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REVIEW

Prostate Cancer and Immunoproteome: Awakening and Reprogramming the Guardian Angels

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Abstract Prostate cancer is a life-threatening molecular disorder that is undruggable to date because of stumbling blocks in the standardization of therapy. An emerging framework of research is addressing how pathways that are derailed during tumorigenesis are linked to immunological responses, which are instrumental in immunosurveillance of cancer. However, interestingly, cancer cells circumvent such immunosurveillance through development of poorly immunogenic tumor cell variants (immunoselection) and through subversion of the immunological nanomachinery (immunosubversion). Detailed mechanistic insights of molecular specificities that regulate natural killer (NK) cell function suggest that it might be promising to design NK cell-based immunotherapeutic interventions against prostate cancer. Here, we elucidate evidence for NK cell targeting of prostate cancer proteome and address critical questions that, in our view, need thoughtfulness for the development of successful NK cell-based therapies. This review also disproves our contemporary understanding of the versatile regulators of DNA damage repair (ATM, ATR) that trigger cell surface expression of NKG2D ligands and consequent elimination of the tumor cells by NK cells and other lymphocytes that express NK cell receptors. Substantial fraction of information has been generated that guarantees productive future for this technology as more optimized constructs, better trial designs, and improved platforms are being brought from benchtop to bedside.

Keywords Prostate cancer · Immunoproteome · DNA damage · Major histocompatibility complex proteins

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Introduction

It is becoming progressively more prominent that communication across intercellular contacts is fundamental in establishing appropriate immunological responses. Keeping in view recent imaging of lymphocyte interactions, it is obvious that a multifaceted orchestration of cell–cell contact is a major determinant of proper immune responses. A complex barcode underlies regulation of activating and inhibitory receptor signals, and the resultant transduction cascade properly fine-tunes the appropriate outcome for individual cell–cell interactions. Recent reports of genetically engineered DNA-based reconstructs have begun to shed light on underpinnings of prostate cancer immunoproteome and to illuminate other puzzles of molecular immunology, including their developmental regulation and homeostatic equilibrium with other leukocytes. Various mediators of the immune system that are localized in tissues are appreciated to eliminate early neoplastic cells, thereby counteracting advanced tumors. This review addresses our current interpretations of the molecular mechanisms that identify cellular stresses that are connected with tumorigenesis and various means to achieve such immune responses. Emerging body of information

indicates recently engineered novel delivery systems that allow the introduction of nucleic acids to the cytosol of immune cells. We also discuss models of delivery of functional recombinant DNA to mammalian antigen-presenting cells, including natural killer (NK) cells and human dendritic cells (DCs).

DNA Vaccines: Well-Equipped Swordsman for the Battlefield

It is important to note that efficient cancer immunotherapy requires the release of wide-ranging tumor antigens in the perspective of potent immune activation. In justification of this opinion, an overview of different documentations unveil the fact that viral vectors can be delivered systemically, without the need for tumor targeting, and are amenable to clinical grade production. In the upcoming section we discuss how these bioengineered entities represent a novel paradigm for cancer treatment and identify many of the intricacies that have undermined the efficacy of immunotherapy to date.

Recently, a DNA vaccine was designed by incorporation of domain of tetanus toxin fused to candidate tumor-derived peptide sequences. Vaccine design triggered high levels of $CD8^+$ T cells in opposition to various peptides and peptide-loaded tumor cells in a HLA-A*0201 preclinical model (Vittes et al. 2011).

While comparing monomeric and multimeric monoclonal antibodies (mAb), emerging evidence suggests that multimeric versions are more potent in inducing apoptosis. Data emerging from various trials have indicated that IgM mAb-mediated apoptosis is dependent on the pentameric structure of the mAbs. Contrarily, disruption of pentameric IgM into monomeric IgM considerably suppressed their ability to induce cell apoptosis because of lesser trafficking of major histocompatibility complex (MHC) class I molecules into lipid rafts (Cao et al. 2011).

