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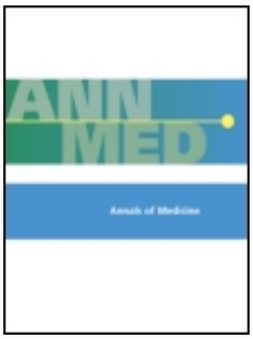

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REVIEW ARTICLE

Regulation of self-ligands for activating natural killer cell receptors

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Natural killer (NK) cells are able to lyse infected and tumor cells while sparing healthy cells. Recognition of diseased cells by NK cells is governed by several activating and inhibitory receptors. We review numerous pathways that have been implicated in the regulation of self-ligands for activating receptors, including NKG2D, DNAM-1, LFA-1, NKp30, NKp44, NKp46, NKp65, and NKp80 found on NK cells and some T cells. Understanding how the regulation of self-encoded ligand expression is regulated may provide novel avenues for future therapeutic approaches to infections and cancer.

Key words: Cancer, DNAM-1, infection, innate immunity, NCR, NKG2D, NKp80

Key messages

- Self-ligands for activating NK cell receptors are absent or expressed at low levels on most healthy cells.
- The expression of ligands is up-regulated in response to a variety of cellular changes associated with infection and tumorigenesis.
- Cellular changes regulate the expression of self-ligand at different stages of biogenesis.

Natural killer (NK) cells are lymphocytes of the innate immune system that contribute to the defense against pathogens and cancer (1). NK cells are able to discriminate healthy from diseased cells despite the lack of the highly variable antigen-specific receptors found on T and B cells. Recognition of diseased cells by NK cells is governed by a number of activating and inhibitory receptors. Among the best-described activating receptors in the context of recognition of tumor cells and infected cells are NKG2D, DNAM-1, LFA-1, NKp30, NKp44, NKp46, Nκp65 and NKp80 (2). Ligands for these activating receptors are absent or poorly expressed on most healthy cells, but their expression is up-regulated on infected cells and tumor cells. This type of 'induced self-recognition' acts alongside other modes of recognition such as 'missing-self recognition' in which loss of major histocompatibility complex (MHC) ligands for NK inhibitory receptors leads to lysis of cells (reviewed in (3)). The purpose of this review is to provide an overview of the pathways and cellular stimuli that regulate the expression of ligands for activating receptors.

Regulation of ligands for activating NK cell receptors

NKG2D ligands

The activating receptor NKG2D is a C-type lectin-like family molecule that is expressed on nearly all NK cells (4). It is also expressed on human $CD8^+$ T cells, activated mouse $CD8^+$ T cells, subsets of $\gamma\delta^+$ T cells, and NK T cells. NKG2D is a homodimeric, type II transmembrane glycoprotein that binds members of the MHC class I chain-related (MIC) and retinoic acid early transcript 1 (RAET1) protein families (4–6). These distant homologues of MHC class I proteins do not heterodimerize with β-2-microglobulin or present antigenic peptides (5). The two *MIC* gene family members MICA and MICB are encoded in the human major histocompatibility complex (MHC), while *RAET1* gene family members map to the human chromosome 6, and *Raet1* genes are present on a syntenic segment on mouse chromosome 10. No mouse equivalents of human *MIC* gene homologues have been identified in the mouse genome. The human *RAET1* gene family, also called UL16-binding proteins (ULBPs), consists of ten genes with six loci encoding for potentially functional proteins. The mouse RAET1 protein family comprises three subfamilies including *Rae1* (α-ε), histocompatibility 60 (*H60*) (a-c), and murine ULBP-like transcript 1 (*Mult1*). NKG2D ligands share little sequence identity between and within the MIC and RAET1 protein families. The mouse RAET1 proteins, ULBP1, ULPB2, ULBP3, and ULBP6, are glycosylphosphatidylinositol (GPI)-linked proteins, whereas the human MIC proteins, ULBP4, ULBP5, mouse H60, and MULT1 are type I transmembrane glycoproteins.

