKG2C^{+}$ and KIR^{+} [8].

*CD57 – marker of terminally differention of NK cells [34].

*$CD57^{++}NKG2C^{+}CD56^{dim}$ (terminally differentiated NK cells); NKP extensively proliferatate in response to ligation of receptor [23].

*CD69 – marker of activation of NK cell differentiation [16].

*$CD94^{+}NKG2^{+}$ – synergistical cofunctioning NKP CD94/NKG2A and CD94/NKG2C [8, 24, 30], CD94 – important factor of antiviral protection [8, 30, 34, 46].

*$CD94^{+}NKG2A^{+}$, $NKG2D^{+}$ and $NKp46^{+}$ as cofuinctioning populations of NKP [24, 41].

*CD158a, CD158b – markers of restoration and increase of NKP producing perforin together with granzymes [21].

*CD161 (C-type lectin receptor [CLR] expressed on the majority of NK cells) defines a functionally distinct subset of pro-inflammatory NKP; reduced CD161 expression in acute HCV infection (as a result of viral clearance); blocking LLT1 (CLEC2D, OCIL)-NKRP1A (CD161) interaction enhances natural killer cell-mediated lysis of triple-negative breast cancer cells [22, 27].

Cytokines and NKP

Antitumor action of innate immunity is realized through modulation of production and delivery of panels of cytokines needed in tumor localizations within organism (as in cases of NKP- and $CD8^{+}$ T cells inducing cytotoxicities). Antitumor NK-production of IFNγ [4, 13, 14 ,17, 19, 24, 32, 37] or TNFα [13, 24, 32] are induced. Control of NK cells materialized by IL-2, IL-5, IL-12, IL-13, IL-15 and IL-18 [13, 24, 33] and involves participation of colonie-stimulating factor (CSF-1) [43]. IL-15 reveals domination in NK cell maturation, differentiation and survival; potentiates cytotoxicity of NKG2-populations [4, 24, 33]. Transforming growth factor (TGF-β) of tumor origin influences suppression of NKP functions [7, 47]. CSF-1 induces on infiltrating tumor macrophages the appearance of specific ligand RAE-1-delta – regulator of NKG2D-populations [43].

Capability of NKP to produce cytokines is associated with steps of development of NK cells. TNFα is produced by NK cells during their differentiation while IFNγ is produced later (against the background of CD56 expression and decrease of production of IL-5 and IL-13 [24]. $CD56^{bright}$ NKP effectively produces cytokines in responses to stimuli. $CD56^{bright}$ NK cells secrete little IFNγ compared to $CD56^{dim}$ NK cells [24, 23]. $CD56^{dim}$ NK cells are the earliest and dominant $IFN\gamma^{+}$ cells in responses to activating receptor ligation [23].

Cytotoxic factors of NKP

As a result of phenotype NKP-transformations into cytotoxic cell populations, granzymes A, B, K, perforin and other antitumor agents are released [4, 16, 21]. These factors are systemly opposite to separate tumor factors (lactatedehydrogenases, TGF-β, CSF-1, or others) [7, 43, 47]. $CD56^{bright}$ NK cells are poorly cytotoxic, and $CD56^{dim}$ NK cells are highly cytotoxic (lyse virus-infected and tumor cell lines) [23].

NKP possessing antitumor/antiviral activities

(*NKP; tumor targets coupled to viral infections; effects of NKP).

*$NKG2A^{+}$ from healthy donors ($HLA\text{-}C1^{+}C2^{+}Bw4^{+}$) and activated with IL-2; multiple myeloma cells, K562 cells; addition of daratumumab, an anti-CD38 to trigger antibody-dependent cell-mediated cytotoxicity, improved the antitumor response for all subsets of NKP [25].

*$NKG2A^{+}$; immunodeficient mice, co-infused with human primary leukemia or EBV cell lines and $NKG2A^{+}$ NKP; animals pre-treated with anti-human NKG2A were rescued from disease progression [40].

*$NKG2A^{+}CD56^{bright}$; "humanized" murine B cell lymphoma; release of IFN-gamma by NKP, cooperation to NKp44-receptors for inhibition of B cell transformation coupled to EBV [19].