Dendritic cells reconstructed for tumor-associated antigen and costimulatory molecule 4-1BBL via replication deficient adenoviruses displayed truncated prostate-specific membrane antigen (tPSMA)-directed T-cell responses in vitro and anti-tumor immunity to RM-1-tPSMA in a murine tumor model. It is clear that development of bioengineered DCs expressing tumor antigens and stimulatory molecules by recombinant adenovirus-mediated gene transfer may present a new strategy for prostate cancer immunotherapy (Kuang et al. 2010). An important exemplar of tumor-targeted costimulation is a bi-specific oligonucleotide aptamer conjugate that can deliver costimulatory ligands to tumor cells. Consistent with the concept, systemic delivery of an agonistic 4-1BB aptamer ligand conjugated to a prostate specific antigen-binding tumor-targeting aptamer led to tumor regression (Pastor et al. 2011). On a similar note, intratumoral injection of macrophage reconstructs (an adenoviral vector carrying Glipr1 gene) into an orthotopic, metastatic mouse model of PCa resulted in cancer regression. These bioengineered macrophages displayed greater surface expression of MHC class II and better production of interleukin 12 (IL-12) and IL-6 (Tabata et al. 2011).

An interesting piece of evidence is that prostate stem cell antigen (PSCA)-based vaccine counteracts prostate cancer development in prostate cancer-prone transgenic adenocarcinoma mouse prostate (TRAMP) mice. Eight-week-old TRAMP mice that developed prostate intraepithelial neoplasia were vaccinated with a gene gun-delivered PSCA-cDNA that resulted in 90 % survival rate at 12 months of age (Garcia-Hernandez Mde et al. 2008).

A series of cell constructs consisting of DNA plasmids encoding human PSCA, human HSP70, and their conjugates were constructed and injected into male mice. The result depicted that mice vaccinated with PSCA-HSP plasmids triggered strongest PSCA-specific $CD8^+$ T cell immunological response (Zhang et al. 2007). Consistent with same concept, recombinant adeno-associated virus (AAV) type 2 vectors are useful for antigen gene-loading of human DCs and for the rapid generation of cytotoxic T lymphocytes (CTL). It was found that AAV-loading of DC with the prostate-specific antigen (PSA) gene is superior to PSA protein loading of the same antigen for generating effective CTL (Mahadevan et al. 2007).

Another exciting piece of evidence is that DCs transduced with the PSA gene can trigger PSA-specific CTL against prostate cancer cells. Moreover, bacillus Calmette-Guérin (BCG) cell-wall skeleton (CWS) stimulated the maturation of DC-PSA and the killing activity of PSA-specific CTL. DC-PSA can modulate PSA-specific $CD8^+$ CTL responses and a combinatorial drug design, consisting of DC-PSA with BCG-CWS might be a positive approach for treating advanced prostate cancer (Fujii et al. 2009).

Another interesting study recently conducted underscored the fact that injection of rAd/six-transmembrane epithelial antigen of prostate (STEAP) alone followed by pulsed DC was sufficient to counteract tumorigenesis. In the study male C57BL/6 mice were immunized first by intravenous injection of recombinant adenoviruses and afterward by subcutaneous injection of DCs pulsed with TRAMP-C1 tumor lysate. The results substantiated the fact that considerable numbers of STEAP-specific CD8 T cells were detected in the peripheral blood and the spleen of immune mice using MHC I tetramers (Kim et al. 2009).

Replication competent oncolytic herpes simplex viruses have wide-ranging implications against prostate cancer. In support of this notion, an IL-12 expressing oncolytic herpes virus was documented to be efficient in retarding

tumorigenesis in the poorly immunogenic TRAMP-C2 mouse prostate tumors (Varghese et al. 2006).