Regulation of NKG2D ligands by cellular changes associated with tumorigenesis

Activators of the E2F family were shown to regulate the transcription of mouse *Raet1*, but not *H60* or *Mult1* family members

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in primary fibroblasts (7). In human T cells and HCT116 cells the expression of MICA, MICB, ULBP2, ULBP3, and possibly ULBP1 was found to be associated with proliferation (8,9). Hence, cellular proliferation, which is often induced by oncogene activation, may serve as an important signal in activating NKG2D-mediated immune reactions.

Mouse and human NKG2D ligands are up-regulated in response to DNA damage, which is constitutively activated in several precancerous and early cancerous lesions, but not in normal tissue (10–16). The DNA damage sensor kinase ataxia telangiectasia and RAD3 related (ATR) and the protein kinase ataxia telangiectasia, mutated (ATM) are activated in presence of nuclear DNA damage and initiate a protein kinase cascade including the tumor suppressor p53. The DNA damage response induces cell cycle arrest, DNA repair, or apoptosis if the DNA damage is beyond repair (15–17). Up-regulation of NKG2D ligands in response to DNA damage requires ATM or ATR depending on the nature of the DNA damage (10,13,14). p53 is dispensable for induction of NKG2D ligand expression in response to DNA damage, but p53 was found to induce the expression of ULBP1 and ULPB2. Paradoxically, p53 was also shown to down-regulate *ULBP2* by inducing the expression of microRNAs (miRNAs) that target *ULBP2* transcripts, suggesting a complex regulation of NKG2D ligands by p53 (10,11,18). In addition to p53-induced miRNAs, a group of ubiquitously expressed and interferon (IFN)-γ-inducible cellular miRNAs control MIC protein expression by binding to the 3′ UTR sites of MICA or MICB in various human tissues and in cell lines (19–22). Interestingly, the expression of some miRNAs that target NKG2D ligands is deregulated in tumors (19).

A number of oncogenes were reported to up-regulate the expression of NKG2D ligands. Overexpression of the adenovirus E1A oncogene induces mouse NKG2D ligands and human NKG2D ligands (23). Inhibition of the oncogene BCR/ABL down-regulates MICA and MICB cell surface expression in the K562 chronic myelogenous leukemia cell line (24). Similarly, HER2/HER3 was shown to regulate MICA and MICB in breast cancer cell lines via the phosphoinositide 3-kinase (PI3K)/AKT pathway (25). The DNA damage response was not required for HER2/HER3-induced expression of MIC proteins. We recently found that H-RASV12 up-regulates the expression of *Rae1* by enhancing the activity of the rate-limiting translation initiation factor eIF4E (26). The H-RASV12 effect depended on MAPK and PI3K, but not the DNA damage response. In summary, NKG2D ligand up-regulation was shown for several oncogenes, some of which induce ligand expression via the PI3K pathway. The DNA damage response appears to be dispensable for oncogene-induced expression, although it contributes to the constitutive NKG2D ligand expression in some tumor cell lines (10,27).

Soluble forms of MICA, MICB, ULBP1, ULBP2, and ULBP3 were detected in the supernatant of several cancer cell lines and in the sera of cancer patients. MICA (28,29), MICB (30), and ULBP2 (31) are cleaved by matrix metalloproteases (MMPs) belonging to the 'a disintegrin and metalloproteinase' (ADAM) family, including ADAM10, ADAM17, and MMP14 (31–33). Cleavage of MICA also depends on the membrane-associated disulfide isomerase endoplasmic reticulum protein 5 (ERP5). Shedding of NKG2D ligands was shown to impair NK and T cell-mediated lysis of established tumors (34,35).

Regulation of NKG2D ligands by cellular changes associated with infection

Cells infected with bacteria or viruses up-regulate NKG2D ligands (36–41). A role for Toll-like receptors (TLRs) in the induction of NKG2D ligands in infection was suggested by the up-regulation of RAET1 surface expression in peritoneal macrophages and dendritic cells (DCs) in response to TLR agonists (42–44).

Some of the pathways that regulate the expression of ligands in tumorigenesis may also play a role in virus-induced ligand expression. The HIV-encoded gene *Vpr* induces surface expression of ULBP1 and ULBP2 in an ATR-dependent manner (45–47), and up-regulation of RAE-1 surface expression in cytomegalovirus (CMV) mutant-infected cells requires PI3K activity (48).

