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MHC Class 1-Related Chain A and B Ligands are Differently Expressed in Cancer Cell Lines

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Abstract

The MHC class I related chain A and B have been of much interest in the recent past. MHC class 1 related gene A/B (MICA/B) are ligands of the NKG2D, which is an activating receptor expressed on T and NK cells (NK cells are effector cells of the innate immune system and their functions are regulated by a number of killer cell-inhibitory and -activating receptors.).Their expression on normal tissues is highly restricted but in the event of tissue transformation and infected cells, MICA/B expression is up-regulated leading to NK killing activity. MICA/B are shedded in the serum of cancer patients (sMICA/B) whereby sustained expression of this MIC affects the killing activity of NK cells and T cells. In this summary review we look at how differently MIC A/B is expressed in Cancer cell.

Keywords: MHC class 1 related chain A and B; Natural killer; NKG2D; Soluble MIC A/B; Perth beta block transcript

Introduction

In 1994, a new set off loci related to MHC class 1 genes called MHC class 1 chain-related genes (MIC) or Perth beta block transcript 11 (PERB11) were identified independently by Bahram et al. and Leelayuwat et al. [1,2] in which five copies existed. The nomenclature was then standardized as MIC, which since then is in current use. Major Histocompatibility complex class 1chain related molecule is known to play an important role in tumor immune-surveillance.

MICA/B is encoded in the MHC (major histocompatibility complex) region, and they share structural and sequence similarity with MHC class I proteins (28-35%). MICA/B has α1-α2-α3 extracellular domains and short transmembrane tails similar to MHC class 1. MICA/B does not associate with β2-microglobulin or antigenic peptides like their counterpart MHC class 1. They are highly polymorphic, with close to 60 recognizable MICA and 25 MICB alleles. Although much is not known about the significance of their polymorphism, MICA alleles might vary in their affinity for NKG2D binding and thus affect the thresholds of recognition by NK cells and T lymphocytes [3].

The MIC molecules have been detected in broader range of tumors-hematological malignances and various adenocarcinomas such as breast, lung, colon, kidney, ovary and prostate tumors, gliomas, neuroblastomas and melanomas [4-7]. Previous studies show that MIC genes are widely and transcribed and therefore possibly translated and membrane bound with exception of the Central Nervous system.

In human, NKG2D recognizes two structurally distinct families of ligands namely (MIC) molecules and the UL 16 binding proteins (ULBPs) 1-5 molecules which is also known as RAET1: retinoic acid early transcript 1, originally identified through interaction with Cytomegalovirus UL 16 glycoproteins. MIC and ULBP both engage NKG2D, which then triggers cytokine production and cytotoxic activity seen in activated NK cell. NK cells are mainly involved in recognition of transformed cells; the killing activity is majorly controlled by an exquisite balance of competing inhibitory and activating receptor. NKG2D, is a C type lectin activating immunoreceptor whose expression is confined to NK cells, CD 8+TCR T cell receptors (alpha beta and gamma delta T cells) [8-11].

In humans, the MICA/B is the most investigated NKG2D ligands which have been proposed to play roles in tumor rejection. MIC is rarely expressed by normal human tissues [1-12] but induced in most human epithelial tumors [13-15]. Expression of MIC on the tumor cell surface can markedly enhance the sensitivity of tumor cells to NK cells *in vitro* and has been shown to inhibit the growth of human gliomas or small lung carcinomas in experimental models.

MIC genes are transcribed in fibroblast and epithelial cell lines [13-15], and reputedly in most tissues with epithelial cell type. MIC A/B over expression is as a result of DNA damage response involves ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia-mutated rad-related protein kinase) [16,17]. Although MIC A and B share high homology at the protein and DNA level, there is evidence for differential regulation of their promoters indicating that these molecules could respond differently to several damage stimuli.

Tumors can escape the host immune system by secreting a soluble form of MIC (sMIC). sMIC binds to NKG2D and down regulates its expression, leading to loss of the NK/T cell activation trigger [18,19].

This review summarizes findings of MIC A/B differential expression in cancer cell lines and the ability to alter immune response.