Accumulating evidence suggests that MHC-restricted recombinant antibodies with an equivalent specificity of T cell receptors (TCR) provide efficacy in killing tumor cells. In a set of experimentation using isolated human recombinant Fab antibodies obtained by phage display that have remarkable potential in detection of specific HLA-A2/TARP T cell epitopes on antigen-presenting cells. It therefore provides an effective targeting moiety killing tumor cells (Epel et al. 2008).

Cell Surface Expression of Tumor Markers: Greater the Placards, Better is the Gameplay

It is a well-established fact that carcinogenesis results in suppression of cell surface appearance and enhances shedding of proteins which act as communicator between cells and are involved in attracting much attention of the killer cells (Figs. 1, 2). In the forthcoming section we discuss various strategies to enhance cell surface expression inhibiting the shedding of communicator proteins.

Recent data highlight the important role of hydralazine and valproate to increase the NK activity against epithelial cancer cell lines by enhanced expression and suppression of soluble MHC class I-related molecules A and B (MICA and MICB), respectively. This upregulation occurs at the transcriptional level because of increase of the H3K4 activating mark at the promoter of MICA and MICB genes. Therefore, these compounds offer broader potential in enhancing cytotoxicity of NK cells by escalating NKG2D ligands on tumor cells (Chávez-Blanco et al. 2011).

It is worth mentioning that exposure to samarium-153-ethylenediaminetetramethylenephosphonate [(153)Sm-EDTMP] resulted in enhanced LNCaP cells susceptibility to killing by CTLs specific for PSA, carcinoembryonic antigen, and mucin-1. Fluorescence-activated cell sorting analysis and quantitative real-time PCR analysis displayed up-regulated expression of tumor antigens in LNCaP cells upon treatment with radiopharmaceutical (153)Sm-EDTMP (Chakraborty et al. 2008).

It is noteworthy that MIC shedding may participate considerably in tumor formation, and inhibition of MIC shedding underlies targeted intervention by enabling

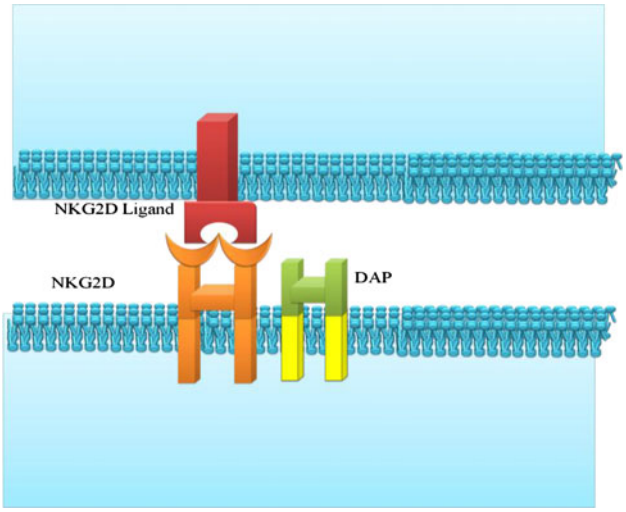

Fig. 1 Interaction of NKG2D ligands with its native receptor displayed on NK cells