*$NKG2A^{+}$; population is stronger expressed in the presence of VACV [16].

*$NKG2A^{+}$ against EBV [8].

*$NKG2A^{+}KIR^{-}$; populations influence lytic EBV-replication [31].

*$NKG2C^{+}$; U266 (human multiple myeloma cells) from CMV-seropositive donors, K562 (human leukemiya cells); stimulation of population expansion within organism [4, 9], the presence of latent CMV in healthy donors results in increasing NK-cytotoxicity [4].

*$NKG2C^{+}CD57^{+}$; lymphomas; expansion of population in response to CMV [34].

*$NKG2C^{+}CD57^{++}$; primary CMV infection or reactivation (CD161 expression on these cells is reduced) [22].

*$NKG2C^{+}$ (mainly); murine lymphoma; the action of population after allogenic transplantation depended of the presence of CMV [33].

*$NKG2C^{+}$; antitumor use of ligands for NKG2C [38].

*$NKG2C^{+}$; CMV-infected endothelial cells; the character of modulation of population depends on type of CMV-infected cells [9].

*$NKG2C^{+}NKG2A^{-}$; 221.AEH (transfected $HLA\text{-}E^{+}$ cells of human lymphoma); NK-cytotoxicity is 3 times higher than in case of non-transfected cerlls,

221.AEH and IL-15 help for population expansion within organism [4, 38].

*NKG2C$^+$CD94$^+$; Burkitt lymphoma; population participates in protective cooperation to γδ-T cells [8].

*NKG2C$^+$NKG2A$^-$KIR$^+$; co-infection EBV and CMV; stimulation of NKP [8].

*NKG2C$^+$CD56^{dim}/CD57$^+$ (mature, cytotoxic); leukemic T cell lymphoma; after blood transplantation and reactivagtion of CMV, population in 2 years is increased up to 33% of all lymphocytes; produce TNFα and IFNγ against leukemiya T cell lymohoma cells [32].

*NKG2D$^+$; patients with anogenital cancer (HPV is detected); increase of NKG2D-modulated cytotoxicity, decrease of sensitivity to cancer [12]; in humans, only the NKG2D-L isoform is expressed (receptor exclusively signals through DAP-10) [48]; NKG2D receptor is equally expressed by CD56^{bright} and CD56^{dim} cells and is able to synergistically activate human NK cells when they were simultaneously stimulated through CD16, NKp46 and 2B4 [23].

*NKG2D$^+$; patients with HCV-induced HCC; increase of NKG2D expression on monocytes upon action using ligands for NKG2D [7].

NKG2D$^+$ (NK92 – chimeric TN cells); xenographts of HCV-induced HCC; population expressing NKG2D, producing IFNγ and effective against TGF-β -producing tumor cells [47].

Aforamentioned data indicate that mostly significant and studied NKP are mainly characterized such RL as multifunctional NKG2A$^+$, NKG2C$^+$ and NKG2D$^+$. They act as glycopatterns recognizing agents, initiators (in reactions of modulation/choice/switching pathways of intercellular communications) and as the basis for further NK cell education (increasing selectivity in intercellular chain action towards final target when additional steps of current NK cell development through additional tuning receptors is needed). There are known other combination of receptors within NKP [8, 10, 23, 25, 42, 46, 48]. In whole, set of NKP acts as a network (at the levels of: own NKP spectrum; NKP in combinations with DC [according to NK-DC Cross-Talk], monocytes, macrophages and other innate immunity cells [innate like cells]; or NKP Cross-Talking to T and B cell populations of antibodies-producing system) within total protective network of organism.

Strategies using antitumor NKP

Protective NKP are synergistic together with other protective cells (CD8$^+$ T cells, blood cells, macrophages, DC) and supercellular immunity systems. Accumulation and expansion of antitumor/antiviral circulating monocytes into extended surroundings in organism are important for further their delivery to tumor/tumor microenvironment (infiltration of tumor space with selected NKP is achieved).

