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Transcription Regulation and Epigenetic Control of Expression of Natural Killer Cell Receptors and Their Ligands

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1. Introduction

Throughout the life of an individual organism, a successful host defense relies on the coordination of innate and adaptive immunity (McQueen and Parham, 2002). Natural killer (NK) cells are characteristic cytolytic cells that are integral components of innate immunity and play a major role both in the direct destruction of infected or transformed cells and in the production of cytokines and chemokines that mediate inflammatory responses and exert a regulatory effect on the adaptive immune responses (McQueen and Parham, 2002; Moretta et al., 2006). Cells become susceptible to NK cell-mediated killing following downregulation of cell surface MHC class I expression after virus infection, which ultimately leads to escape from the MHC-restricted adaptive immune system; a phenomenon also seen in metastasized tumor cells. MHC class I-specific NK receptors (NKR) have acquired the ability to detect immune escape variants and in rodents and primates can be grouped into two distinct classes of MHC class I-specific receptor families based on protein structure: the C-type lectin superfamily (Cl-SF) and the immunoglobulin superfamily (Ig-SF). Humans possess a large family of killer cell immunoglobulin-like receptors (KIR) that belong to the Ig superfamily, whereas mice express lectin-like Ly49 receptors that are now not present in humans, except for a single nonfunctional gene fragment (Lanier, 1998, 2001; Vilches and Parham, 2002; Takei et al., 2001). A third family of NKR, the lectin-like CD94/NKG2 heterodimers, are structurally and functionally conserved between rodents and primates and interact with their ligands: nonclassical MHC class I molecules and some specific ligands that are differentially expressed in different tissues in response to different stresses (McQueen and Parham, 2002; Moretta et al., 2006; Raulet et al., 2001; Uhrberg et al., 1997; Valiante et al., 1997). The actions of NK cells, therefore, are thought to be mediated by the complex interactions between inhibitory and activating signals sent by cell-surface receptors following ligation (Lanier, 2005; Ravetch and Lanier, 2000).

Malignant cells in tumor growth frequently demonstrate alterations in MHC class I expression that play a major role in their ability to escape immune recognition and killing (Dunn et al., 2002; Campoli et al., 2005). NK cells enhance their cytotoxic function and immune regulation by using their stimulatory and inhibitory receptors to maintain the constant balance in the immune system (Chang and Ferrone, 2006). There are major

questions, however, regarding the molecular mechanisms that govern the shape of the NK-cell receptors and MHC class I molecules or other ligands that exhibit an exceptionally high degree of genetic polymorphism in a clonally distributed fashion. Studies, therefore, that focus on the molecular mechanisms that govern the expression of NK-cell receptors and their ligands may provide improved strategies of active-specific immunotherapy for the treatment of cancer, infection and other diseases (Campoli and Ferrone, 2008; Krukowski et al., 2011; Gao et al., 2009). Some stimulators, including viruses, tumor cells and heat shock, could promote the expression of NK-cell receptors and their ligands via activation of certain transcription factors that are capable of regulating activity of NKG2 promoters. Epigenetic mechanisms, including DNA methylation and histone posttranslational modification, are also critical for expression of NK-cell receptors and their ligands, and may control the clonal distribution of some NK-cell receptors. These effects may influence the performance of NK-cell functions. In this review, we will discuss the recent advances in transcriptional regulation and epigenetic control of the expression of NK-cell receptors and their ligands (and of KIR and NKG2 receptor families in particular).

2. Regulation of gene expression – An introduction in the transcriptional level

Mechanisms that underlie the control of gene expression, which drives the processes of gene morphogenesis and distribution, are complex. Transcription regulation at every step of the process is subject to dynamic regulation in the cell (Beckett, 2009; Pan et al., 2010). This regulation includes structural changes in the chromatin to make a particular gene accessible for transcription, transcription of DNA into RNA, splicing of RNA into mRNA, editing and other covalent modifications of the mRNA, translation of mRNA into protein, and, finally, posttranslational modification of the protein into its mature functional form. Information on molecular details of each of these regulatory steps is becoming increasingly available (Fry and Peterson, 2002; Mitchell and Tjian, 1989).