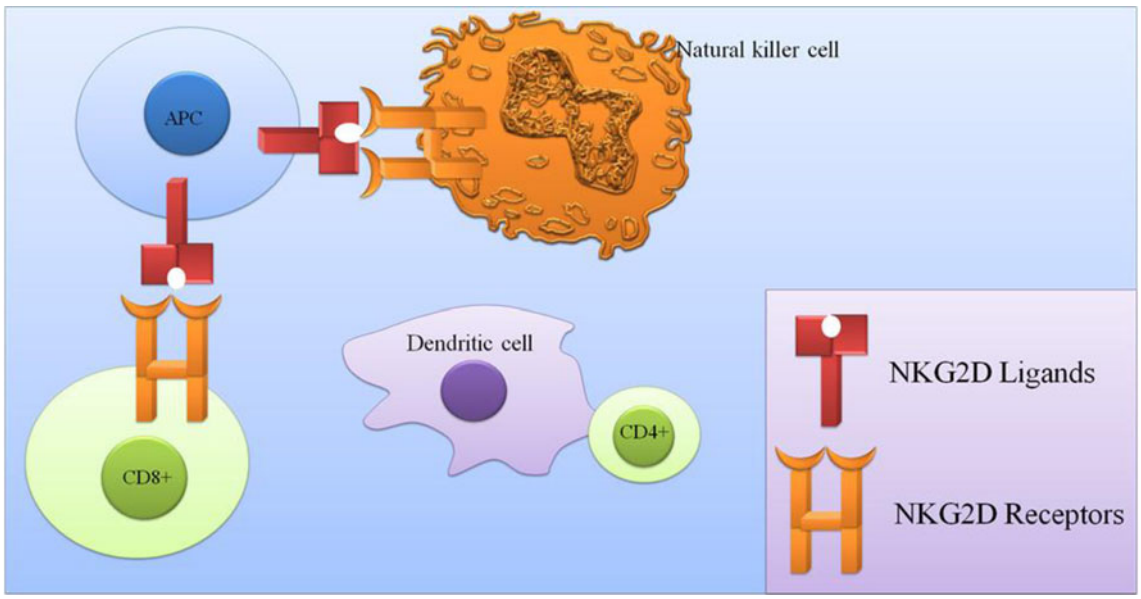

Fig. 2 Recognition and interaction of NK cells and CD8 T cells with tumor cells

interaction between NKG2D receptor-MIC ligand. TRAMP-C2 (TC2) cells reconstructed for shedding-resistant non-cleavable form MICB.A2, the wild-type MICB, and the recombinant soluble MICB (rsMICB) were implanted into severe combined immunodeficient mice. It was intriguing to note that there was no tumorigenesis in animals that were implanted with TC2-MICB.A2 reconstructs, while all the animals that were implanted with TC2, TC2-MICB, or TC2-rsMICB cells developed tumors (Wu et al. 2009a).

Confluence of information suggests that TRAMP-PSA tumors were frequently rejected by HLA-DR2b$^-$ mice, but HLA-DR2b$^+$ littermates were tumor prone. HLA class II allele has differential behavioral pattern towards antigen-specific CD8 T cell responses and antibodies. While drawing a parallel between levels of PSA-specific CD8 T cell responses in HLA-DR2b deficient and competent mice, it was observed that PSA-specific CD8 T cell responses were appreciably higher in the HLA-DR2b$^-$ mice. Likewise, Ab responses to PSA were strong in HLA-DR2b$^+$ as compared with HLA-DR2b deficient mice (Klyushnenkova et al. 2009).

It is a well appreciated aspect that NKG2D are expressed on NK cells and play a decisive role in recognition and elimination of tumor cells; however, NKG2D has a "split personality" as it is also involved in immunoediting of tumors. Laboratory investigations revealed the fact that in a prostate cancer model, aggressive tumors arising in NKG2D-deficient mice expressed higher amounts of NKG2D ligands than did similar tumors in wild-type mice (Guerra et al. 2008).

Peptide Vaccines

Substantial fraction of information has been added to existing list of peptide epitopes capable of stimulating CTLs that killed STEAP-expressing tumor cells. In accordance with this assumption, two peptides [STEAP(102-116) and STEAP(192-206)] were found to be efficient in stimulating in vitro antitumor helper T lymphocyte (HTL)-mediated immunological responses in both normal individuals and prostate cancer patients. Outstandingly, both STEAP HTL peptides behaved as promiscuous T cell epitopes as they stimulated T cells in the context of more than one MHC class II allele (Kobayashi et al. 2007).