MIC A/B Cell Surface Expression

MIC A/B are both expressed on the surface of most cells but also can be intra-cellular retained, In chronic myeloid leukemia, the BCR/ABL (breakpoint cluster region/Abelson) fusion oncoprotein induces the expression of MICA on the surface of leukemic cells [20] which is not necessary similar with MIC B. The expression of MIC A in Human melanomas cell lines and freshly isolated metastases is not on the cell surface but occur as intracellular deposits. This retention of MIC A in the endoplasmic is associated with accumulation of immature form

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of MIC A (endoH-sensitive), retrograde transport to the cytoplasm, and degradation by the proteasome. Melanoma cells evade NK cell-mediated immune surveillance based on the intracellular sequestration of immature forms of MICA in the endoplasmic reticulum [21].

MIC B has been proved to have a much shorter half-life at the plasma membrane than MIC A molecules and this depends on both recycling to internal compartment and shedding to the extracellular medium. It was observed that internalization of MICB depends partially on clathrin but importantly the lipid environment of the membrane also plays a crucial role in the process [22] also human cytomegalovirus (HCMV) evolving proteins such as UL16, causes the intracellular retention of MICB, ULBP1 and ULBP2, but not MICA and ULBP3 [23] and UL142, which is able to retain certain MICA alleles [24].

MIC A/B expression has also been proved in tissue surface and mRNA expression although the levels of expression will differ.

Soluble MICA/B

Metalloproteases are endopeptidases capable of degrading extracellular matrix involved in tissue morphogenesis, repair, and angiogenesis and have been shown to play an important role in the pathophysiology of tumors [25]. MICB similarly to MICA is released from epithelial by the activity of metalloproteases. Proteolytic shedding has been proposed as the key mechanism by which MICA is released from the cell surface, similar to the cleavage occurring with other membrane-bound protein [26]. It was elucidated that metalloproteinases were responsible for the cleavage of the MICA α1α2α3 extracellular domain from the cell surface in several tumor lines [27]. A report that proteolytic cleavage in the stalk of MICA ectodomain where deletion but not alanine substitution impede MIC A, a member of ADAM (a disintegrin and metalloproteinase) mediated inhibition and stimulation of MICA shedding.

Metalloproteinases, aside from playing an important role in invasion, metastasis, and angiogenesis processes, also have a role in allowing MICA shedding tumor cells to evade immune attack. However, we cannot discard the possibility that other different proteases are also participating in the cleavage of MICA as has been recently reported by Kaiser et al. In that report, the authors demonstrated that MICA shedding was facilitated by a disufide-isomerase interacting directly with MICA α3 [28]. Thus, it appears that different enzymes could be enabling tumor cells to escape from the immune attack.

Surface expression levels of NKG2DL critically determine the outcome of NKG2D-mediated immune responses *in vitro and in vivo* [22,29]. Thus, release of MIC molecules may locally reduce immunogenicity of tumor cells by diminishing ligand densities on the cell surface. In addition, soluble MICA/B has been reported to cause systemic down regulation of NKG2D and to impair NKG2D functionality in tumor antigen-specific cytotoxic lymphocytes and NK cells activity in other cancer cells [30-32]. Interestingly, high concentrations of sMICA in sera of recently described MICA-transgenic mice likewise did not significantly alter NKG2D surface expression in contrast to cell-bound MICA [28].

MICB as MICA can modulate NKG2D surface expression [30]. An important emphasis is that NKG2D down regulation by CIR-MICB cells was less pronounced than that by CIR-MICA cells [32] which was further explain to be presumably mainly due to a five- to ten-fold lower expression of MICB on C1R-MICB transfectants. In the same studies they found that a marked number of patient sera contained elevated levels only of sMICA or sMICB, while others revealed presence of both sMICA and sMICB. This can be reasoned that sMICA and sMICB as independent tumor markers in a specific malignancies [33].

Note that, surface expression and release of soluble forms of MICA and MICB are modulated by metalloproteases that is sMICB like sMICA is present in sera of many patients with gastrointestinal malignancies, and that elevated sMICA levels are not necessarily linked with elevated sMICB level [33].