2.1 Transcriptional factor regulation

Regulation at the transcriptional level is a critical mechanism of controlling gene expression. Transcription is controlled by trans-acting factors that regulate spatiotemporal gene expression by associating with cis-acting elements such as promoters, enhancers, and other regulatory regions. Transcription factors perform this function either alone or with other proteins in a complex and by promoting or blocking the transcription of genetic information from DNA to RNA (Mitchell and Tjian, 1989; Alexander and Beggs, 2010; Brivanlou and Darnell, 2002; Karin, 1990). A defining feature of transcription factors is that they contain one or more DNA-binding domains (DBDs), which attach to specific DNA sequences adjacent to the genes that they regulate. In eukaryotes, an important class of transcription factors, called general transcription factors (GTFs), is necessary for transcription to occur. Many of these GTFs do not actually bind to DNA but are parts of the large transcription preinitiation complex that interact directly with RNA polymerase. The most common GTFs are transcription factor II members (TFIIA/B/D/E/F and TFIIH). There are also some nonclassical transcription factors that play crucial roles in gene regulation, including coactivators, chromatin remodelers, histone acetylases, deacetylases, kinases, and methylases, which lack DNA-binding domains (Brivanlou and Darnell, 2002; Karin, 1990; Dowell, 2010; van Nimwegen, 2003).

2.2 Epigenetic control

Transcription is also controlled by epigenetic regulation that is defined as gene-regulation activity that does not involve changes in the underlying DNA code and includes DNA methylation and a variety of histone protein posttranslational modifications (Feng et al., 2010; Furumatsu and Ozaki, 2010). DNA methylation usually occurs in CpG islands, CG-rich regions that are "upstream" of the promoter region. The letter "p" here signifies that C and G are connected by a phosphodiester bond. In humans, DNA methylation is carried out by a group of enzymes called DNA methyltransferases. These enzymes not only determine DNA methylation patterns during early development, but are also responsible for copying these patterns to the strands generated from DNA replication. DNA methylation can alter condensed chromatin structure by influencing histone–DNA and histone–histone contact. Methylation of the promoter and 5′ region of the gene and methylation of histone are associated with transcriptional silencing (Bird, 2002; Bird and Wolffe, 1999; Law and Jacobsen, 2010).

Acetylation and methylation of histones are the most general and important histone modifications associated with transcriptional activation. Histone acetylation is catalysed by histone acetyl transferases (HATs), whereas the reverse reaction is performed by histone deacetylases (HDACs) (Furumatsu and Ozaki, 2010). HATs and HDACs are classified into many families that are often conserved throughout evolution from yeast to humans. Histone H3 is primarily acetylated at several lysine residues, Lys9, 14, 18, 23, 27 and 56, whereas histone H4 is acetylated at Lys5, 8, 12 and 16 (Su et al., 2004). Interestingly, methylation is often modified at lysine and arginine residues in histones H3 and H4. It has been suggested that these modifications constitute a "histone code"; the "code" hypothesis speculates that this modification pattern is read by proteins that recognize distinct modifications specifically and then regulate chromatin dynamics and genome function (Wang et al., 2004; Kisliouk et al., 2010). Whether these modifications form a true code is still under discussion. The processes of histone modification and DNA methylation can both influence each other. Moreover, DNA methylation and suppressive histone modifications may prevent transcription, even when transcription factors are abundant. In turn, transcription factors may cause alterations in DNA methylation and histone modifications (Furumatsu and Ozaki, 2010; Fernandez-Morera et al., 2010; Strahl and Allis, 2000). Molecular details of the transcriptional regulators involved in expression of many NK-cell receptors and their ligands are becoming increasingly available, especially for the NKG2 and KIR receptor families and their ligands.

3. Transcription factor regulation and epigenetic control of the expression of NK-cell receptors and their ligands

3.1 NKG2 receptor family

In humans, the NKG2 receptor family comprises seven members called NKG2A, NKG2B, NKG2C, NKG2D, NKG2E, NKG2F and NKG2H; NKG2A/B and NKG2E/H pairs are splice variants of the same gene (Brostjan et al., 2000; Glienke et al., 1998). All members of the NKG2 family, except NKG2D, share substantial sequence homology, are closely linked, and of the same transcriptional orientation; they contain conserved sequences at the transcriptional start site and at other transcription factor-binding sites, such as the TCF-1 (testosterone conversion factor-1) and GATA-1 (GATA-binding factor 1) sites. These