It is worth mentioning that expansion of interferon γ (IFN-γ)-secreting CD8$^+$ T cells specific for PSA-derived peptides was detected in healthy individuals and lacked in patients with prostate cancer. PSA-specific CD8$^+$ T cells are severely impaired in patients as they failed to release IFN-γ and to kill targets independent of NK activity. HLA-A2/peptide tetramers and flow cytometric cytotoxicity assays substantially revealed that expanded modulators from healthy individuals killed the PSA-expressing epithelial cell line LNCaP and the peptide-pulsed T2 cells in a MHC class I-restricted mode exclusive of NK activity (Elkord et al. 2005).

PSMA is an integral non-shed type 2 membrane protein that is highly and particularly expressed on prostate epithelial cells and is upregulated in prostate carcinogenesis. Keeping in view the multipronged approach and a better recognition of tumor markers, and interaction between tumor cell and NK cell, recently a research group has engineered fusion proteins that displayed higher NK-mediated cytotoxicity. Basic framework of fusion protein was composed of a single-chain antibody fragment to target PSMA and ULBP2 to activate host NK cells by targeting the activatory receptor NKG2D (Jachimowicz et al. 2011).

Consistent with the same approach, another research group constructed a novel bispecific single-chain (bsc) diabody directed to the PSMA and the TCR-associated CD3 molecule on T cells. Efficacy was evaluated using PSMA-expressing prostate cancer cells and PSMA-deficient Jurkat cell line by flow cytometry. For in vivo assessment, the diabody was co-administered with lymphocytes in a C4-2 xenograft-SCID mouse model. Data indicated specific co-attachment of the PSMA $\times$ CD3 bsc diabody both to CD3-positive Jurkat cells and PSMA-expressing C4-2 cells as shown by flow cytometry (Fortmüller et al. 2011).

Accumulating data suggest that these CTLs were able to respond to tumor cells that express HLA-A2 and STEAP. STEAP is an immunogenic peptide that induced CTL recognition of these STEAP-containing tumors and offers astonishing potential as an antitumor peptide vaccine (Rodeberg et al. 2005).

MHC and NKG2D

The touchstone to evaluate accurately responsiveness of immune system towards normal and infected cells is something of a holy grail in the facet of molecular immunology. Consistent with same approach, undeniable requirement for lymphocytes to respond to transformed or infected cells while remaining tolerant of normal cells cannot be overlooked. NK cells clearly differentiate between self and non-self by scrutinizing the expression of MHC class I molecules. Keeping in view the "missing-self" hypothesis, which suggests that cells that express self-MHC class I molecules evade NK cells, however, those that lack this self-marker are eliminated by NK cells.

It is well-established fact that NKG2D ligands encompass an assorted array of MHC-class-I-related proteins that are upregulated by cellular stress. It is nonetheless

advantageous for the cell to have so many ligands for similar receptor. Confluence of information points towards the fact that cell-surface receptors interact with ligands expressed on other cells to trigger cell-to-cell communication (trans interactions). Captivatingly, it has currently been found that these receptors specific for MHC class I molecules not only interact with MHC class I molecules expressed on opposing cell surfaces, rather they might also interact on the similar cell. This new paradigm of cis interactions is acclaimed as a hallmark feature of immunoreceptors that activate cellular functions. In support of this notion, fluorescence-activated cell sorting analysis revealed that LNCaP cells are deficient in sufficient number of MHC class I molecules expressed on cell surface; however, they express MICA/B molecules, ligands for the NKG2D receptors found on NK cells. LNCaP cells transfected with the Ad5IL-12 vector-restricted tumorigenesis in NOD.SCID mice because of enhanced tumor killing in trans manner. On a different note, Ad5IL-12 vector treatment also induced remarkable killing of MICA/B-negative MHC class I-positive PC3 cells formed in NOD.SCID mice. It is becoming progressively clearer that tumor cells resistant to lysis by resting NK cells may be sensitized by priming of NK cells with cytokines or by binding of NK activating receptors to ligands expressed on target cells (Raja Gabaglia et al. 2007). A recent study suggested that priming NK cells with genetically modified influenza A virus lacking the non-structural gene 1 (DeltaNS1 IAV)-infected tumor cells resulted in an exceptional attenuation of inhibitory effects posed by MHC-I expression on DU145 cells. Contrary to this, MHC-I-deficient LNCaP cells were lysed by (DeltaNS1 IAV)-infected tumor cells primarily because of an enhanced extracellular signal-regulated kinase phosphorylation and increased granule release in NK cells (Ogbomo et al. 2010).

