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Gene Section
Review

NCR2 (natural cytotoxicity triggering receptor 2)

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Abstract: Review on NCR2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CD336, LY95, NK-p44, NKP44, dJ149M18.1

HGNC (Hugo): NCR2

Location: 6p21.1

Local order: NKp44 is centromeric to the Major Histocompatibility Complex on Chromosome 6 in a cluster of single immunoglobulin variable domain receptors.

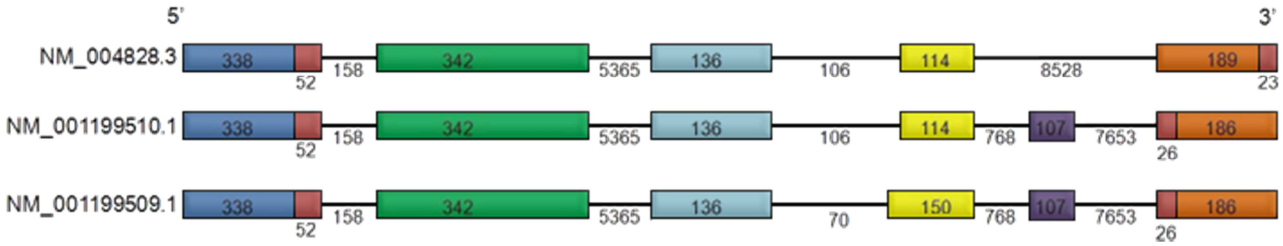
NKp44 is centromeric by 49071 bp to triggering receptor expressed on myeloid cells (Trem-1), located on the negative strand, and telomeric to forkhead box p4 by 195539 bp.

Note

NKp44 is a transmembrane glycoprotein of the Immunoglobulin (Ig) superfamily expressed on the surface of IL-2 and IL-15 activated Natural Killer (NK) cells (Cantoni et al., 1999; de Rham et al., 2007; Rosental et al., 2011; Horton et al., 2013). NKp44, NKp30, and NKp46 make up the Natural Cytotoxicity receptors of the NK cell and cooperate with each other for optimal recognition and elimination of target cells (Augugliaro et al., 2003). NKp44 can either activate or inhibit NK cell effector function through recognition of separate ligands.

NKp44 recognition of its unknown activating ligand facilitates signalling through Dap 12, resulting in release of cytotoxic agents, Tumor Necrosis Factor-α, and IFN-γ (Vitale et al., 1998). Recognition of cell surface Proliferating Cell Nuclear Antigen (PCNA) colocalizing with HLA I on the cell surface inhibits NK cell cytotoxicity and IFN-γ release (Rosental et al., 2011; Horton et al., 2013).

NKp44 expression is inhibited by IL-21 (de Rham et al., 2007).



Three splice variants of NKp44. NKp44 is encoded on 5 exons (NM_004828.3). One splice variant contains an additional exon (NM_001199510.1), adding 35 amino acids resulting in a shift in the reading frame, truncating the cytoplasmic tail by 18 amino acids (Allcock et al., 2003). A second splice variant (NM_001199509.1) adds 12 amino acids, but maintains the reading frame with a 36 base pair extension on the 5' side of exon 4 (Allcock et al., 2003).

DNA/RNA

Note

NKp44 is located on chromosome 6, centromeric to the Major Histocompatibility Complex. It is located in a cluster of single immunoglobulin variable domain receptors including Trem-1 and Trem-2 (Allcock et al., 2003).

Description

NKp44 gene spans 15098 bases located on positive strand of chromosome 6 from 41303528 to 41318625 bp. NKp44 is centromeric to Trem-1, with its leader sequence nearest to Trem-1 on the telomeric side and its cytoplasmic domain encoded towards the centromere (Allcock et al., 2003). NKp44 is encoded in 5 exons with one splice variant containing an extra exon (NM_001199510.1), adding 35 amino acids (Allcock et al., 2003). This addition alters the reading frame which truncates the cytoplasmic tail by 18 amino acids (Allcock et al., 2003). A second splice variant (NM_001199509.1) with an extra exon contains a 36 base pair extension of exon 4 on the 5' side, adding 12 amino acids, but maintaining the reading frame (Allcock et al., 2003).