members of the NKG2 family form disulfide-linked heterodimers with CD94. Each member of the NKG2 family, however, has a unique repeat Alu sequence that functions as a gene promoter. Alu repeats are the putative binding sites for several transcription factors: activator protein-1/3 (AP-1/3), cAMP response element binding/activating transcription factors (CREB/ATF), CCAAT/enhancer binding protein (C/EBP), transcription factor-1 (Sp1), nuclear factor-1/CCAAT transcription factor (NF-1/CTF) and lymphocyte-specific DNA-binding protein-1 (LyF-1), and may contribute to differences in gene regulation among family members (Brostjan et al., 2000; Glienke et al., 1998). The CD94 protein associates with different NKG2 isoforms to form heterodimeric receptors that function either to inhibit or to trigger cytotoxicity of NK cells, depending on the NKG2 isoform. Functionally, therefore, CD94/NKG2 heterodimers are divided into activating (NKG2C, NKG2E/H) or inhibitory (NKG2A/B) isotypes (Glienke et al., 1998). It has also been shown that several cytokines, including interleukin (IL)-12 (Derre et al., 2002), transforming growth factor (TGF)-β (Bertone et al., 1999), IL-15 (Mingari et al., 1998) and IL-10 (Romero et al., 2001), are capable of inducing expression of CD94/NKG2 in human NK or T cells, in which IL-15 and TGF-β can upregulate CD94/NKG2A, but not other CD94/NKG2 receptors (Wilhelm et al., 2003). NKG2D is a special activating receptor that is not covalently associated with CD94. NKG2D is downmodulated by TGF-β, but markedly upregulated by IL-15, interferon (IFN)-α and IL-12 stimulation in primary NK cells (Dasgupta et al., 2005). IFN-α can stimulate the expression of NKG2D, but inhibits the expression of the inhibitory receptor NKG2A, and therefore alters the balance of stimulatory and inhibitory receptors in favor of activation, leading to NK-cell-mediated cytotoxicity. IFN-γ addition exerts the opposite effect (Zhang et al., 2005).

CD94 is a C-type lectin and is required for the dimerization of the CD94/NKG2 family of receptors, which are expressed on NK cells and T-cell subsets. The CD94 and NKG2 genes are located in the center of the NK-gene complex between the NKRP1 and PRB3 loci in the region containing the STS markers D12S77 and D12S1093. All six genes are closely linked and are situated 100 to 200 kb proximal to the D12S77 STS marker (Sobanov et al., 1999). The CD94 gene is placed in the opposite orientation relative to the NKG2 gene family members (which all have the same transcriptional orientation). CD94 gene expression is regulated by distal and proximal promoters that transcribe unique initial exons specific for each promoter. Both promoters contain elements with IFN-γ-activated and E26 transformation-specific (ETS)-binding sites (called GAS and EBS respectively). The two promoters differentially regulate expression of the CD94 gene in response to treatment with IL-2 or IL-15 (Lieto et al., 2003).

3.2 Ligands of NKG2D-MIC

The two types of NKG2D ligands are MHC class I chain-related proteins (MICA and MICB) and UL16-binding proteins (ULBP) (Sutherland et al., 2001; Bauer et al., 1999). MICA and MICB are located in the MHC complex within the 6q21.3 chromosomal region. The ULBP family contains 10 genes, of which five are expressed (ULBP1–5). ULBPs are located outside the MHC gene complex, in the 6q24.2–25.3 region (Samarakoon et al., 2009). These molecules exhibit highly restricted expression in healthy tissues but are widely expressed on epithelial tumors. In hematological malignancies they are upregulated in nontumor and tumor cells by genotoxic stress (Kim et al., 2006; Venkataraman et al., 2007). Aligned cosmid-derived regions 1.5 kb upstream of the translation start codon (ATG) in MICA and MICB share approximately 90% sequence identity. The 5′-end flanking regions of MICA and