Multifunctionality of silent inclusions into human genome is still lowly studied as in case of inclusions similar to retroviral type (around 8% of repeats in human genome [15]. There are cases of close co-localization of some protective genes together with silent gene regions (for example, human complement subcomponents of C4B interacting to GC) that can provide their cofunctioning in directions needed [15]. As expected events of such protection, initiation and prolongation of the presence of specific control/supervisor spectra of NKP hoding back viral (for extended panel of viruses) expansion in organism could be taken place. For example, there are known latent CMV-infections (for CMV-seropositive healthy contingents of individuals. Besides, more than 90% of adults are characterized with asymptomatic EBV [6]. Thus, the status of NK compartment characterizes resistance of individuum (contingent of individuums) to viral infections, plays important role in anti-epidemic protection of the region population. More over, adaptive repertuar of prophylactical and therapeutic varying NKP opens the prospects of their applications against active epidemiologically significant viral infections as well as against initiations and progressive developments of of tumors.

NKG2-receptors and their ligands form metabolic supervisor axis of communications between lymphoid and myeloid immune cells; co-stimulate cytotoxic NKp46-receptors of NK cells and cytotoxic receptors of T cells (NKG2D [CD314] and NKp46 [CD335] as functionally coupled receptors [44]); induce sets of antitumor/antiviral cytokines; support proliferation and survival of effector cells [41]. It may be used upon search the ways and strategies of fight against tumors (also throuph antiviral action). As a result, increase of a number of effective NK cells and NKP and their intratumor-tissue expansion (expansion of needed NK cell types and complex NKP combinations) take place [8, 11, 13, 30]. Actions of NKP are in the synergistic accordance to protective actions of the complement system [18].

Below some perspective possibilities of using NKP are presented.

*NKG2$^+$ populations for creation of new antiviral strategies (as in cases of HIV-1) [34, 46].

*Directed using NKG2D$^+$ populations against tumors through NKG2D-receptors of NK cells which perfom on duty monitoring of revealing/initiation of tumor cell ligands (tumor indicators) on stress cells [7, 11]. During these events the cells exposing NKG2D-ligands (as in case of superexpressed complexes on intestinal mucosal stress cells) are recognized and eliminated by supervising cells that is in final result may be directed in prevention of carcinogenesis as in case of rectum cancer [11].

*CD56^{bright}NKG2A$^+$ population in correction of EBV-associated limphomas [19].

*Therapy of acute lymphoblast leukemiya by recovery and expansion of NKP followed by expression of CD158a, CD158b, perforin and granzyme K [21].

*Using blood transplantation of therapeutic NKP (NKP selected from healthy donors can be additionally activated with IL-2) against haematological tumors for; eradication of cancer cells (there are known phase I/II clinical trials of adoptive infusion of either selected or ex vivo-activated NKP from family or non-family donors) [25, 29, 33].

*Directed regulation of NKP type needed in special interactions involving adaptor DAP-12 or DAP-10 [10, 30, 38, 48].

*Using NKP on the basis of ortologs and paralogs of mammals for therapy [46].

*Constructing and application of antitumor genetically modified chimeric NKP such as CAR-T cells (for example, expressed chimeric receptor TN including extracellular and transmembrane domains of TGF-β-type-II-receptor and intracellular domain of activator NK cell receptor NKG2D [47]).

*Soluble lectins as ligands for RL-exposing NK cells (on example of CD161) wich are become to increase lysis of cancer cells [27].

Synbiotics (as in case of *Bifidobacterium longum bv. infantis* CCUG 52486 plus gluco-oligosaccharide) influence NKP responses to viral infections that can be of vaccine aspect significance [37]. Probiotic cell surface proteins (adhesins, factors of aggregation, ensemble proteins, mucin- and peptidoglycan-binding, lectins, other lectin-like ligands) are capable to increase human antiinfectious potential of NKP of mucosal immunity [5, 36]. Prophylactic and therapeutic possibilities of prevention of transformation of dysbiotic states of human open cavity mucosal biotopes into tumor states are new and of great potential (for example, with participation of activator DDR-pathway (DNA damage response) of the system NKG2D/NKG2D-ligands of NKP; or action of system probiotic lectins (PL) imitating probiotics and possessing cytokines-like activities [3, 11, 12]. As upon microbial-viral dysbioses PL can be selectively directed to relative pathogens (also changed microorganisms during prolonged inflammation) and can carry out functions of probiotics when probiotics and probiotic like microflora is absent in pathological biotopes against the background the presence of HPV – potential inducers of vaginal cancer, it is possible to expect anticancer/antiviral synergism between PL (as ligands for RL, agents cofunctioning to enzymes) and NKG2D-depended cytotoxicity decreasing sensitivity to cancer [11, 12, 45].