Human CMV and other viruses encode miRNAs that specifically target NKG2D ligands for degradation (49–51). The microRNA hcmv-miR-UL112 has been shown to down-regulate MICB expression during viral infection (49). *ULBP3* transcripts are targeted by an identical miRNA present in the genome of the human polyoma viruses BKV and JCV (51).

Cytokines associated with viral infections can differentially regulate NKG2D ligand expression in distinct cell types. In human DCs, IFN-α induces the surface expression of MICA (52), but down-regulates *H60* transcripts in mouse sarcoma cells in a STAT-1-dependent manner (53). IFN-γ was shown to decrease *MICA* and *H60* transcript levels (54), and the transforming growth factor-β (TGF-β) suppresses the transcription of *MICA*, *ULBP2*, and *ULPB4* (55,56). Finally, TNF-α up-regulates NKG2D ligands via nuclear factor-kappaB (NF-κB), and a NF-κB responsive regulatory site was described in the *MICA* promoter (57–59).

Regulation of NKG2D ligands by other cellular changes

Some stimuli that induce NKG2D ligand expression have not directly been linked to tumorigenesis or infection. Heat shock regulates the expression of MIC proteins by inducing the binding of the heat shock transcription factor (HSF1) to heat shock response elements (HSE) in the *MICA* promoter (60,61). Binding sites for Sp-family transcription factors are necessary for optimal induction of NKG2D ligands in response to heat shock (9). No heat shock elements have been described for mouse *NKG2D* ligand genes, but heat shock stabilizes the mouse NKG2D ligand MULT1 by preventing its ubiquitination and degradation (62). MULT1 levels are also stabilized in response to ultraviolet treatment. A subsequent study demonstrated that degradation of MULT1 was mediated by MARCH4 and MARCH9, members of the MARCH family of transmembrane E3 ubiquitin ligases (63).

DNAM-1 ligands

Another activating NK receptor is the DNAX accessory molecule-1 (DNAM-1), also known as CD226. DNAM-1 is a leukocyte adhesion molecule belonging to the immunoglobulin superfamily. The gene encoding *DNAM-1* is located on chromosome 18 in humans and mice (64–66). DNAM-1 is expressed on monocytes, NK cells, $CD8^+$ and $CD4^+$ T cells in humans (64,67). In mice, 25%–50% NK cells express variable levels of DNAM-1 (68). Naïve $CD4^+$ and all $CD8^+$ T cells constitutively express DNAM-1, while NK T cells and $\gamma\delta^+$ T cells express DNAM-1 upon activation (66,68). DNAM-1-mediated cytotoxicity and adhesion of NK cells to target cells depend on their physical and functional interaction with leukocyte function-associated antigen-1 (LFA-1) (69). Experiments using *Dnam-1*-deficient mice and blocking antibodies suggest that DNAM-1 plays an important role for NK and T cell-mediated immune surveillance against tumors expressing DNAM-1 ligands and may be critical for immune surveillance of tumors lacking NKG2D ligands or tumors that are considered poorly immunogenic (70–75).

Ligands for DNAM-1 comprise the immunoglobulin superfamily members CD112 (Nectin-2) and CD155 (also known as poliovirus receptor, Necl-5, Tage4) (66,74,76–79). Alternative

splicing of *CD155* transcripts can result in two different membrane-bound forms and two soluble forms of CD155 (77).

Regulation of DNAM-1 ligands by cellular changes associated with tumorigenesis

Cd112 and *Cd155* mRNAs are expressed in many tissues at low levels (77,80). Both ligands are highly expressed on the cell surface of a number of tumor cell lines, especially those of epithelial or neuronal origin. DNAM-1 ligands are also up-regulated in primary acute myeloid leukemias, multiple myelomas, ovarian carcinomas, and melanomas (73–75,81,82). In addition, CD112 and CD155 can be expressed by monocytes, DCs, and activated $CD4^+$ T lymphocytes (83,84).

The transcription factor activator protein AP-1 was found to regulate mouse *Cd155* expression in response to the stimulation of the RAS-MAPK pathway by growth factors (85). No AP-1 binding sites are present in the core promoter of human *CD155*. The promoter region of murine *Cd112* contains AP-1 and AP-2 binding sites, suggesting that AP-1 may regulate the expression of murine *Cd112* and *Cd155* (86). AP-2 binding sites are also present in the promoter of human *CD155* and may drive CD155 expression during embryogenesis (87).