MICB contain putative heat shock elements (HSE) that are prototypic transcription inducer sites in heat shock protein-70 (HSP70) genes and that bind activated trimeric heat shock factor protein-1 (HSF1). Cytomegalovirus (CMV) infection results in up to a 10-fold increase in cell surface MIC expression and is associated with induced HSP70 expression. TATA-like elements and Sp1 consensus sites, as with HSE, are located unusually far "upstream" from MIC gene, but can also moderately or profoundly affect stress-induced and proliferation-associated induction. The common integrating conjugative element (ICE), however, appears to be a negative regulator of MICB, but not of MICA. It is an important to note, although the sequences of MICA and MICB promoters are very similar, the baseline transcriptional activity of MICA is higher than that of MICB and they have different regulatory mechanisms for expression. Most MICA transcripts start downstream of the conserved AP-1 TATA-like motif, a region that lacks a recognizable RNA start site. In contrast, most MICB transcripts initiate further upstream, proximal to the HSE–Sp1–ICE elements (Venkataraman et al., 2007). Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) regulates MICA expression on activated T lymphocytes and on HeLa tumor cells by binding to a specific sequence in the long intron 1 region of the MICA gene (Molinero et al., 2004). Histone deacetylase inhibitor (HDAC-I) and sodium valproate (VPA) induced transcription of MICA and MICB in hepatocellular carcinoma cells, leading to increased cell surface, soluble and total MIC protein expression (Armeanu et al., 2005). Similar results have been obtained using histone deacetylase inhibitors FR901228 and SAHA (Skov et al., 2005). In our laboratory, we found that VPA can increase the expression of HSP70 and Sp1 and increase the binding of transcription factors Sp1 and HSF1 to the MICA/B promoter. This activation leads to the upregulation of MICA/B in HeLa and HepG2 tumor cells (Zhang et al., 2009).

3.3 Ligands of NKG2D-ULBPs

All expressed ULBPs (ULBP1–5) have good conservation of the coding sequence, but the 5′-end flanking regions of these genes have little homology. This situation suggests that ULBPs are regulated specifically in response to different stimuli or pathogens (Lopez-Soto et al., 2006). Mechanisms that regulate the expression of ULBP1 have been described previously. In the core region of the ULBP1 promoter, there are many binding sites for transcription factors, including a canonical TATA box, three GC boxes, one overlapping sequence GC(4)/AP-2, two cytokinin response element (CRE)-like sequences (CRE1 and CRE2) (Zeng et al., 1997; Wajapeyee and Somasundaram, 2003), and one NF-κB site. Transcription of ULBP1 depends strictly on binding of Sp1 and Sp3 to a CRE1 site located in the ULBP1 minimal promoter. The mutation or deletion of this Sp1/Sp3 binding site abolished ULBP1 transcription; Sp3 is the main transcription factor that regulates ULBP1 through the CRE1 site. AP-2α, however, repressed the expression of ULBP1 by binding to the GC(4)/AP-2α site and interfering with the binding of Sp3 and Sp1 to the ULBP1 promoter (Lopez-Soto et al., 2006). It has been shown that heat shock and ionizing radiation treatment can induce the expression of ULBP1/2/3 in human cancer cell lines; HSP 70 is induced by heat shock but not by ionizing radiation (Kim et al., 2006). Human cytomegalovirus (HCMV) can also induce the expression of ULBP1/2/3 proteins that are predominantly localized in the endoplasmic reticulum of infected fibroblasts together with UL16 (Rolle et al., 2003). There is interplay, however, between virus and host cells depending on the viral dose. At low viral dose, ULBP1 or ULBP2 surface expression is completely inhibited compared with ULBP3, while at a higher viral doses cell surface expression of ULBP1 and ULBP2 is delayed (Rolle

et al., 2003). Whether this phenomenon is mediated through the ULBP promoter or through transcription factors needs to be investigated further.
Epigenetic modulations are also likely to play a large part in the observed alteration in ULBP expression. Current observations imply that loss of DNA methylation (deficient in DNA methyltransferase cells) is correlated with increased ULBP2 mRNA levels. It has been shown that both demethylation of the ULPB2 promoter, necessary for increased protein levels, and the RAS/MEK signaling pathway, shown to control DNA methylation (Lund et al., 2006), are necessary for maximal protein expression (Sers et al., 2009). In addition, the HDAC inhibitor trichostatin A (TSA) is reported to upregulate ULBP1–3 expression in tumor cells; Sp3 was found to be crucial for activation of the ULBP1 promoter by TSA. One report showed that HDAC3 is recruited to the ULBP1 promoter and acts as a repressor of ULBP expression in epithelial cancer cells. TSA treatment interfered with this interaction and caused the complete release of HDAC3 from the ULBP1–3 promoters (Lopez-Soto et al., 2009).