RL (on example of NKG2D) act like multipotent key messengers (after HLA-A/B/E-signalling [39]) recognizing panels of GC-pattern-targets ordered/ranked on RL-specificity/affinity and availability/minimal distance as in case of NK cell surface receptor mosaics [20]. Extended panels of receptors of NK cell surface are perspective for RL-depending directed sequential tuning (RL-KIR/NCR/CD/their combinations) to initiate further support and enhancement of human antitumor/antiviral protection.

Conclusion

The controlled influence of network of NKP containing dynamic panels of lectin, Ig-like, cytotoxic and known CD-receptors and receptor ligands takes place in organism. It is of reason to perform preliminary diagnostics of patient current specktrum of some key types of NKP to create the mostly acceptable immunotherapeutic strategies for antitumor/antiviral treatments (infusions of NKP, the use of special constructs of chimeric NKP). It seems, diversity and ordering of protective NKP impair active destructive actions of epidemiologically significant viruses all over the organism, hold back and prophylactically prevent initiation or further progression of tumors. The data indicate new potential and new resources in development of new antitumor/antiviral and vaccine preparations and strategies. In this context, PL will serve perspective ligands cofunctioning to the NKP network.

Список литературы / References

1. Лахтин М.В., Лахтин В.М., Алёшкин В.А., Афанасьев М.С., Афанасьев С.С. Лектины в антираковых стратегиях // Acta Biomedica Scientifica, 2018. Т. 3, № 4. С. 69-77. [Lakhtin M.V., Lakhtin V.M., Alyoshkin V.A., Afanasiev M.S., Afanasiev S.S. Lectins in anticancer strategies. *Acta Biomedica Scientifica, 2018, Vol. 3, no. 4, pp. 69-77.* (In Russ.)]

2. Лахтин М.В., Лахтин В.М., Алёшкин В.А., Афанасьев С.С. Лектиновые рецепторы в коммуникациях // News of Science and Education, 2018. Т. 2, № 3. С. 76-98. [Lakhtin M.V., Lakhtin V.M., Alyoshkin V.A., Afanasiev S.S. Lectin receptors in communications. *News of Science and Education, 2018, Vol. 2, no. 3, pp. 76-98.* (In Russ.)]

3. Лахтин М.В., Лахтин В.М., Афанасьев С.С., Байракова А.Л., Алёшкин В.А., Афанасьев М.С. Кандидные маркеры болезней урогенитальных биотопов: реактивность к лектинам пробиотиков // Acta Biomedica Scientifica, 2018. Т. 3, № 1. С. 49-53. [Lakhtin M.V., Lakhtin V.M., Afanasiev S.S., Bayrakova A.L., Aleshkin V.A., Afanasiev M.S. *Candida* markers of diseases of urogenital biotopes: Reactivity to lectins of probiotics. *Acta Biomedica Scientifica, 2018, Vol. 3, no. 1, pp. 49-53.* (In Russ.)]

4. Bigley A.B., Rezvani K., Shah N., Sekine T., Balneger N., Pistillo M., Agha N., Kunz H., O'Connor D.P., Bollard C.M., Simpson R.J. Latent cytomegalovirus infection enhances anti-tumour cytotoxicity through accumulation of NKG2C$^+$ NK cells in healthy humans. *Clin. Exp. Immunol., 2016, Vol. 185, no. 2, pp. 239-251.*

5. do Carmo F.L.R., Rabah H., de Oliveira Carvalho R.D., Gaucher F., Cordeiro B.F., da Silva S.H., le Loir Y., Azevedo V., Jan G. Extractable bacterial surface proteins in probiotic-host interaction. *Front. Microbiol., 2018, Vol. 9, p. 645.*