Human *CD155* mRNA levels are up-regulated by sonic hedgehog (SHH)-induced expression of GLI1 and GLI3, which may contribute to oncogenesis of neuroectodermal and cutaneous cancers (88,89).

Similar to NKG2D ligands, CD112 and CD155 levels are increased by DNA damage-induced activation of ATM and ATR (14). Transcript levels of *CD112* and *CD155* are also induced by oxidative stress and the subsequent activation of the DNA damage response (90–92). A more direct regulation of human *CD155* transcript levels by oxidative stress was suggested by the presence of binding sites for the nuclear respiratory factor-1 (NRF-1), an oxidant-sensitive transcription factor that binds DNA in response to reactive oxygen species, in the core promoter region of the human *CD155* gene (87,93,94).

Regulation of DNAM-1 ligands by cellular changes associated with infection

CD112 and CD155 are up-regulated on antigen-presenting cells (APCs) in response to different TLR agonists (83). We found that up-regulation of CD155 in response to TLR agonists on APCs depends on the TLR downstream mediators myeloid differentiation primary response gene 88 (MYD88), TIR-domain-containing adapter-inducing interferon-β (TRIF), and NF-κB (95). In addition, CD155 expression was modulated by interferon-responsive factor 3 (IRF3) in response to TLR agonists that activate TRIF (95,96). Preliminary analysis of the *Cd155* promoter indicates potential NF-κB and IRF transcription factor binding sites in close proximity to the transcriptional start site of murine *Cd155* (N. Kamran and S. Gasser, unpublished observation).

The expression of CD112 and CD155 is also induced by viral infections (97). When Epstein–Barr virus (EBV)-infected B cells switch from the latent to the lytic stage, they increase the expression of CD112 and ULBP1 rendering the lytic B cells susceptible to NK cell-mediated lysis (97). Moreover, CD155 expression is up-regulated in human monocyte-derived DCs upon CMV infection (98), but the role of TLRs in virus-induced expression of DNAM-1 ligands has not been addressed. Our data suggest that TLR agonists do not induce CD112 expression on APCs (95).

Regulation of DNAM-1 ligands by other cellular changes

Heat shock-mediated expression of DNAM-1 ligands has not been described. One study showing up-regulation of NKG2D ligands following activation of the heat shock response found no induction of CD155 (61).

ICAM-1

Intercellular adhesion molecule-1 (ICAM-1, CD54) is a member of the immunoglobulin gene superfamily. It is a type I transmembrane protein that also exists in a soluble form (sICAM-1) (99). ICAM-1 is expressed at low levels by several cell types including endothelial cells, fibroblasts, epithelial cells, keratinocytes, and leukocytes (100). It mediates cell–cell interactions by binding to the integrins LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) on leukocytes (101–103). Binding of ICAM-1 to its receptors is important for facilitating extravasation of leukocytes. ICAM-1 also acts as a co-stimulatory molecule for $CD4^+$ and $CD8^+$ T cell activation (104–106). Overexpression of *ICAM-1* in *Drosophila* insect cells is sufficient for the polarization of cytotoxic granules in human NK cells towards ICAM-1 (107). The polarization is mediated via LFA-1 and constitutes an early signal for NK cell activation.

Regulation of ICAM-1 by cellular changes associated with tumorigenesis

Senescent cells and many cancer cell types up-regulate ICAM-1 expression (108–112). Furthermore, soluble forms of ICAM-1 are often elevated in the plasma of cancer patients (113,114). Blocking studies suggest that ICAM-1 plays an important role in cancer metastasis (115–117). Up-regulation of ICAM-1 in senescent human cells and in response to genotoxic stress depends on p53 (118,119). p53 directly regulates *ICAM-1* expression by binding to p53 response elements present in the introns of the *ICAM-1* gene (see reference (120) for a comprehensive review of the regulation of ICAM-1 by p53).

ICAM-1 expression is induced by a variety of extracellular stresses including oxidation and radiation (121). These stress responses are primarily mediated by reactive oxygen and nitrogen species and the ensuing binding of NF-κB to the promoter of *ICAM-1*, but they also depend on other transcription factors including AP-1/2, E-twenty six (Ets), and signal transducer and activator of transcription 3 (STAT3) (121,122).