3.4 KIR receptor family and their ligands

The KIR family is of particular interest because individual members bind to specific subgroups of HLA allele products, such as HLA-A, HLA-B, HLA-C, and HLA-G, although most KIRs show 90–95% amino acid identity. The high level of homology can facilitate exchange of exons between different KIR loci, by some form of crossing over or gene conversion (Wilson et al., 2000). One study found that due to the polymorphism of KIR genes, two KIR haplotypes segregated at roughly equal frequency in a largely Caucasian population. Group A haplotypes contained seven KIR genes and had KIR2DS4 as the only activating receptor. Group B haplotypes had a greater diversity of KIR genes, had more activating receptors, and were characterized by the KIR2DL2, KIR2DS1, KIR2DS2, KIR2DS3, and KIR2DS5 genes (Uhrberg et al., 1997). KIR can also be further subdivided into inhibitory receptors that carry an inhibitory signal motif within their cytoplasmic domain (KIR2DL and KIR3DL) and into stimulatory receptors (KIR2DS and KIR3DS) that lack this motif. Most of the inhibitory KIRs are specific for the products of HLA class I genes like such as HLA-A/-B and HLA-C (Bellon et al., 1999; Colonna et al., 1993; Dohring et al., 1996). The ligand specificities of many stimulatory KIR are uncertain and might include non-HLA class I ligands. KIR2DL4, however, combines structural and functional features of both stimulatory and inhibitory KIR and is reported to bind to the nonclassical class I protein HLA-G (Chan et al., 2003; Martin et al., 2000; Trompeter et al., 2005; Santourlidis et al., 2002). The expression of KIR appears to be largely independent of each other and the impact of the requirement for inhibition by self class I molecules on the shape of the KIR repertoire is rather subtle.

3.4.1 Transcriptional factors regulation of KIR

Different groups of 2–9 KIR genes are expressed in NK clones, but the sequences of the KIR promoters are homogeneous in their 5′-untranslated regions (5′ UTR), except for that of KIR2DL4 (Valiante et al., 1997; Wilson et al., 2000). The sequences of KIR genes comprise a continuous loop that extends seamlessly from gene to gene. The repeat of the loop is broken only by a region 14 kb upstream of the KIR2DL4 locus, which displays some unique features and is characterized by L1 repeats. The sequence upstream of KIR2DL4 may be significant because this gene is unique in this group in being expressed in 100% of NK clones (Valiante

et al., 1997; Wilson et al., 2000; Martin et al., 2000). Moreover, KIR2DL4 is the only KIR gene that lacks the repeat region in intron 1. All KIR genes lack typical promoter features such as TATA and CAAT boxes, so many transcription factor binding sites have been predicted to be present in the upstream regions of KIR, including sites for transcription factors CREB, SP1, ETS, AP-1 and AP-4 (Chan et al., 2003; Santourlidis et al., 2002). None of these elements alone, however, is required for or significantly increases promoter activity, except for a CREB site located outside the core promoter region. To date, the basic KIR promoter appears to either require undefined transcription factors or alternatively only interacts with the basic transcription machinery of RNA polymerase II (Trompeter et al., 2005). It has been suggested previously that a binding site for the transcription factor AML/Runx (Runt Homology Domain Transcription Factors) at –100 bp can be essential for KIR expression (Vilches et al., 2000). However, a further study suggested that AML has a general inhibitory influence on KIR expression in mature NK cells and that AML exerts its repressor function by binding directly to the promoter of the different KIR genes (Trompeter et al., 2005). Recently, it was reported that the transcription factor c-Myc upregulated KIR gene transcription through direct binding to an upstream distal promoter element in peripheral blood NK cells, and that IL-15 promoted this effect (Cichocki et al., 2009). It was suggested that the role of the traditional transcription factors in KIR gene expression is different from that in other genes.

3.4.2 Histone modifications of KIR

It was found that histone H3 and H4 proteins are substantially acetylated at the Lys9 and Lys14 positions and H4 acetylation at the 5th, 8th, 12th, and 16th positions in both KIR3DL1+ and KIR3DL1– NK cells (Chan et al., 2005). The level of KIR3DL1-associated histone acetylation and methylation was higher in KIR3DL1+ NK cells than in KIR3DL1– NK cells; however, histone H3 methylation at Lys4 (H3K4) is only 2.6-fold higher in KIR3DL1+ NK cells than that in KIR3DL1– NK cells, although the histone H3K4 methylation levels correlated well with the KIR3DL1 promoter to lead to upregulation of KIR3DL1 gene expression, named KIR3DL1-associated histone H3K4 methylation. These findings indicate that histone acetylation and trimethylated modifications, but not histone H3 methylation, are preferentially associated with the transcribed allele in NK cells with monoallelic KIR expression (Santourlidis et al., 2002; Chan et al., 2005).