6. Chijioke O., Landtwing V., Münz C. NK cell influence on the outcome of primary Epstein–Barr virus infection. *Front. Immunol., 2016, Vol. 7, p. 323.*

7. Crane C.A., Austgen K., Haberthur K., Hofmann C., Moyes K.W., Avanesyan L., Fong L., Campbell M.J., Cooper S., Oakes S.A., Parsa A.T., Lanier L.L. Immune evasion mediated by tumor-derived lactate dehydrogenase induction of NKG2D ligands on myeloid cells in glioblastoma patients. *Proc. Natl. Acad. Sci. USA, 2014, Vol. 111, no. 35, pp. 12823-12828.*

8. Djaoud Z., Guethlein L.A., Horowitz A., Azzi T., Nemat-Gorgani N., Olive D., Nadal D., Norman P.J., Münz C., Parham P. Two alternate strategies for innate immunity to Epstein–Barr virus: One using NK cells and the other NK cells and gamma-delta T cells. *J. Exp. Med., 2017, Vol. 214, no. 6, pp. 1827-1841.*
9. Djaoud Z., Riou R., Gavlovsky P.J., Mehlal S., Bressollette C., Gérard N., Gagne K., Charreau B., Retière C. Cytomegalovirus-infected primary endothelial cells trigger NKG2C$^+$ natural killer cells. *J. Innate Immun., 2016, Vol. 8, no. 4, pp. 374-385.*
10. Dukovska D., Fernández-Soto D., Valés-Gómez M., Reyburn H.T. NKG2H-expressing T cells negatively regulate immune responses. *Front. Immunol., 2018, Vol. 9, p. 390.*
11. Espinoza J.L., Minami M. Sensing bacterial-induced DNA damaging effects via natural killer group 2 member D immune receptor: From dysbiosis to autoimmunity and carcinogenesis. *Front. Immunol., 2018, Vol. 9, p. 52.*
12. Espinoza J.L., Nguyen V.H., Ichimura H., Pham T.T., Nguyen C.H., Pham T.V., Elbadry M.I., Yoshioka K., Tanaka J., Trung L.Q.,Takami A., Nakao S. A functional polymorphism in the NKG2D gene modulates NK-cell cytotoxicity and is associated with susceptibility to Human Papilloma Virus-related cancers. *Sci. Rep., 2016, Vol. 6, 39231.* doi: 10.1038/srep39231.
13. Fehniger T.A., Cooper M.A. Harnessing NK cell memory for cancer immunotherapy. *Trends Immunol., 2016, Vol. 37, no. 12, pp. 877-888.*
14. Georgountzou A., Papadopoulos N.G. Postnatal innate immune development: From birth to adulthood. *Front. Immunol., 2017, Vol. 8, 957.* doi: 10.3389/fimmu.2017.00957.
15. Grandi N., Cadeddu M., Pisano M.P., Esposito F., Blomberg J., Tramontano E. Identification of a novel HERV-K(HML10): Comprehensive characterization and comparative analysis in non-human primates provide insights about HML10 proviruses structure and diffusion. *Mob. DNA, 2017, Vol. 8, p. 15.*
16. Hatfield S.D., Daniels K.A., O'Donnell C.L., Waggoner S.N., Welsh R.M. Weak vaccinia virus-induced NK cell regulation of CD4 T cells is associated with reduced NK cell differentiation and cytolytic activity. *Virology, 2018, Vol. 519, pp. 131-144.*
17. Heiberg I.L., Pallett L.J., Winther T.N., Høgh B., Maini M.K., Peppa D. Defective natural killer cell anti-viral capacity in paediatric HBV infection. *Clin. Exp. Immunol., 2015, Vol. 179, no. 3, pp. 466-476.*
18. Janelle V., Langlois M.P., Tarrab E., Lapierre P., Poliquin L., Lamarre A. Transient complement inhibition promotes a tumor-specific immune response through the implication of natural killer cells. *Cancer Immunol. Res., 2014, Vol. 2, no. 3, pp. 200-206.*
19. Jud A., Kotur M., Berger C., Gysin C., Nadal D., Lünemann A. Tonsillar CD56^{bright}NKG2A$^+$ NK cells restrict primary Epstein–Barr virus infection in B cells via IFN-gamma. *Oncotarget, 2017, Vol. 8, no. 4, pp. 6130-6141.*