Regulation of ICAM-1 by cellular changes associated with infection

ICAM-1 expression is induced by viral and bacterial infections (123–127). Direct induction of ICAM-1 expression has been shown for the hepatitis B X protein and the human T-lymphotropic virus Type I Tax protein, which transactivate the ICAM-1 promoter (128,129). Respiratory syncytial virus and bacterial infections appear to induce *ICAM-1* transcription through NF-κB, possibly by inducing an inflammatory response (123,130). A number of inflammatory mediators, including IL-1, TNF-α, IFN-γ, retinoic acid, and oxidative stress induce ICAM-1 expression (99,131–133). Many of these factors activate protein kinase C (PKC) and NF-κB (134–137). They often synergistically co-operate to activate *ICAM-1* transcription. IFN-γ induces *ICAM-1* transcription via Janus kinase (JAK) and STAT signal transduction pathway (129,138,139). Anti-inflammatory cytokines such as IL-10 and TGF-β can impair ICAM-1 expression by inhibiting the activation of transcription factors required for its transcription (139–143).

NKp30 ligands

Human NKp30 (natural cytotoxicity receptor (NCR) 3, CD337) contains an Ig-like domain and associates with CD3ζ (144). It displays only limited sequence homology to NKp44 and NKp46.

NKp30 is expressed on resting and IL-2-activated NK cells. Lysis of some tumor cells critically depends on NKp30, and the expression of NKp30 isoforms predicts clinical outcome of patients with gastrointestinal stromal tumors (145,146). In mice, NKp30 is a non-functional pseudogene in most strains with the exception of the wild mouse strain *Mus caroli* (147).

Regulation of NKp30 ligands by cellular changes associated with tumorigenesis

B7-H6 was recently identified as an NKp30 ligand (148). B7-H6 expression is not detected in normal human tissues, but is expressed in several human tumor cell lines and primary leukemias and lymphomas. Various conditions of cellular stress such as heat shock, genotoxic stress, or inhibition of proteasomal degradation (MG-132 treatment) fail to induce cell surface expression of B7-H6. No functional *B7-H6* gene has been identified in mice.

The nuclear factor HLA-B-associated transcript 3 (BAT3, BAG6) was shown to be another NKp30 ligand that is present in humans and mice (149). Nuclear BAT3 is important for p300-mediated p53 acetylation and also interacts with B cell lymphoma 2 (BCL-2) (150,151). BAT3 is secreted and expressed at the cell surface of tumor cells in response to heat shock and triggers NK cell cytotoxicity (149,152). The mechanisms leading to secretion of BAT3 will require further research as BAT3 contains a C-terminal nuclear localization signal, but lacks a putative secretory leader peptide.

Regulation of NKp30 ligands by cellular changes associated with infection

BAT3 is an IFN-γ-inducible gene. It was shown to be expressed on the membrane of exosomes released from immature DCs and macrophages (150,153,154).

NKp30 binds pp65 of human CMV, which is released by CMV upon entry into cells. This interaction results in the dissociation of the CD3ζ subunit from the NKp30-ζ receptor complex, resulting in the inhibition of NKp30 signaling (155).

NKp44 ligands

NKp44, also known as NCR2 or CD336, is a receptor that is exclusively expressed on the surface of activated NK cells and a subset of γ/δ^+ T cells in humans. It is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily containing a single extracellular V-type domain and associates with the signal transducing molecule killer activating receptor-associated polypeptide (KARAP)/DAP12 (156). Engagement of NKp44 can stimulate both cytotoxicity and cytokine production, in particular IFN-γ (156,157).

Regulation of NKp44 ligands by cellular changes associated with tumorigenesis

Blocking experiments using monoclonal antibodies suggest that NKp44 mediates NK recognition of various tumor cell lines (157). The putative ligand(s) for NKp44 on tumor cells has not been identified. Heparan sulfate (HS)/heparin-type structures with differential specificities may contribute to recognition of some cancer cells by NKp44 (158,159). Another study suggested that the proliferating cell nuclear antigen (PCNA), a gene involved in many aspects of tumorigenesis, is a potential ligand for NKp44 (152). Similar to BAT3, PCNA does not contain a signal peptide and it is possible that PCNA is exported by non-classical protein secretion pathways (160). Paradoxically, PCNA inhibits lysis and IFN-γ secretion by NK cells that depends on an ITIM motif in the NKp44 cytoplasmic domain (152).