Another important feature is that co-incubation of peripheral blood mononuclear cells with activated DCs enhanced cytotoxic response and simultaneously suppressed telomerase gene expression in LNCaP and DU-145 cells (Turkeri et al. 2010).

Using immunocytochemistry, distinct expression patterns of MHC class I and class II on cryopreserved human and mouse prostate tumor samples were examined. It was exciting to note that prostate tumor cells and hematopoietic lineage, dispersed in the tumor microenvironment, showed considerable expression of MHC class I and MHC class II molecules correspondingly (Nanda et al. 2006). *Lactobacillus rhamnosus* GG (LGG) has recently been documented to successfully induce cancer regression. Genetically engineered LGG activated neutrophils (upregulated MHC class I expression) triggered DC maturation, T cell proliferation, and PSA specific cytotoxic T lymphocyte (CTL) activity. In addition, IL-15 stimulated direct DC activation of CTL (Kandasamy et al. 2011).

Tumor cells circumvent immunosurveillance by preventing tumor antigens from being recognized by the immune system. An underlying mechanism that dampens immunological response is that Ii protein that usually co-localizes with MHC class II molecules blocks the antigenic peptide-binding site of MHC class II molecules during synthesis in the endoplasmic reticulum. However, abrogation of Ii protein resulted in promoting the potential of MHC class II molecules to pick up endogenous tumor antigenic peptides, which have been transported into the endoplasmic reticulum for binding to MHC class I molecules. It is therefore evident that MHC class II^{+}/Ii^{-} tumor cells are persuasive tumor cell vaccines against prostate tumors (Humphreys et al. 2004).

Dendritic cells are fundamental in the synchronization and harmonization of the various forms of immunity. Their undeniable immunoregulatory role essentially relies on the ligation of specific receptors that orchestrate DC maturation, resulting in the expansion of multifunctional and diverse effector DC subsets that selectively promote T helper 1 (TH1), TH2, or regulatory T cell responses. It is becoming increasingly understandable that the differential development of T cell-polarizing DC subsets is interconnected to the ligation of particular receptors that are involved in DC maturation; several inconsistencies with this concept still persist. On a similar note, DC were purposely pulsed with multiple T cell epitopes derived from four dissimilar PSAs in patients with advanced hormone-refractory prostate cancer. Immune monitoring for the duration of time span of continuing vaccinations included MHC tetramer analysis and in vitro cytotoxicity assays. DC-based multi-epitope immunotherapy with frequent boosting in men with hormone-refractory prostate carcinoma is practicable and has remarkable outcomes in terms of an efficient cellular antitumor response (Waeckerle-Men et al. 2006).

It is important to note that PSA peptide-loaded tetramer might play a role in the quantitative analysis of $CD8^{+}$ T cells elicited by PSA-specific immunotherapies and cancer vaccines that are evaluated in mouse models (Lemke et al. 2011).

SIGLEC12 gene encodes one of the CD33-related Siglec family of signaling transduction cascade in immune cells. Recent data indicate expression of SIGLEC12 on certain human prostate epithelial carcinomas. To further investigate these findings, prostate cancer cells were stably transfected with Siglec-XII that consequently enhanced proliferation potential of the cells in nude mice. However, interestingly, mAb directed against the protein were internalized by Siglec-XII-expressing cancer cells, allowing targeting of a toxin to prostate cancer cells (Mitra et al. 2011). In the context of targeted therapy, the possibility of developing a drug delivery nanocarrier capable to

specifically reach cancer cells cannot be overlooked. On a similar note, targeting and internalization of mAb carbon nanotubes might result in an effective thermal ablation of tumor cells following their exposure to near infrared light.

