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Source / Izvornik: **Medicinski Razgledi, 2004, 43, 139 - 140**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:705026>

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Download date / Datum preuzimanja: **2025-01-16**



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Nastanek tumorjev in virusnih okužb je povezan z zmanjšanjem množine ligandov za receptor NKG2D

Immune Evasion of Viruses and Tumors by Down-regulation of Cellular Ligands for NK Receptor NKG2D

IZVLEČEK

KLJUČNE BESEDE: ubijalke naravne-imunologija, virusi, novotvorbe

Receptor (NKG2D) aktivira celice NK. Spodbujajo ga molekule, ki jih v majhni meri sintetizirajo normalne telesne celice, v povečani meri pa celice okužene z virusi, tumorske celice in celice, ki so pod stresom. Omenjene molekule sodijo po nekaterih značilnostih med molekule MHC I. Pri miših so to beljakovine, ki se sintetizirajo kmalu po spodbujanju celic z retinoično kislino (RAE-1), šibki antigen tkivne skladnosti H60 in transkriptni 1-glikoprotein (MULT-1), ki je podoben beljakovini, ki veže mišji UL-16. Celice NK s posebnimi receptorji spoznavajo molekule MHC I in se tako inaktivirajo. Spodbujanje receptorja NKG2D lahko takšen zaviralni signal preglasi. Iz navedenega sklepajo, da imajo receptorji NKG2D pomembno, če ne vodilno vlogo pri omejevanju virusnih okužb, kjer so celice NK poglavitni obrambni način.

Avtorji poročajo o treh pred kratkim odkritih glikoproteinih, ki so jih osamili pri miših, okuženih s CMV (MCMV). Te tri beljakovine so povezane z zmanjševanjem množine ligandov za receptor NKG2D. Glikoprotein MCMV *m152/gp40* ima dvojno nalogo – uravnava nivo molekul MHC I in ligandov za NK2D vrste RAE-1 (3–5). Proizvod gena *m145* MCMV je virusni regulator MULT-1 (Krmptic, A. et al. *J Exp Med* – še neobjavljeno), medtem ko protein, ki je kodiran z *m155* uravnava nastajanje molekul H60 (Hasan, M. et al. *J Virol* – še neobjavljeno). Pomen zmanjšanja nastajanja ligandov za receptor NK2D so potrdili s poskusi *in vivo*, ki so jih naredili z virusnimi mutantami, ki niso imele navedenih genov. Avtorji menijo, da so njihove ugotovitve ključne za razumevanje načina, s katerim si virusi, tako da zmanjšajo draženje receptorja NKG2D, zagotovijo preživetje (2).

Tumorji, ki izražajo ligande za receptorje NKG2D, so potencialne tarče za celice NK (1). Takšni tumorji lahko te ligande izločajo tudi v okolico. Topni ligandi za receptor NKG2D neposredno zmanjšajo učinkovitost receptorja NKG2D in tako zavrejo s celicami NK posredovano lizo. O pomenu navedenih načinov, ki omogočajo, da se virusi in tumorske celice izognejo s celicami NK posredovani lizi, bodo podrobneje razpravljali na predavanju.

ABSTRACT

KEY WORDS: killer cells natural-immunology, viruses, neoplasms

The activating NK cell receptor NKG2D binds ligands that are poorly expressed on normal cells but are up-regulated on infected, transformed or stressed cells. These ligands are distantly related to MHC class I molecules. Known mouse NKG2D ligands, comprise the retinoic

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acid early inducible-1 (RAE-1) family of proteins, the minor histocompatibility antigen H60 and the murine UL16-binding protein-like transcript-1 (MULT-1) glycoprotein. NKG2D receptor triggering can override signals by MHC class I specific inhibitory NK cell receptors. This suggests a pivotal position of NKG2D in NK cell-mediated control of viral infections.

We have recently characterized three mouse CMV (MCMV) glycoproteins responsible for subversion of NK cell response during virus infection by down-modulation of cellular ligands for NKG2D receptor. MCMV *m152/gp40* glycoprotein has a double role and not only modulates the plasma membrane expression of MHC class I molecules but also of NKG2D ligands of RAE-1 protein family (3-5). The product of *m145* MCMV gene is the viral regulator of MULT-1 (Krpmotic, A. et al. *J Exp Med* submitted) whereas the protein encoded by *m155* modulates H60 molecule (Hasan, M. et al. *J Virol* in press). The importance of surface down-regulation of NKG2D ligands in NK cell regulation *in vivo* was confirmed by the attenuating effect of virus mutants possessing deletion of any of these immunoregulatory genes. Our findings underline the significance of escaping signalling *via* NKG2D receptor for viral survival and maintenance (2).

NKG2D ligands expressing tumors are a potential target for NK cell lysis (1). However, tumors can evade NK cells recognition by secretion of soluble NKG2D ligands in order to cause down-regulation of NKG2D receptor on the surface of effector cells. Significance of above mentioned viral and tumors evasion mechanisms of NK cells mediated control will be discussed.

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Protitumorski LaSota virus

Antitumorous
Virus Strain

IZVLEČEK

KLJUČNE BESEDE: melanom eksperimentalni

Številni virusi lahko na tumor (NDV). Lentogeni sev LaSota virusa se uspešno uporablja za pripravo. Namen naše raziskave je bil preveriti, ali se LaSota virus lahko uporablja za zdravljenje B16F10 in normalne celice L929. Posebej nas je zanimalo, ali ima virus kakšen učinek.

Virus LaSota je bil citotoksičen za normalne fibroblaste L929 in za melanom B16F10. Intrapertitonealni rasti melanoma B16F10. Intrapertitonealni rasti melanoma B16F10.

Splenociti in limfociti iz bezgavnic so bili citotoksični za melanom B16F10. Najmočnejši učinek je bil opazen 24 ur po vbrizganju virusa. V obeh skupinih celic sta se, kot tisto pričakujemo, enako burno razvijali.

ABSTRACT

KEY WORDS: melanoma experimental - in

Many viruses including Newcastle disease virus (NDV) have an inhibitory effect on tumor growth in its natural host (poultry) and can be used for disease in birds.

The aim of this study was to test the effect of LaSota virus on tumor and L929 normal cells in mice. In addition to the effect on tumor-bearing mice was also investigated.

In vitro results showed that LaSota virus was cytotoxic to cells and that the effect was dose-dependent.

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