Regulation of NKp44 ligands by cellular changes associated with infection

NKp44 was shown to bind bacterial and viral proteins including mycobacteria family members, the envelope protein of flavivirus, hemagglutinin, and hemagglutinin-neuraminidase of different viruses (161–164). In addition, NKp44 may recognize virus-induced ligand(s). Vieillard et al. provided evidence that the 3S motif of HIV-1 envelope protein gp41 triggers NK cell-mediated lysis of infected $CD4^+$ T cells by inducing the expression of a putative cellular ligand of NKp44 (165,166). Some viruses including Kaposi's sarcoma-associated herpesvirus and HIV have developed mechanisms to escape NKp44-mediated recognition (167,168).

NKp46 ligands

Another immunoglobulin superfamily member of the natural cytotoxicity receptors is NKp46 (NCR1, CD335), which is specifically expressed on all human and mouse NK cells. Upon cross-linking of NKp46, NK cells secrete cytokines and show enhanced cytolytic activity (169–171).

Regulation of NKp46 ligands by cellular changes associated with tumorigenesis

Putative NKp46 ligands were shown to mediate NKp46-dependent recognition of tumor cells (172). Cell surface heparan sulfate proteoglycans present on the membrane of some tumor cells were suggested as potential ligands of NKp46.

Regulation of NKp46 ligands by cellular changes associated with infection

Similar to NKp44, NKp46 was found to directly interact with influenza, vaccinia, and ectromelia virus hemagglutinin and hemagglutinin-neuraminidases of sendai and Newcastle disease virus (163,173,174). Vimentin expressed on *Mycobacterium tuberculosis*-infected human monocytes was implicated in binding to NKp46 (175). In addition, NKp46 is involved in the recognition of Plasmodium falciparum erythrocyte membrane protein-1 (PfEMP-1) expressed on parasitized erythrocytes (176).

NKp65 ligand

NKp65 is a novel NK-activating receptor that has recently been described (177). It is a close relative of NKp80 and is encoded by the *KLRF2* gene in the human natural killer gene complex. NKp65 is a C-type lectin-like type II transmembrane glycoprotein of 32 kDa, but forms non-disulfide-linked homodimers. NKp65 is a high-affinity receptor for keratinocyte-associated C-type lectin (KACL), which is encoded by the gene *CLEC2A* located a few thousand base pairs away from the *KLRF2* gene. KACL is expressed exclusively by human keratinocytes and exists as a 32-kDa glycoprotein with three predicted N-glycosylation sites. Like NKp65, KACL also forms non-disulfide-linked homodimers. Engagement of KACL to NKp65 was shown to stimulate NK cytotoxicity. Human peripheral blood NK cells express only low levels of *NKp65* transcripts. It is possible that NKp65 is specifically expressed by a subset of skin-associated lymphocytes or that its expression is induced in NK cells under particular circumstances. The regulation of KACL expression has not been studied.

NKp80 ligand

NKp80 is expressed by all human NK cells and by a subset of T cells characterized by the expression of the CD56 surface antigen (178). No murine NKp80 homologue has been identified. NKp80 contains an atypical hemi-ITAM that binds the SYK kinase to trigger cellular cytotoxicity (179). The cellular ligand of NKp80

is the activation-induced C-type lectin (AICL) (180). The *NKp80* and *AICL* genes are found in close proximity in the NK cell gene complex on chromosome 12.

Regulation of NKp80 ligands by cellular changes associated with tumorigenesis

In transformed cells, AICL is expressed on both hematopoietic and non-hematopoietic cells, but the signals leading to the induction of AICL are unknown (181).

Regulation of NKp80 ligands by cellular changes associated with infection

AICL is specifically expressed in myeloid cells. It is up-regulated in response to TLR stimulation and down-regulated during differentiation of monocytes to immature DCs (180). The Kaposi's sarcoma-associated herpesvirus (KSHV) immune evasion gene, K5, was shown to reduce the surface expression of AICL (182). Blocking studies indicate that phytohemagglutinin-induced

Table I. Inducers of self-ligands for activating immune receptors.