KIR expression is increased on T cells with increasing age, and can contribute to age-related diseases (van Bergen et al., 2004). In these cells, the KIR2DL4 promoter is partially demethylated, and dimethylated H3L4 is increased; all other histone modifications are characteristic of an inactive promoter. In comparison, NK cells have a fully demethylated KIR2DL4 promoter and have the full spectrum of histone modifications indicative of active transcription with H3 and H4 acetylation. These findings suggest that an increased T-cell ability to express KIR2DL4 with age is conferred by a selective increase in H3L4 dimethylation and limited DNA demethylation (van Bergen et al., 2004; Li et al., 2008).

3.4.3 DNA demethylation of KIR

Methylation status of CpG islands in NK cells correlates with transcriptional activity of KIR genes. The overall structure of the CpG islands is similar in all expressed KIR, with complete conservation of four CpG dinucleotides upstream of the transcriptional start site, with the exception of KIR2DL4, which shows a highly divergent profile with lower CpG density. In

addition, CpG islands with <70% of methylated CpGs are exclusively found in the expressed KIR2DL3, whereas CpG islands of nonexpressed KIR2DL3 and KIR3DL2 are consistently methylated at 70–100% of CpG dinucleotides (Santourlidis et al., 2002). Analysis of the methylation status at individual CpG sites demonstrated that differential methylation of expressed versus nonexpressed KIR is not restricted to specific CpGs, but is consistently found throughout the CpG islands. That is to say, the methylated CpG islands are associated with transcriptionally silent KIR and unmethylated CpG islands with expressed KIR genes (Chan et al., 2003; Santourlidis et al., 2002).

In addition, exposure to a DNA methyltransferase inhibitor, 5-aza-2′-deoxycytidine (5azaC), effectively induced the whole range of KIR expression in NK cells (Gao et al., 2009; Chan et al., 2003; Santourlidis et al., 2002; Chan et al., 2005), but not in other cells of lymphoid or nonlymphoid origin. A weak induction of KIR3DL2 following treatment with 5aza-dC was observed in a T-cell line (Li et al., 2008; Santourlidis et al., 2008). These results suggested that repression of KIR gene transcription is dependent on DNA methylation only in NK cells and T cells, and that allele-specific KIR3DL1 gene expression is not only correlated with promoter but also with 5′-gene DNA hypomethylation. Further studies showed that methylation influenced KIR expression both in immature NK cells and in mature NK cells, because KIR promoter-associated CpG islands are indeed DNA-methylated at an early developmental stage (Li et al., 2008; Liu et al., 2009).

3.4.4 A two-step model of epigenetic regulation of KIR

Recent studies suggested that CpG methylation is functionally linked to histone deacetylation, which, in turn, leads to the formation of condensed, transcriptionally repressive chromatin (Bird, 2002; Bird and Wolffe, 1999). Altering the state of histone acetylation using the deacetylase inhibitor TSA did not change transcriptional activity of either expressed or silent KIR genes. Additionally, combined treatment of 5aza-dC and TSA did not lead to a synergistic effect compared with 5aza-dC alone. In particularly, the expression of KIR2DL4, which is expressed by all human NK clones, was not affected by either demethylating or histone-acetylating treatment. This finding indicated that KIR genes in NK cells might have already acquired a state of transcriptionally competent chromatin. Methylation of KIR CpG islands appears to be the priority epigenetic modification required for silencing of specific KIR genes (Santourlidis et al., 2002). In a further study, this point was addressed. Hematopoietic progenitor cell KIR genes exhibited the major hallmarks of epigenetic repression: dense DNA methylation; inaccessibility of chromatin; and a repressive histone signature, characterized by strong H3K9 dimethylation and reduced H4K8 acetylation. In contrast, KIR genes in NK cells showed active histone signatures characterized by absence of H3K9 dimethylation and presence of H4K8 acetylation. In KIR-competent lineages, active histone signatures were also observed in silenced KIR genes and, in this study, were found in combination with dense DNA methylation of the promoter and nearby regions. The study suggested a two-step model of epigenetic regulation in which lineage-specific acquisition of euchromatic histone is a prerequisite for subsequent gene-specific DNA demethylation and expression of KIR genes (Santourlidis et al., 2008).

