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

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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 (Krmpotic, 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 *(Krmpotic, 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.

REFERENCES

1. Cerwenka A, Lanier LL. Natural killer cells, viruses and cancer. *Nat Rev Immunol 2001; 1 (1):* 41–9.
2. Krmpotic A, Bubic I, Polic B, Lucin P, Jonjic S. Pathogenesis of murine cytomegalovirus infection. *Microbes Infect 2003; 5 (13):* 1263–77.
3. Krmpotic A, Busch DH, Bubic I, Gebhardt F, Hengel H, Hasan M, et al. MCMV glycoprotein gp40 confers virus resistance to CD8+ T cells and NK cells *in vivo*. *Nat Immunol 2002; 3 (6):* 529–35.
4. Krmpotic A, Messerle M, Crnkovic-Mertens I, Polic B, Jonjic S, Koszinowski UH. The immunoevasive function encoded by the mouse cytomegalovirus gene m152 protects the virus against T cell control *in vivo*. *J Exp Med 1999; 190 (9):* 1285–96.
5. Lodoen M, Ogasawara K, Hamerman JA, Arase H, Houchins JP, Mocarski ES, et al. NKG2D-mediated natural killer cell protection against cytomegalovirus is impaired by viral gp40 modulation of retinoic acid early inducible 1 gene molecules. *J Exp Med 2003; 197 (10):* 1245–53.

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Protitumorsk
LaSota virus
r

Antitumorous E
Virus Strain

IZVLEČEK

KLJUČNE BESEDE: melanom eksperimenta

Številni virusi lahko na tumor
(NDV). Lentogeni sev LaSota
se uspešno uporablja za pripra

Namen naše raziskave je bi
B16F10 in normalne celice L92
Posebej nas je zanimalo, ali ima
učinek.

Virus LaSota je bil citotoks
Normalni fibroblasti L929 so
bil citotoksičen. Intraperitonea
rast melanoma B16F10. Intrape

Splenociti in limfociti iz be
do s konkanavalinom A manj
najmočnejši 24 ur po vbrizgan
obe skupini celic sta se, kot tist
vali enako burno .

ABSTRACT

KEY WORDS: melanoma experimental – in

Many viruses including Newca
to have an inhibitory effect o
for its natural host (poultry) a
disease in birds.

The aim of this study was t
tumor and L929 normal cells in
in mice. In addition to the
tumor-bearing mice was also i

In vitro results showed that
cells and that the effect was d

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