In an experiment significant sMICA levels in patients with cervical cancer were observed [34], Moreover strong surface MICA expression on tumor cells was also observed; when they blocked the TGF-β production promoting a strong recognition by immune cells [35]. It is well known that this cytokine is largely produced by many tumor cells and it is also common in cervical squamous intraepithelial lesions [36].

For instance, it has been shown that HPV-11 transformed human tissue over-expresses TGF-β1 [18] and benign cervical lesions, particularly, have been associated with HPV-6 or -11. There is a report by Osaki et al., which showed that sMICA levels were not different between gastric cancer patients and normal controls, indicating that sMICA was not responsible for inducing the NKG2D down-modulation on CD8+ T cells

Wu JD et al. observed prevalent MICA/B expression in prostate carcinoma and the susceptibility of MICA/B-NKG2D expressing prostate cancer cells to NK cell activation, suggesting that MICA/B-NKG2D tumor can also in immune surveillance play an important role in the eradication of prostate cancer cells [32]. Data showed the loss of predominant surface localization of MIC in high-grade prostate carcinomas and although it was highly expressed on prostate carcinomas, membrane-bound surface MIC was prevalent in low-grade cancers. Being the first to correlate the levels of sMIC and deficiency in NK cell function with the degree of disease in prostate cancer MIC expression is induced on many epithelial tumors [13-15] and, as presented here, on 95% of prostate carcinomas. They suggested that sMIC may potentially be an additional marker for prostate cancer [32].

Stefan Holdenrieders et al. analyzed MICB in sera of 512 individuals which revealed slightly higher MICB levels in patients with various malignancies (N=296; 95th percentile 216 pg/ml; P=0.069) in contrast to healthy individuals (N=62; 95th percentile 51 pg/ml)although his findings showed that Patients with benign diseases (N=154; 95th percentile 198 pg/ml) exhibited intermediate MICB levels, the finding also showed that In cancer patients, elevated MICB levels correlated significantly with cancer stage and metastasis (P=0.007 and 0.007, respectively). Between MICB and MICA levels, only a weak correlation was found (r=0.24). Thus, sMICB seems not to be helpful for cancer detection particularly not in early stages. Another study regarding sMICA showed statistically significant differences between MICA levels in cancer patients and healthy controls as well as with patients with benign diseases [37]. Other studies show elevated levels of soluble MICA were found in sera of patients with various malignancies [31,32,37-40].

Response to Stimuli

MICA/B expression has been described to be regulated by the transcription factor heat shock factor 1 (HSF1). Inhibition of heat shock protein 90 (Hsp90) is known to induce the heat shock response via activation of HSF1 which is associated with tumor development, metastasis and therapy resistance and also with an increased susceptibility to NK cell-mediated lysis. The promoters of MICA/B genes contain regulatory elements responsible for both heat shock

and oxidative stress responses associated with the transcriptional up regulation of MHC class I chain–related protein (MIC) levels upon cellular stress

Susana Arreola et al. study showed that response to stimuli affects the modulation of cervical cancer cell line where by MICA/B are differently expressed in response to damage stimuli [41], also experimental evidence that MICB mRNA expression of upon heat-shock or HCMV infection is more tightly controlled as compared to MICA [42,43]

Michael et al. [44] demonstrated that similar concentrations of H_2O_2 (0.2-1.0 mM) induce oxidative stress and a continuum of pathologies including injury and both apoptotic and necrotic cell death, epithelial cell death occur in the many lung pathologies, the induction of NKG2D ligands following H_2O_2 exposure represents a relevant model system in which to investigate the regulation of these ligands in the airways.