Transcription

There are three transcript variants of NKp44. Isoform 1 (NM_004828.3) encodes the longest isoform. Isoform 2 (NM_001199509.1) encodes a frame shift due to an extra in-frame segment and an additional exon compared to isoform 1. This results in an additional internal segment and a shorter C-terminus. Isoform 3 (NM001199510.1) has an additional exon with a shorter C-terminus similar to isoform 2.

Protein

Note

NKp44 is a type I transmembrane protein belonging to the Ig Superfamily (Vitale et al., 1998; Cantoni et al., 1999; Cantoni et al., 2003). Surface expression of the receptor and signalling physically requires the transmembrane accessory protein DAP12 which bears Immunoreceptor Tyrosine Activation Motifs (Cantoni et al., 1999). NKp44 activates NK cells through DAP12 linked directly to Lysine 183 in the transmembrane domain (Campbell et al., 2004). NKp44 inhibits NK cells through a tyrosine-based inhibitory motif located in the cytoplasmic tail of the receptor (Rosental et al., 2011).

Description

NKp44 has a molecular weight of 44 kDa and consists of a 169 amino acid extracellular domain followed by 23 and 63 amino acid sequences in the transmembrane and cytoplasmic tail domains respectively (Cantoni et al., 1999; Cantoni et al., 2003). A 55 amino acid domain connects the extracellular Ig domain to the transmembrane segment and has 13 predicted O-glycosylation sites and a single N-glycosylation site (Cantoni et al., 1999; Cantoni et al., 2003). Crystallography of the receptor demonstrates a surface groove made by two facing β hairpin loops extending from the Ig fold core stabilized by a disulfide bridge between Cystine 37 and Cystine 45 (Cantoni et al., 2003). The Ig domain contains an arrangement of positively charged residues at the groove surface, suggesting NKp44 ligands are anionic (Cantoni et al., 2003).

The groove appears wide enough to host a sialic acid or an elongated branched ligand. The cytoplasmic tail of NKp44 also contains a tyrosine sequence resembling a tyrosine-based inhibitory motif (Cantoni et al., 1999; Campbell et al., 2004). This motif is functional and inhibits the release of cytotoxic agents and IFN-γ (Rosental et al., 2011).

Expression

NKp44 is expressed on IL-2 and IL-15 activated NK Cells and NK cells in the decidua (Cantoni et al., 1999; de Rham et al., 2007; Manaster and Mandelboim, 2010). The receptor is also expressed on isolated polyclonal γδ T cells when cultured for 2 weeks in IL-15 and IL-2 (Cantoni et al., 1999; von Lilienfeld-Toal et al., 2006; Hudspeth et al., 2013). Natural Interferon-producing cells located in the T-cell zone in lymph nodes draining a site of viral infection are reported to express NKp44, believed to be induced by IL-3 from local memory CD8 T cells (Fuchs et al., 2005). NKp44 is also induced in TCR αβ intestinal intraepithelial lymphocytes by IL-15 (Meresse et al., 2004). Cytolytic T cells isolated from cord blood express NKp44 when induced with IL-2 or IL-15 (Tang et al., 2008). Finally NKp44 is expressed on a subset of cells located in human tonsils, similar to lymphoid tissue induce cells, which produce IL-22 and express Rorγt (Fuchs et al., 2005; Cella et al., 2009).

Localisation

NKp44 is a type I transmembrane protein expressed on the surface of IL-2 activated NK cells and induced in γδ T cells by IL-15 and IL-2 (Cantoni et al., 1999; von Lilienfeld-Toal et al., 2006; Hudspeth et al., 2013). Expression is also reported on the cell surface of natural interferon-producing cells exposed to IL-3 (Fuchs et al., 2005).

Function

NKp44 may functions as either an activating or inhibitory receptor on the surface of the NK cell. The identities of activating ligands are currently unknown, but bind NKp44 to induce activating signals through Dap12 (Vitale et al., 1998; Cantoni et al., 1999; Campbell et al., 2004). NKp44 inhibits NK cell function through recognition of cell surface exosomal PCNA which colocalizes with HLA I (Rosental et al., 2011; Horton et al., 2013).