Receptor	Ligand	Inducer	Cell type	Pathway	Ref.
NKG2D	RAE1	Mitogens	Fibroblasts	E2F1-3	(7)
		DNA damage	Fibroblasts, endothelial cells, T cells	ATM, ATR, CHK1	(10,13)
		TLR agonists	Peritoneal macrophages	MYD88 (LPS)	(42)
		MCMV	Fibroblasts	PI3K	(48)
		RA	F9		(189,190)
	H60	Wounding	C57BL/6 skin		(191)
	MULT1	Heat shock, UV	Fibroblasts	MARCH4, 9	(62,63)
	MICA	Mitogens	Fibroblasts, HeLa		(9)
		DNA damage	Various cell lines	ATM, ATR	(10)
		Heat shock	Epithelial cells	HSF	(60)
		TNF-α	Epithelial cell lines, normal skin explants	NF-κB, JNK	(59)
		IFN-α	DCs		(52)
	MICB	Mitogens	Fibroblasts, HeLa		(9)
		DNA damage	HepG2, HEK293T	ATM	(192)
		Heat shock	Epithelial cells	HSF	(60)
		TNF-α	Epithelial cell lines, normal skin explants	NF-κB, JNK	(59)
	ULBP1	DNA damage	Various cell lines	ATM, ATR, p53	(10,193)
		EBV	Lytic AKBM cells		(97)
		HIV VPR	T cells	ATR	(45)
		APOBEC3	T cells	ATM, CHK2	(46)
		LPS, RSV	mDCs		(44)
		TNF-α	Epithelial cell lines, normal skin explants	NF-κB, JNK	(59)
	ULBP2	DNA damage	Various cell lines	ATM, ATR, p53	(10,193)
		HIV VPR	T cells	ATR	(45,47)
		LPS, Poly I:C	DCs		(44)
		TNF-α	Epithelial cell lines, normal skin explants	NF-κB, JNK	(59)
	ULBP3	DNA damage	Various cell lines	ATM, ATR	(10)
		TNF-α	Epithelial cell lines, normal skin explants	NF-κB, JNK	(59)
	ULBP4-6				
DNAM-1	CD112	DNA damage	MM cells	ATM/ATR	(14)
		ROS	T cells		(90,92)
		TLR agonists	Macrophages, DCs		(83)
		EBV	Lytic AKBM cells		(97)
	CD155	GF, KRASV12	NIH/3T3 cells	RAF, MEK, ERK, AP-1	(85)
		DNA damage	MM cells	ATM, ATR	(14)
		ROS	T cells		(90)
		TLR agonists	Macrophages, DCs	MYD88, TRIF, NF-κB, IRF3	(83,95)
		HCMV	DCs		(98)
		SHH	Ntera2	GLI1-3	(89)
LFA-1	ICAM-1	DNA damage, Senescence	SAOS-2, fibroblasts	p53	(118,119)
		ROS, RNS	Various cell lines	NF-κB, AP-1/2, ETS, STAT	(121)
		RA	Breast and thyroid cancer cell, Cos-1	RAR-β/RXR-α	(194)
		IL-1, TNF-α	Various cells	NF-κB, PKC, MAPK	(134–137,195)
		IFN-γ, IL-6	Various cell lines	JAK/STAT	(139,196–199)
		HBV X protein, HTLV-1 Tax	MT-2, MoT, C8166, HepG2, HuH-7, Hep3B		(126,128)
NKp30	BAT3	Heat shock	Tumor cells		(149)
		IFN-γ	Various cell lines		(150,153,154)
	B7-H6	Transformation	Tumor cells		(148)
	pp65	CMV	Fibroblasts, BW cells		(155)
NKp44		Infection	Various cell lines		(148,161–164)
	PCNA	Transformation	Various cell lines		(152)
NKp46		Transformation	Various cell lines		(172)
		Mtb Vimentin	Monocytes		(175)
		Viral proteins	Various cell lines		(163,173,174)
NKp80	AICL	TLR agonists	Myeloid cells		(180)
		Transformation	Myeloid cells		(180)

CMV = cytomegalovirus; DC = dendritic cell; EBV = Epstein–Barr virus; GF = growth factor; HBV = hepatitis B virus; HSF = heat shock factor; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; IFN = interferon; IL = interleukin; LPS = lipopolysaccharide; MM = multiple myeloma; Mtb = *Mycobacterium tuberculosis*; RA = retinoic acid; RAR = retinoic acid receptor; RNS = reactive nitrogen species; ROS = reactive oxygen species; RSV = respiratory syncytial virus; RXR = retinoid X receptor; TLR = Toll-like receptor; TNF = tumor necrosis factor; UV = ultraviolet.

