Platelet-Derived MHC Class I Confers a Pseudonormal Phenotype to Cancer Cells That Subverts the Antitumor Reactivity of Natural Killer Immune Cells

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Abstract

Natural killer (NK) cells are cytotoxic lymphocytes that play an important role in tumor immunosurveillance, preferentially eliminating targets with low or absent expression of MHC class I and stress-induced expression of ligands for activating NK receptors. Platelets promote metastasis by protecting disseminating tumor cells from NK cell immunosurveillance, but the underlying mechanisms are not well understood. In this study, we show that tumor cells rapidly get coated in the presence of platelets in vitro, and circulating tumor cells of cancer patients display coexpression of platelet markers. Flow cytometry, immunofluorescent staining, confocal microscopy, and analyses on an ultrastructural level using immunoelectron microscopy revealed that such coating may cause transfer of MHC class I onto the tumor cell surface resulting in high-level expression of platelet-derived normal MHC class I. The resulting "phenotype of false pretenses" disrupts recognition of tumor cell missing self, thereby impairing cytotoxicity and IFN-γ production by NK cells. Thus, our data indicate that platelets, by conferring an unsuspicuous "pseudonormal" phenotype, may enable a molecular mimicry that allows metastasizing tumor cells to downregulate MHC class I, to escape T-cell–mediated immunity without inducing susceptibility to NK cell reactivity. Cancer Res; 72(2); 440–8. ©2011 AACR.

Introduction

Cancer is the second leading cause of death in western countries. Although novel therapies have improved treatment options for localized cancer, most cases of metastatic disease remain incurable and account for more than 90% of cancer-related deaths (1). Metastatic disease results of a complex series of events, during which malignant cells invade blood vessels, travel with the blood stream, and settle down at distant sites causing a clonogenic accumulation of tumor cells. Elucidation of the yet incompletely understood mechanisms facilitating tumor spread may be key to reduce cancer mortality.

The role of platelets in cancer metastasis/progression has been debated since the 19th century, when Reiss and colleagues reported on the relationship of elevated platelet counts and malignancy and Billroth described viable malignant cells in blood clots of tumor patients (2, 3). Since then, data showing that platelets promote tumor progression and metastasis have been accumulating (for excellent reviews see refs. 4, 5). This includes evidence from thrombopenic (thpo−/− or cmpl−/−) mice, in which xenotransplanted tumors displayed reduced local progression, and this tumor-protective effect of thrombopenia was even more pronounced with regard to metastasis (6). Although platelets may play an important role as biosuppliers of proangiogenic factors early on in tumor development (7), they likely are most relevant following invasion of single tumor cells into the blood stream. Platelet adhesion to circulating tumor cells may facilitate subsequent extravasation to metastatic niches. Moreover, platelet–tumor cell interaction leads to platelet activation causing release of factors conducive to tumor cell survival and proliferation. Finally, platelets may guard tumor cells from elimination by the immune system (4).

Nieswandt and colleagues have introduced the concept that the tumor-protective effect of thrombopenia in mouse models is mediated by modulation of natural killer (NK) cell function (8). NK cells are cytotoxic lymphocytes that are considered components of innate immunity, even if they also have attributes of adaptive immunity (9). Their reactivity is guided by recognition of "missing self" and "induced self", implying that NK cells kill target cells with low or absent expression of MHC class I ("missing self") and/or stress-induced expression of ligands for activating NK receptors ("induced self"; refs.
10–12. Several elegant studies showed that thrombopenia abrogates the formation of pulmonary metastasis after tail-vein injection of tumor cells in mice, and this antimetastatic phenotype is reversed by additional depletion of NK cells (8, 13–16). Thus, platelets protect tumor cells from NK-mediated immunosurveillance. However, NK reactivity is also influenced by the plasmaticolagulation system (13, 17), and a thorough elucidation of effects exclusively mediated by platelets is, to our opinion, thus not fully achievable in mouse models. Rather, in vitro and ex vivo studies, in which suitable experimental conditions can be applied, are required to specifically define the mechanisms by which platelets influence NK cell antitumor reactivity. Here we provide evidence that platelets can confer an immune phenotype of false pretenses, or "pseudoself", to (metastasizing) tumor cells by lending MHC class I, which disrupts "missing self" recognition and thereby impairs NK cell immunosurveillance.