Homology

- NCR 2 Natural Cytotoxicity Trigger Receptor 2 [Pan troglodytes] NC_006473.3
- NCR 2 Natural Cytotoxicity Trigger Receptor 2 [Macaca mulatta] NC_007861.1
- NCR 2 Natural Cytotoxicity Trigger Receptor 2 [Canis lupus familiaris] NC_006594.3

Mutations

Note
None identified.

Implicated in

Various cancers

Note
NKp44 is implicated in recognition of numerous types of cancer (neuralblastoma, choriocarcinoma, pancreatic, breast, lung adenocarcinoma, colon, cervix, hepatocellular carcinoma, Burkitt lymphoma, diffuse B cell lymphoma, prostate) (Sivori et al., 2000a; Sivori et al., 2000b; Byrd et al., 2007; Rosental et al., 2011; Horton et al., 2013). Ligands for NKp44 appear to be cell cycle regulated, with down regulation of expression during mitosis (Byrd et al., 2007). Recognition of tumor cells is partially mediated through charged based binding of NKp44 with heparin sulfate proteoglycans (HSPG) on the surface of tumor cells (Hershkovitz et al., 2007). Specifically, the 2-O-sulfation of iduronic acid and N-acetylation of glucosamine on HSPGs are important for interaction with NKp44 (Hecht et al., 2009). Glycans containing α2,6-N¬-acetylneuraminic acid are also recognized on the surface of cancer cells by NKp44 (Ito et al., 2012). HSPGs are believed to be a coligand for NKp44 and the other NCRs, potentially facilitating binding with other cellular ligands. Recognition of HSPG only evokes IFN-γ release by NK cells, not cellular cytotoxicity (Hershkovitz et al., 2007).

Tumor escape of immunosurveillance

Note
Tumors employ numerous mechanisms to avoid killing by NK cells. By engaging NKp44, as well as the other NCRs, tumors can induce NK cell death via up regulation of Fas Ligand in the NK cell, inducing Fas mediated apoptosis (Poggi et al., 2005). NKp44 surface expression can be down regulated by soluble MHC Class I chain-related molecules shed by colorectal tumors or by indoleamine 2,3-dioxygenase and prostaglandin E2 released by melanoma cells (Doubrovina et al., 2003; Pietra et al., 2012). Mesenchymal stem cells also release indoleamine 2,3-dioxygenase and prostaglandin E2 which inhibit NKp44 induction in the tumor microenvironment, but may also be harnessed as a therapeutic approach to inhibit Graft-versus-host or autoimmune disease (Spaggiari et al., 2008). Tumors may also down regulate NKp44 ligand expression to escape NK cell killing, as is the case with acute myeloid leukemia (AML) (Nowbakht et al., 2005). In the case of normal myelonocytic differentiation of bone marrow cells, a ligand for NKp44 is expressed upon loss of the CD34 hematopoietic marker and acquisition of CD33 and CD14 myeloid markers (Nowbakht et al., 2005). Ligand expression if further increased by the presence of IFN-γ (Nowbakht et al., 2005). Yet in AML, ligand expression is absent, possibly contributing to disease manifestation. Finally, tumor cells may also induce expression of exosomal PCNA when physically contacted by NKp44 expressing NK cells to inhibit NK cell effector function (Rosental et al., 2011).