T cell blasts express other NKp80 ligand(s) than AICL that await identification (178,180).

Synthesis

Numerous signals and pathways regulate the expression of self-ligands for activating NK cell receptors (Table I). Some signals are activated by processes, such as proliferation, that occur in normal cells, but may pose a potential threat to multicellular organisms. Others signals appear to be associated with direct threats to the organism such as infections and cancer. It is possible that changes that are not immediately threatening the survival of an organism, such as mitogen-induced proliferation, are not sufficient to render cells susceptible to NK cell recognition and require additional changes in cells to take place. Consistent with this possibility, it was shown that mitogen-induced signals induce transcription of *Raet1* genes by activating E2F transcription factors, but only transiently activate the DNA damage response (7). In contrast, aberrant proliferative signals of oncogenes induce E2Fs, the collapse of replication forks, and DNA breaks, resulting in the constitutive activation of the DNA damage response and the stabilization of Rae1 transcripts (7,15,16,183). Such a mechanism would allow the immune system to distinguish the proliferation of normal cells from the excessive proliferation of cancer cells and protect normal cells against recognition by NK cells while at the same time preparing proliferating normal cells for recognition in case control is lost.

The available data also suggest that fail-safe mechanisms are built into the regulation of ligand expression. Inappropriate proliferative signals of oncogenes activate the DNA damage response, which induces cell cycle arrest or apoptosis (183). It was suggested that tumor progression therefore requires the loss of DNA damage checkpoints to allow tumor outgrowth (184). The loss of DNA damage checkpoints would impair the ability of tumor cells to up-regulate ligands for NKG2D, DNAM-1, and LFA-1 in response to danger posed by DNA damage. However, tumor cells that lack functional p53, an important DNA damage checkpoint protein, were found to depend on HSF1, which is up-regulated in several cancer cell lines (185–187). Overexpression of HSF1 induces the expression of MIC proteins, which may therefore at least partially restore the ability of NK cells to recognize tumor cells that are deficient in p53.

Do different threats induce specific ligands? The current data suggest that different threats such as DNA damage induce the expression of ligands for several, but not necessarily all, activating receptors (Table I). However, it is possible that some ligands respond to a particular stress. Consistent with this possibility, ULBP3 appears to be mainly regulated by DNA damage.

Why do different ligand systems exist for NK cell-activating receptors? In the case of NKG2D, the best-characterized activating receptor, the current data suggest that ligands differ in their affinities for NKG2D, tissue expression pattern, and expression levels. The differences likely reflect various degrees of regulation of ligands by different stress pathways and threats. This complex regulation may enable NKG2D, to initiate stress or threat-specific responses. The diversity of ligands for NK cell-activating receptors could also be driven by evolutionary pressure exerted by loss of specific stress signals in some diseases and infections. Certain pathogens and tumor cells were shown to impair recognition of cells by inhibiting the expression of particular ligands. It is also possible that a number of ligands or a specific combination of ligands need to be expressed on cells for efficient recognition, thereby providing a safeguard against lysis of normal cells that accidently up-regulate ligands. Finally, ligands may bind to additional receptors with different functions. Consistent with such as conclusion, RAE-1 expression was reported to be important for cell proliferation in neural cell (188). In summary, the diversity of ligands and their complex regulation may ensure that 'diseased' cells are recognized by the immune system, thereby providing an advantage to the survival of the organism. Qualitative and quantitative differences in the expression of self-ligands may also define the threat level posed by diseased cells and initiate the appropriate immune response. Future investigations that focus on the regulation of ligand expression will provide a better understanding of the role of activating receptors in immunity and disease.

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