20. Keydar Y., le Saux G., Pandey A., Avishay E., Bar-Hanin N., Esti T., Bhingardive V., Hadad U., Porgador A., Schvartzman M. Natural killer cells' immune response requires a minimal nanoscale distribution of activating antigens. *Nanoscale, 2018, Vol. 10, no. 30, pp. 14651-14659.*
21. Koltan S., Debski R., Koltan A., Grzesk E., Tejza B., Eljaszewicz A., Gackowska L., Kubicka M., Kolodziej B., Kurylo-Rafinska B., Kubiszewska I., Wiese M., Januszewska M., Michalkiewicz J., Wysocki M., Styczynski J., Grzesk G. Phenotype of NK cells determined on the basis of selected immunological parameters in children treated due to acute lymphoblastic leukemia. *Medicine (Baltimore), 2015, Vol. 94, no. 52, e2369.* doi: 10.1097/MD.0000000000002369.
22. Kurioka A., Cosgrove C., Simoni Y., van Wilgenburg B., Geremia A., Björkander S., Sverremark-Ekström E., Thurnheer C., Günthard H.F., Khanna N., Walker L.J., Arancibia-Cárcamo C.V., Newell E.W., Willberg C.B., Klenerman P. CD161 defines a functionally distinct subset of pro-inflammatory natural killer cells. *Front. Immunol., 2018, Vol. 9, 486.* doi: 10.3389/fimmu.2018.00486.
23. Kurioka A., Klenerman P., Willberg C.B. Innate-like CD8$^+$ T-cells and NK cells: converging functions and phenotypes. *Immunology, 2018.* doi: 10.1111/imm.12925.
24. Mahapatra S., Mace E.M., Minard C.G., Forbes L.R., Vargas-Hernandez A., Duryea T.K., Makedonas G., Banerjee P.P., Shearer W.T., Orange J.S. High-resolution phenotyping identifies NK cell subsets that distinguish healthy children from adults. *PLoS ONE, 2017, Vol. 12, no. 8, e0181134.* doi: 10.1371/journal.pone.0181134.
25. Mahaweni N.M., Ehlers F.A.I., Sarkar S., Janssen J.W.H., Tilanus M.G.J., Bos G.M.J., Wieten L. NKG2A expression is not *per se* detrimental for the anti-multiple myeloma activity of activated natural killer cells in an *in vitro* system mimicking the tumor microenvironment. *Front. Immunol., 2018, Vol. 9, 1415.* doi: 10.3389/fimmu.2018.01415.
26. Malone D.F.G., Lunemann S., Hengst J., Ljunggren H.G., Manns M.P., Sandberg J.K., Cornberg M., Wedemeyer H., Björkström N.K. Cytomegalovirus-driven adaptive-like natural killer cell expansions are unaffected by concurrent chronic hepatitis virus infections. *Front. Immunol., 2017, Vol. 8, 525.* doi: 10.3389/fimmu.2017.00525.
27. Marrufo A.M., Mathew S.O., Chaudhary P., Malaer J.D., Vishwanatha J.K., Mathew P.A. Blocking LLT1 (CLEC2D, OCIL)-NKRP1A (CD161) interaction enhances natural killer cell-mediated lysis of triple-negative breast cancer cells. *Am. J. Cancer Res., 2018, Vol. 8, no. 6, pp. 1050-1063.*
28. Martinez D.R., Permar S.R., Fouda G.G. Contrasting adult and infant immune responses to HIV infection and vaccination. *Clin. Vaccine Immunol., 2015, Vol. 23, no. 2, pp. 84-94.*
29. Mavers M., Bertaina A. High-risk leukemia: Past, present, and future role of NK cells. *J. Immunol. Res., 2018. Vol. 2018, 1586905.* doi: 10.1155/2018/1586905.
30. Muntasell A., Vilches C. Angulo A. López-Botet M. Adaptive reconfiguration of the human NK-cell compartment in response to cytomegalovirus: A different perspective of the host-pathogen interaction. *Eur. J. Immunol., 2013, Vol. 43, no. 5, pp. 1133-1141.*
31. Münz C. Epstein–Barr virus-specific immune control by innate lymphocytes. *Front. Immunol., 2017, Vol. 8, 1658.* doi: 10.3389/fimmu.2017.01658.
32. Muta T., Yoshihiro T., Jinnouchi F., Aoki K., Kochi Y., Shima T., Takenaka K., Ogawa R., Akashi K., Oshima K. Expansion of NKG2C-expressing natural killer cells after umbilical cord blood transplantation in a patient with peripheral T-cell lymphoma with cytotoxic molecules. *Intern. Med., 2018, Vol. 57, no. 6, pp. 861-866.*