Viral infection

Note
NKp44 recognizes α2,6-N¬-acetylneuraminic acid of hemagglutinin of Influenza and Sendai viruses and hemagglutinin-neuraminidase of the Newcastle disease virus, requiring sialyation of the receptor (Arnon et al., 2001; Jarahian et al., 2009; Ito et al., 2012). Binding of NKp44 to hemagglutinin enables lysis of viral infected cells. Specifically, NKp44 recognizes hemagglutinins from H5-type influenza virus strains (Ho et al., 2008). Two flaviviruses, Dengue and West Nile, are directly recognized by NKp44. Envelope proteins of these viruses, in particular domain III of West Nile, directly bind to NKp44, increasing lysis of infected cells and NK cell IFN-γ release (Hershkovitz et al., 2009). NKp44 is also implicated in recognizing a ligand expressed on cells infected with Vaccina virus (Chisholm and Reyburn, 2006). Viruses have also evolved immune escape mechanisms by down regulating expression of the ligand for NKp44. In the case of Kaposi's sarcoma-associated herpes virus, the extracellular ligand expression is reduced during de novo infection. Interestingly, during lytic infection, only surface levels of the NKp44 ligand are reduced as overall cellular levels are unchanged, indicating a defect in cellular trafficking (Madrid and Ganem, 2012). Also, while the NKp44 ligand is typically located outside of the nucleus, during lytic infection the ligand is found localizing to the nucleus (Madrid and Ganem, 2012). This localization is concurrent with a burst of lytic gene expression, mainly consisting of immune related genes (Madrid and Ganem, 2012).

HIV

Note
A hallmark of HIV infection is the progressive depletion of $CD4^+$ T cells via destruction of both uninfected $CD4^+$ T cells and HIV-infected $CD4^+$ T cells. In regards to NK cells, HIV modulates both the expression of NK cell receptors and their ligands. NKp44 is no exception as it is expressed at a lower surface density on in vitro activated NK cells from

HIV-1 patients compared to healthy controls, resulting in decreased killing of various tumor target cells (De Maria et al., 2003; Mavilio et al., 2003; Fogli et al., 2004). HIV also modulates NK cell receptor ligand expression. NKp44 cellular ligand (NKp44L) is expressed on uninfected $CD4^+$ T cells during an HIV infection, correlating with the loss of $CD4^+$ T cells and increase of viral load (Vieillard et al., 2005). NKp44L is only expressed in high amounts on uninfected $CD4^+$ T cells and is not responsible for inducing NK lysis of HIV-infected cells (Ward et al., 2007). To avoid NK killing of HIV infected $CD4^+$ T cells, the Nef protein of HIV-1 retains NKp44L intracellularly, preventing cell surface expression and interaction with NKp44 (Fausther-Bovendo et al., 2009). Studies by Vieillard et al. have shown a highly conserved 3S peptide motif of the HIV-1 gp41 protein is involved in the induction of NKp44L on the surface of uninfected $CD4^+$ T cells. An envelope protein of the HIV virus, gp41 is vital for viral entry into target cells (Vieillard et al., 2005). The 3S peptide of gp41 binds to its receptor gC1qR, a receptor for the globular domain of complement component 1q, on $CD4^+$ T cells (Fausther-Bovendo et al., 2010). Binding of the 3S motif to this receptor activates a signaling cascade involving PI3K, NADPH-oxidase, Rho-A, and TC10 (Fausther-Bovendo et al., 2010). NKp44L is translocated from the cytoplasm to the plasma membrane and is expressed on the cell surface, where it can bind to NKp44 of activated NK cells. $NKp44L^+$ expressing $CD4^+$ T cells are more susceptible to lysis by activated NK cells (Vieillard et al., 2005). Understanding the role of NKp44L during HIV infection could help identify new therapeutic strategies to prevent the progressive loss of uninfected $CD4^+$ T cells. Possible therapeutic strategies are to inhibit the expression of NKp44L by using an anti-gp41 Ab or an anti-gC1qR Ab to block the 3S motif and gC1qR interaction (Vieillard et al., 2005; Fausther-Bovendo et al., 2010). Anti-3S immunization has also proven efficacious in preliminary studies in macaques (Vieillard et al., 2008).