The synovial sarcoma X (SSX) chromosome breakpoint proteins encompass a set of cancer-testis antigens that are frequently upregulated in cells lacking MHC class I and in different types of advanced cancers with a poor prognosis. Recent findings suggest that multiple SSX family members are expressed in metastatic prostate cancers (Smith et al. 2011).

ATM and Cell Surface Expression of Receptor Ligands

Escalating evidence underscores the fact that the immunoproteome makes a crucial contribution to the antitumor effects of conventional chemotherapy-based cancer treatments. Upcoming section focuses on the important roles of these DNA-damage responses in the activation of immunity and the targeting of the immunological response to infected or transformed cells. Latest findings give an idea that ATM/ATR calibrate the baseline expression of mRNAs encoding stress-inducible ligands of the activating NKG2D receptor.

It has recently been established that pharmacological reactivation of p53 triggers the expression of ULPB2, a ligand for NK cell activating receptor NKG2D in human cancer cells. Using high-throughput technologies, it was investigated that p53 acted as a direct transcriptional regulator of ULBP2 as it harbored a p53 response element. It was also noted that demethylation of p53-binding region within ULBP2 gene was necessary to modulate p53-dependent transcription of ULPB2 via repression of DNA methyltransferases by p53 (Li et al. 2011). Recent data suggest that DNA damage and oxidative stress are instrumental in cell surface display of various proteins. It is noteworthy that superantigen-stimulated T cells display Nectin-2 (CD112) and poliovirus receptor (PVR; CD155), the ligands of the activating NK receptor DNAX accessory molecule-1 (DNAM-1; CD226). However, up-regulation of PVR expression was correlated with DNA-damage response (DDR) pathways. In a set of experimentations it was noticed that abrogation of ATM and ATR kinases reduced PVR expression and that PVR was displayed on surfaces of the cells expressing the DDR marker γH2AX (Ardolino et al. 2011).

It is becoming increasingly apparent that various compounds are effective in modulating expression of NKG2D ligand (NKG2DL) in various cell lines. Several evidences indicate that Valproic acid (VPA), a histone deacetylase inhibitor, stimulates the expression of NKG2DLs on some monocytic and lymphoid leukemic cells. Consistent with same approach, in a chronic myelogenous leukemia cell line (OUN-1) it was observed that VPA treatment resulted in upregulation of MICA/B and ULBP2. Another interesting underlying mechanism that triggered upregulation of NKG2DL was DNA damage response. It was noteworthy that ATM/ATR modulated the expression of NKG2DL on cellular surface, and pharmacological targeting of ATM/ATR abolished the expression of surface markers (Fig. 3) (Lu et al. 2010).

Increasing evidence using carboxyfluorescein diacetate succinimidyl ester labeling and real-time RT-PCR suggests that NKG2DLs are expressed mainly on T cells undergoing cellular division. T cell activation enhanced phosphorylation of DNA damage repair protein, ATM, essential for cell surface expression of NKG2DLs after DNA damage (Cerboni et al. 2007).