Hypoxia in tumor also enhances the shedding of MICA/B through impaired Nitric Oxide in human prostate cancer, this is a potential mechanism of escape from NKG2D-mediated immune surveillance escape [45,46]. The MIC gene transcriptional regulatory sequences contain heat shock elements similar to those in the hsp70 promoter, and studies have shown that MIC expression can be upregulated by heat shock treatment [47]. Recently, Jinushi et al showed that retinoic acid upregulates MIC expression in hepatoma cells [15], and Molinero et al. showed that activation of the MAPK intracellular signaling pathway upregulates MICA expression on activated T lymphocytes [48]. However, the specific mechanisms of the induction of MIC expression remain unclear.

Genotoxic agents, histone deacetylase inhibitors, or proteasome inhibitors, can increase the expression of NKG2D ligands, thus facilitating the activation of NKG2D-expressing lymphocytes (including NK cells, NKT cells, and CTLs) and tumor cell lysis.

Expression in Different Cancer Cell

Broad expression of MICA/B was described for many epithelial tumors [13] and others detected high levels of sMICA in sera of patients with various malignancies [14,15,49,50]. The NKG2D ligand MICA was upregulated in fewer cervical carcinoma biopsies [51]. Levels of sMICB was also elevated in many sera of patients with stomach, colon, and rectum carcinoma [33].

Observation made by Arreygue-Garcia et al. [27] showed that the progression of the cancer lead to higher levels of sMICA in patient, which is in line with the findings by Wu et al. who detected increased amount of sMICA in patients with prostate cancer [32]. In addition to this progression of cancer severity revealed more sMICA as in Wu et al.

Shigehiro Tamaki et al. [52] also examined the linkage between serum levels of soluble MICA and the severity of disease in patients with oral squamous cell carcinoma (OSCC) and they came to this finding that patients with stage IV disease and/or regional lymph node metastasis did exhibit significantly higher serum levels of soluble MICA which may be useful in the diagnosis of advanced stage OSCC and as an indicator of regional lymph node metastasis. Another MICB study showed that although there was not a significant difference of sMICB level from the normal controls, stage IV OSCC had high level of sMICB associated with decreased patient survival rate [53].

Stenfan Holdereider experimented on different cancer cells; colorectal, various other gastrointestinal cancers, lung cancer, breast cancer, ovarian and other gynecologic cancers, renal and prostate cancer. sMICB seems not to be helpful for cancer detection-particularly not in early stages in contrast to previous finding regarding sMICA which have shown statistically significant differences between MICA levels cancer patients and healthy controls as well as with patients with benign diseases [28]. Indeed, serum levels of sMIC in prostate cancer patients were found to correlate significantly with the grade of the disease [47].

The high level of MICB found in a study suggested that this ligand might play a different role than MICA [33], they continue to support of this fact that elevated soluble MICB correlated with disease activity in patient with multiple sclerosis during relapses soluble MICA did not show any association with the disease rather the level of this ligand were similar to healthy control.

Concluding Remarks

Many studies have been done in regard to MIC molecules as a whole, but compared to the two, MICA had more studies than MIC B,this might be due to low level of MICB expression in tumor cell especially in the benign stages,which is possibly due to reduction of MICB surface expression as reported by Raffaghello et al. who showed that MICB preferentially is sequestered into the cytoplasm of neuroblastoma [40].

Expression of both MICA and B is found in various cancers but the differences in their expression depend on factors that lead to their up regulation or down regulation. Meaning that MIC A orB expression on the same or different cell line is not the same in terms of quantity and disease progression stages.

In different studies it has been shown that the surface expression of theses ligands correlates with the sMic expressed, in that high levels of sMIC lead to low levels of membrane bound MIC molecules especially for MICB.

Different cancer cells also express these ligands differently, study proving than MICA/B differential regulation was previously done on a study where they analyzed the architect and function of MIC genes [54].

MICA/B can be used as a biomarker in tumor surveillance in some cancers although more study can be done on their differential expression in various malignancies Apart from one study that shows how MICA/B are differently expressed in cervical cancer, more studies researching this topic needs to be done in different cancer cell line in order to enhance the difference of these independent molecules which are so much alike and yet so different.

MIC A/B polymorphism is little understood and studies have been done in different population region like china and Iran but there are still more question to be answered, weather the polymorphism of these affect their expression on cells, tissue and mRNA expression.

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