Microbial infection

Note

Nkp44 is reported to directly bind to the surface of Mycobacterium and other related genera. After in vitro stimulation with Mycobacterium bovis bacillus Calmette-Guérin (BCG) for 3 to 4 days, $CD56^{bright}$ NK cells significantly increase NKp44 expression (Esin et al., 2008). The Mycobacterium genus, including the causative agent of tuberculosis, Mycobacterium tuberculosis, express a conserved NKp44 ligand while the mycobacterium related, Gram-positive Nocardia and Corynbacterium genera, also express a ligand (Esin et al., 2008; Esin et al., 2013). Interestingly, both Nocardia, Corynbacterium, and Mycobacterium genera express mycolic acids in their cell walls, which is lacking in other mycobacterium related species which do not express a ligand for NKp44 (Esin et al., 2008). Furthermore, the BCG NKp44 ligand was found to be resistant to trypsin degradation and stable at 80°C, indicating the ligand is most likely not a protein but a heat stable structural component of the cell wall (Esin et al., 2008). In a subsequent study, Esin et al. further proved NKp44 specifically binds mycolyl-arabinogalactan-peptidoglycan, mycolic acid, and arabinogalactan found in the cell wall of Mycobacterium tuberculosis to maintain NK cell activation (Esin et al., 2013). Finally, Pseudomonas aeruginosa also express a ligand for NKp44 (Esin et al., 2008).

Formation of placenta

Note

Decidual NK cells (dNK) make up 50-90% of lymphocytes in the uterine mucosa during pregnancy and constitutively express NKp44 (Kopcow et al., 2005; Hanna et al., 2006; Vacca et al., 2008). In close contact with fetal extravillous trophoblasts cells invading the maternal decidua, dNK cells exhibit reduced cytotoxicity but crucially produce Interleukin-8, Interferon-inducible protein 10, Vascular Endothelial Growth Factor (VEGF), and Placental Growth Factor (PGF) in response to NKp44 triggering (Hanna et al., 2006; Vacca et al., 2008).

Trophoblast cells and maternal stromal cells of the decidua both express unidentified NKp44 ligands (Hanna et al., 2006; Vacca et al., 2008). This ligand may be PCNA as the protein is over expressed in trophoblast cells during the first trimester (Korgun et al., 2006).

As an inhibitory ligand for NKp44, extracellular PCNA expression on trophoblast cells would help explain the diminished ability of dNK cells to lyse trophoblasts despite low levels of classical HLA I expression (Vacca et al., 2008). Invasion of trophoblast into decidua facilitates proper placentation and NK cells help govern how far trophoblasts infiltrate (Moffett and Loke, 2006). dNK cells also help reorganize the spiral arteries to facilitate appropriate blood transfer between the mother and fetus at the placenta (Moffett and Loke, 2006; Vacca et al., 2008).

Alterations in dNK cells and invasion of fetal trophoblast cells are implicated in pregnancy complications, such as pre-eclampsia and tubal pregnancies (Moffett and Loke, 2006). Since fetal trophoblast and maternal decidual cells express a NKp44 ligand, this receptor constitutively expressed on dNK cell plays a crucial role in proper development of the placenta in pregnancy that requires further study.

Spontaneous abortion

Note

NKp44 expression is increased on $CD56^{bright}CD16^-$ dNK cells in patients with spontaneous abortion, resulting in increased cytolytic activity of these NK cells (Zhang et al., 2008).

Crohn's disease and ankylosing spondylitis

Note

$NKp44^+$ NK cells ($CD3^-CD56^+NKp44^+NKp46^-RORC^{high}CD122^-CD127^+$) in the intestinal lamina propria are significantly reduced in inflamed mucosa of patients with Crohn's Disease (CD) while IFN-γ producing $NKp46^+$ NK cells ($CD3^-CD56^+NKp44^-NKp46^+RORC^{dull}CD122^+CD127^-$) are dramatically increased (Takayama et al., 2010). IL-22 is produced by $NKp44^+$ NK cells, which is protective in the onset of murine colitis, and possibly implicated in human colitis. Thus the imbalance of the NKp44+/NKp46+ NK cell axis in the intestinal lamina propria may play a role in colitis onset (Takayama et al., 2010). Contrary to CD, $NKp44^+$ NK cells are increased in the inflamed ileum of patients with Ankylosing Spondylitis (AS) (Ciccia et al., 2012). AS Patients over express IL-23 in the intestines which modulates IL-22 production by $NKp44^+IL\text{-}22^+$ NK cells (Ciccia et al., 2012). IL-22 then promotes mucosal wound healing through increased mucin production by goblet cells.

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