33. Peled J.U., Jenq R.R. Not just leukemia: CMV may protect against lymphoma recurrence after allogeneic transplant. *Leuk. Lymphoma, 2017, Vol. 58, no. 4, pp. 759-761.*
34. Peppa D. Natural killer cells in human immunodeficiency virus-1 infection: Spotlight on the impact of human cytomegalovirus. *Front. Immunol., 2017, Vol. 8, 1322.* doi: 10.3389/fimmu.2017.01322.
35. Phan M.T., Chun S., Kim S.H., Ali A.K., Lee S.H., Kim S., Kim S.H., Cho D. Natural killer cell subsets and receptor expression in peripheral blood mononuclear cells of a healthy Korean population: Reference range, influence of age and sex, and correlation between NK cell receptors and cytotoxicity. *Hum. Immunol., 2017, Vol. 78, no. 2, pp. 103-112.*
36. Prado Acosta M., Ruzal S.M., Cordo S.M. S-layer proteins from *Lactobacillus* sp. inhibit bacterial infection by blockage of DC-SIGN cell receptor. *Int. J. Biol. Macromol., 2016, Vol. 92, pp. 998-1005.*
37. Przemska-Kosicka A., Childs C.E., Maidens C., Dong H., Todd S., Gosney M.A., Tuohy K.M., Yaqoob P. Age-related changes in the natural killer cell response to seasonal influenza vaccination are not influenced by a synbiotic: A randomised controlled trial. *Front. Immunol., 2018. Vol. 9, 591.* doi: 10.3389/fimmu.2018.00591.
38. Pupuleku A., Costa-García M., Farré D., Hengel H., Angulo A., Muntasell A., López-Botet M. Elusive role of the CD94/NKG2C NK cell receptor in the response to cytomegalovirus: Novel experimental observations in a reporter cell system. *Front. Immunol., 2017, Vol. 8, 1317*. doi: 10.3389/fimmu.2017.01317.
39. Ramsuran V., Naranbhai V., Horowitz A., Qi Y., Martin M.P., Yuki Y., Gao X., Walker-Sperling V., del Prete G.Q., Schneider D.K., Lifson J.D., Fellay J., Deeks S.G., Martin J.N., Goedert J.J., Wolinsky S.M., Michael N.L., Kirk G.D., Buchbinder S., Haas D., Ndung'u T., Goulder P., Parham P., Walker B.D., Carlson J.M., Carrington M. Elevated HLA-A expression impairs HIV control through inhibition of NKG2A-expressing cells. *Science, 2018, Vol. 359, no. 6371, pp. 86-90.*
40. Ruggeri L., Urbani E., André P., Mancusi A., Tosti A., Topini F., Bléry M., Animobono L., Romagné F., Wagtmann N., Velardi A. Effects of anti-NKG2A antibody administration on leukemia and normal hematopoietic cells. *Haematologica, 2016, Vol. 101, no. 5, pp. 626-633.*
41. Stojanovic A., Correia M.P., Cerwenka A. The NKG2D/NKG2DL axis in the crosstalk between lymphoid and myeloid cells in health and disease. *Front. Immunol., 2018, Vol. 9, 827.* doi: 10.3389/fimmu.2018.00827.
42. Sundström Y., Nilsson C., Lilja G., Kärre K., Troye-Blomberg M., Berg L. The expression of human natural killer cell receptors in early life. *Scand. J. Immunol., 2007, Vol. 66, no. 2-3, pp. 335-344.*
43. Thompson T.W., Jackson B.T., Li P.J., Wang J., Kim A.B., Huang K.T.H., Zhang L., Raulet D.H. Tumor-derived CSF-1 induces the NKG2D ligand RAE-1-delta on tumor-infiltrating macrophages. *Elife, 2018, Vol. 7, pii: e32919.* doi: 10.7554/eLife.32919.
44. Uemura Y., Isobe Y., Uchida A., Asano J., Nishio Y., Sakai H., Hoshikawa M., Takagi M., Nakamura N., Miura I. Expression of activating natural killer-cell receptors is a hallmark of the innate-like T-cell neoplasm in peripheral T-cell lymphomas. *Cancer Sci., 2018, Vol. 109, no. 4, pp. 1254-1262.*
45. Uppendahl L.D., Dahl C.M., Miller J.S., Felices M., Geller M.A. Natural killer cell-based immunotherapy in gynecologic malignancy: A review. *Front. Immunol., 2018, Vol. 8, 1825.* doi: 10.3389/fimmu.2017.01825.
46. Walter L., Petersen B. Diversification of both KIR and NKG2 natural killer cell receptor genes in macaques – implications for highly complex MHC-dependent regulation of natural killer cells. *Immunology, 2017, Vol. 150, no. 2, pp. 139-145.*
47. Wang Z., Guo L., Song Y., Zhang Y., Lin D., Hu B., Mei Y., Sandikin D., Liu H. Augmented anti-tumor activity of NK-92 cells expressing chimeric receptors of TGF-beta-R II and NKG2D. *Cancer Immunol. Immunother., 2017, Vol. 66, no. 4, pp. 537-548.*
48. Wensveen F.M., Jelenčić V., Polić B. NKG2D: A master regulator of immune cell responsiveness. *Front. Immunol., 2018, Vol. 9, 441.* doi: 10.3389/fimmu.2018.00441.
49. Zingoni A., Molfetta R., Fionda C., Soriani A., Paolini R., Cippitelli M., Cerboni C, Santoni A. NKG2D and its ligands: "One for all, all for one". *Front. Immunol., 2018, Vol. 9, 476.* doi: 10.3389/fimmu.2018.00476.