3.4.5 HLA-ligand of KIR

Recently, epigenetic alterations were shown to play a role in HLA changes associated with malignant transformation of cells (Campoli and Ferrone, 2008). HLA-G, initially discovered

on the fetal–maternal interface, plays a key role in the maintenance of immune tolerance by inhibition of NK cells via the receptor KIR2DL4 (Hofmeister and Weiss, 2003); it is expressed in some surgically removed melanoma lesions, but there is little expression in established cell lines. Treatment of a HLA-G-negative melanoma cell line with 5azaC restored HLA-G expression; similarly 5azaC activated HLA-G expression in human leukemia cell lines, even in malignant hematopoietic cells isolated from patients with acute myeloid leukemia (AML) and chronic lymphocytic leukemia (B-CLL) (Polakova et al., 2009a; Polakova et al., 2009b). Further research found that HLA-G was silenced as a result of CpG hypermethylation within a 5′ regulatory region upstream of the start codon (Moreau et al., 2003; Yan et al., 2005). These results determined that regulation of HLA-G expression also involved epigenetic mechanisms, such as DNA methylation. There was no significant difference in HLA-G expression, however, detected in tumor and normal ovarian surface epithelial cells (OSE) samples, although HLA-G expression was significantly increased after treatment with 5azaC. There was no correlation between methylation and HLA-G gene expression in ovarian tumor samples and OSE, which suggested that changes in methylation may be necessary, but not sufficient, for HLA-G expression in ovarian cancer (Menendez et al., 2008).

In addition, the expression of HLA-A, HLA-B and HLA-C, specific ligands for inhibitory KIR (KIR3DL2, KIR3DL1, and KIR2DL1/3) was lost or downregulated in human gastric cancer, where the percentage of promoter methylation was higher than in adjacent nontumor tissues (Ye et al., 2010). In esophageal squamous cell carcinoma lesions, it was also shown that hypermethylation in the gene promoter regions of the HLA-A, HLA-B and HLA-C, and altered chromatin structure of the HLA class I heavy chain gene promoters have both been implicated as a major mechanism for transcriptional inactivation of HLA genes (Nie et al., 2001). Furthermore, the MAPK (mitogen-activated protein kinases) and DNA methyltransferases were shown to downregulate HLA-A expression (Sers et al., 2009). These findings suggest an association between promoter hypermethylation and the downregulated expression of HLA class I molecules.

4. Regulation expression of NK cell receptors and their ligands as potential therapeutics for cancer

The mechanisms of regulation the gene expression, which requires signalling cascades for transducing and integrating regulatory cues to determine which genes are expressed, are obligatory for tumorigenesis, tumor progression and metastasis (Bhalla, 2005; Samarakoon et al., 2009; Stein et al., 2010). Transcriptional gene regulations, particularly in transcriptional factors and epigenetic level, affect several aspects of tumor cell biology, including cell growth, proliferation, phenotype, differentiation, DNA repair, and cell death. NK cells are the major effector lymphocytes of innate immune system that defend against many forms of viral infections and tumor growth without prior sensitizations, by the interaction of inhibitory and activating receptors with corresponding ligands on the target cells. This raises the strong possibility that regulation expression of NK cell receptors on NK cells and their ligands on tumor cells may be an effective treatment strategy for malignant tumors. This treatment strategy, as mentioned above, including activation and suppression of the transcription factors and promoter activity, modification the DNA methylation in the underlying DNA code, and rearrangement the acetylation and methylation of protein in histone posttranslational level, leads to the induced or suppressed expression of NK cells

receptors and their ligands (Fig. 1), so that the NK cell-mediated immunotherapy can be carried out fully to cure malignancies. So the regulation expression of NK cell receptors and their ligands provides a strategy for targeting gene expression in tumor cells, and may be with minimal offtarget consequences (Villar-Garea and Esteller, 2004; Bhalla, 2005; Szyf, 2005, Stein et al., 2010).