Similarly, HepG2 cells (an HCC cell line) treated with 5-aza-2′-deoxycytidine (5-aza-dC), a DNA methyltransferase inhibitor, triggered the expression of MICA and sensitized cells to NK cell-mediated cytolysis (Fig. 3). It is noticeable that targeted inhibition of ATM resulted in partial prevention of upregulation of MICA (Wu et al. 2009b). On a similar note, upregulation of MICB was tightly linked with promoter DNA demethylation and DNA damage. Moreover, the upregulation of MICB also underwent partial suppression upon impairment of ATM. These findings suggest that promoter DNA demethylation, in

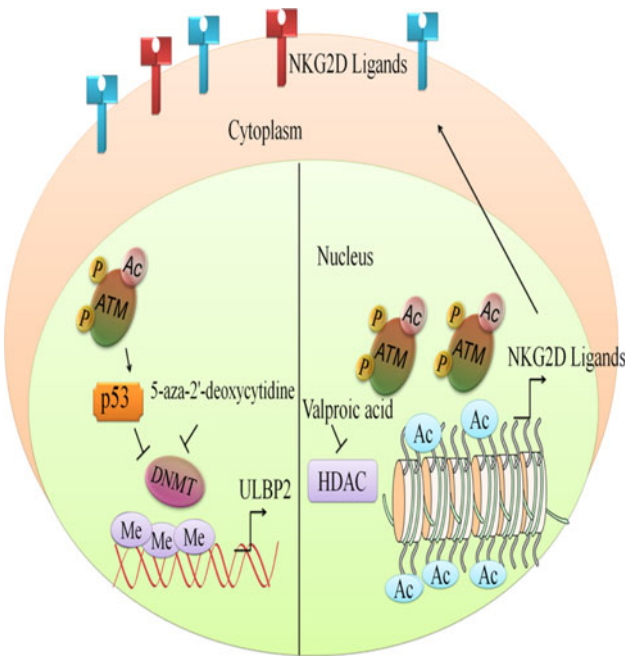

Fig. 3 DNA damage tactfully triggers cell surface expression of NKG2D Ligands

combination with DNA damage, contributes to the upregulation of MICB induced by 5-aza-dC (Tang et al. 2008a).

Controversy surrounds recent NKG2DL expression studies comparing head and neck squamous cell carcinoma (HNSCC) and melanoma cell lines. However, various documentations underscore the fact that ATM/ATR signaling differentially modulates expression of various NKG2DLs in various tissues. Consistent with the same concept, recent explorations have revealed the expression pattern of various NKG2DL in HNSCC cell lines. It was observed that treatment of cell lines with bortezomib and other proteasome inhibitor drugs resulted in up-regulation of HNSCC ULBP1 mRNA and cell surface protein. It is noteworthy that ULBP1 expression in HNSCC cells was not up-regulated upon treatment with ATM/ATR activating compounds, including bleomycin, cisplatin, aphidicolin, and hydroxyurea (Butler et al. 2009). Discordantly, considerable information has been gained about undeniable role of DNA damage repair proteins in enhancing NKG2DL expression, but nothing is known about DNAM-1 ligand regulation. It has recently been established that treatment of melanoma cell line with doxorubicin, melphalan, and bortezomib up-regulate DNAM-1 and NKG2DLs. Additionally, chemical intervention of ATM/ATR resulted in suppression of NKG2DL expression (Soriani et al. 2009). A comparison of the regulated proteins with previously published transcriptomic studies showed a low overlap, highlighting the notion that ATM/ATR activity is cell type specific.

It is exciting to note that RNA interference (RNAi) is indirectly linked to the human innate immune system via the DNA damage pathway. A recent study unravels the fact that abrogation of Dicer expression by RNAi in human cells up-regulates MICA and MICB. Using laboratory methodologies, it was revealed that attenuation of Dicer elicits DNA damage. Set of experimentations indicated that up-regulation of MICA and MICB by Dicer knockdown was suppressed by ablation of DNA damage pathway components (Tang et al. 2008b).

Conclusion

Doubtlessly, during early stages of prostate carcinogenesis, cell-intrinsic barriers to tumor development appear to be connected with stimulation of an active antitumor immune response. However, progressively, tumor development seems to correlate with changes in the immunogenic properties of tumor cells and inability of host immunoproteome to challenge and eliminate it. The major breakthrough in terms of cancer treatments might depend on using immunogenic therapeutics particularly emphasizing reprogramming of immunoproteome.

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