Авторы:

Лахтин М.В. *– к.б.н., старший научный сотрудник ФБУН «Московский научно-исследовательский институт эпидемиологии и микробиологии имени Г.Н. Габричевского» Роспотребнадзора, Москва, Россия*

Лахтин В.М. *– д.б.н., главный научный сотрудник ФБУН «Московский научно-исследовательский институт эпидемиологии и микробиологии имени Г.Н. Габричевского» Роспотребнадзора, Москва, Россия*

Алёшкин В.А. *– д.б.н., профессор, научный руководитель ФБУН «Московский научно-исследовательский институт эпидемиологии и микробиологии имени Г.Н. Габричевского» Роспотребнадзора, Москва, Россия*

Афанасьев С.С. *– д.м.н., профессор, главный научный сотрудник ФБУН «Московский научно-исследовательский институт эпидемиологии и микробиологии имени Г.Н. Габричевского» Роспотребнадзора, Москва, Россия*

Authors:

Lakhtin M.V., *PhD (Biology), Senior Research Associate, G. Gabrichevsky Research Institute for Epidemiology and Microbiology, Moscow, Russian Federation*

Lakhtin V.M., *PhD, MD (Biology), Chief Research Associate, G. Gabrichevsky Research Institute for Epidemiology and Microbiology, Moscow, Russian Federation*

Alyoshkin V.A., *PhD, MD (Biology), Professor, Research Director, G. Gabrichevsky Research Institute for Epidemiology and Microbiology, Moscow, Russian Federation*

Afanasiev S.S., *PhD, MD (Medicine), Professor, Chief Research Associate, G. Gabrichevsky Research Institute for Epidemiology and Microbiology, Moscow, Russian Federation*

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