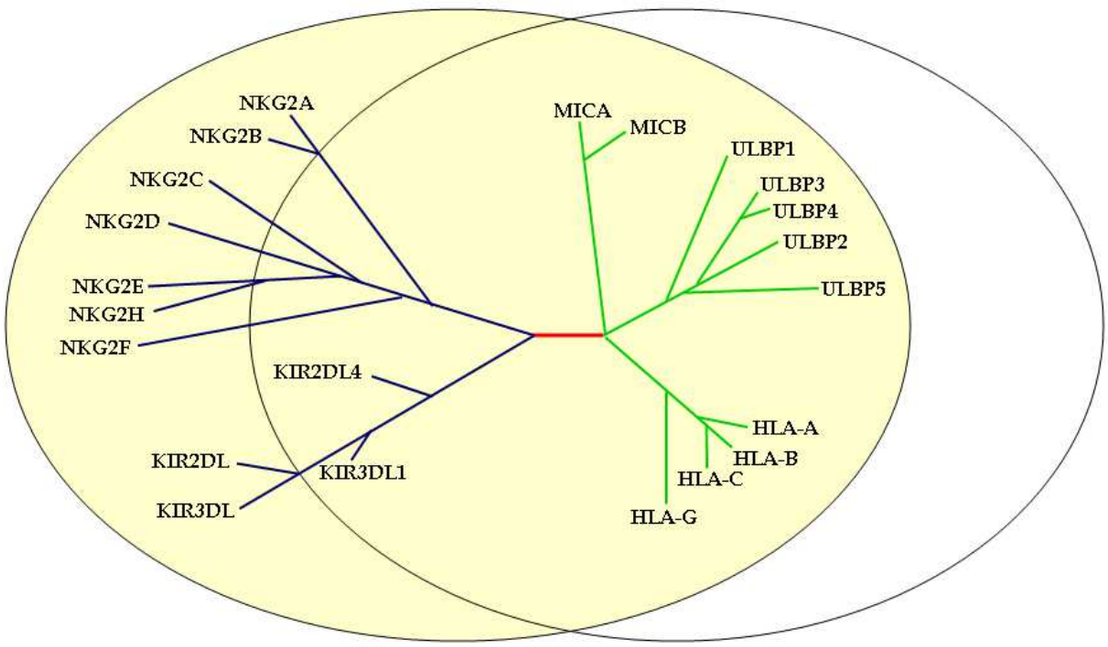

Fig. 1. Transcription regulation and epigenetic control of KIR and NKG2 receptors and their ligands. A dendrogram representing the relatedness of different KIR and NKG2 receptors (blue) and their ligands (green) to each other, and the extent of the sequence relatedness between two genes is shown by the distance of the lines (Raulet, 2003). The left oval shows the gene regulation in transcription factor level, while the right oval shows the gene regulation in epigenetic level, and the overlapping part shows the co-regulation.

5. Concluding remarks

NK cells not only are important players of innate effecter responses, but also participate in the initiation and development of antigen-specific responses through secretion of immunoregulatory cytokines (such as IFN-γ, tumor necrosis factor-α (TNF-α) and granulocyte–macrophage colony-stimulating factor (GM–CSF)) and through cell-to-cell contact (Biron et al., 1999). Regulation of the expression of NK-cell receptors and their ligands refers to the control of the amount, the timing of appearance, and the functional products of these genes, leading to the flexibility of NK cells or other immune cells to adapt to a variable environment, external signals, and damages to target cells (Wu et al., 2005). In particular, the modification of NK-cell receptors and their ligands is a potential therapeutic implication for cancer treatment. Although the regulation mechanism of expression of NK-cell receptors and related ligands has acquired important progress at the transcription level, the regulatory mechanisms of a number of crucial receptors and ligands, for example signaling lymphocytic activating molecule (SLAM)-related receptors (CD150, 2B4, Ly-9,

CD84, and NTB-A) (Sidorenko and Clark, 2003; Engel et al., 2003; Morra et al., 2001), are not well understood. More research is needed into other regulated stages of gene expression, such as posttranscriptional modification, RNA transport, translation, and mRNA degradation. Investigation of the regulatory mechanisms of NK-cell receptors and their ligands might aid in the design of therapy against cancer, infection, inflammation, or autoimmune diseases.

6. Acknowledgment

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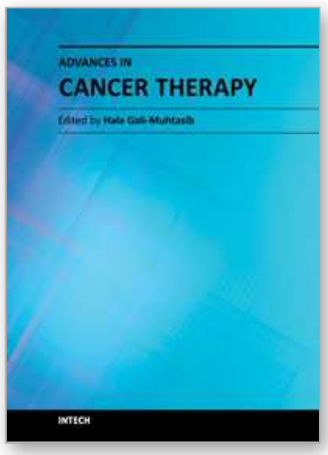

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