Material and Methods

Blood samples

Blood samples from patients were obtained at time of diagnosis prior to therapy. All patients gave their written informed consent in accordance with the Helsinki protocol, and the study was done with the approval of all participating Ethics Committee.

Reagents and cell lines

HLA-A,B,C, CD62P, CD61, CD41a, cytokeratin, and carcinoembryonic antigen (CEA) fluorescence conjugates, and the respective isotype controls were from BD PharMingen, anti-A2/28-Biotin was from OneLambda Inc. The anti-pan-cytokeratin antibody was from DakoCytomation, the Alexa 488– conjugated anti-rabbit antibody was from Invitrogen, Human IgG1 and IL-15 were from R&D Systems. The streptavidin–PE conjugate was from Jackson ImmunoResearch. BATDA and Europium were from Perkin Elmer. W6/32 F(ab

Flow cytometry

Cells were incubated with specific antibodies or isotype control and, in case that biotinylated antibodies were used, subsequently incubated with streptavidin–PE prior to analysis on a FC500 (Beckman Coulter). In analyses of patient blood samples, flow cytometry was done after red cell lysis using OptiLyse B from Beckman Coulter.

Immunofluorescence

Cytospins from coated tumor cells were prepared and processed for immunofluorescence with the indicated antibodies as previously described (19). In brief, after nonspecific protein block, cytokeratin antibody was incubated overnight at 4°C. After successive PBS washes, sections were incubated in Alexa 488– conjugated anti-rabbit secondary antibody and, subsequently, stained with CD61–PeCy3 and MHC class I–PeCy5 conjugates. Sections were counterstained with 4,6-diamidino-2-phenylindole (DAPI).

Confocal microscopy

Platelets, tumor cells, and tumor cells after coating by platelets were fixed with formaldehyde and embedded in paraffin. For immunofluorescence analysis, sections were blocked with donkey serum and then incubated with anti-MHC class I antibody (Abcam). Bound antibody was visualized by incubation with Cy3-donkey anti-mouse serum (Jackson Immunoresearch). Nuclei were stained with Topro-3. Sections were analyzed using a Leica TCS-SP/Leica DM RB confocal laser scanning microscope, a HCX PL APO lens at 63×/1.132-0.6 oil CS, and Moviol medium (Hoechst).

For video production, platelet membranes were stained with DiI (Invitrogen) and tumor cells were stained with DiO (Invitrogen). Sections were analyzed using a Leica TCS-SP/Leica DM RB confocal laser scanning microscope, a HCX PL APO lens at 63×/1.132-0.6 oil CS, and Moviol medium (Hoechst).

Electron microscopy

For transmission electron microscopy, coated tumor cells were centrifuged and the resulting pellets were fixed for 24 hours in Karnovsky’s fixative. Following standard methods (21), ultrathin sections were examined with a LIBRA 120 (Zeiss) at 120 kV. For immunoelectron microscopy, cells were fixed and embedded in Lowicryl K4M (Polysciences) as previously described (22). Samples were stained with anti-MHC class I
antibody (Abcam) and examined using a LIBRA 120 transmission electron microscope (Zeiss) operating at 120 kV.

**Cytotoxicity assay**

Cytotoxicity of NK cells was analyzed by 2-hour BATDA Europium assays as previously described (18). Percentage of lysis was calculated as follows: 100 × (experimental release − spontaneous release)/(maximum release − spontaneous release).

**ELISA**

IFN-γ levels were analyzed using OptEIA sets from PharMingen according to the manufacturer’s instructions. All concentrations are expressed as mean ± SEM of triplicates.

**Results**

**Platelet coating causes enhanced MHC class I expression by cancer cells**

Platelets can rapidly adhere to tumor cells and have been reported to express high levels of MHC class I (4, 25). To enable the detailed analysis of tumor–platelet interaction in a controlled setting in vitro, we employed immunofluorescent staining using 3 human tumor cell lines, which constitutively express no, low, and high MHC class I levels (NCCIT, SK-BR-3, and PC3, respectively) to study tumor–platelet interaction. None of the tumor cell lines expressed β3 integrin (CD61), which was expressed at high levels by platelets. When we analyzed tumor cells after incubation with a thousandfold excess of platelets under shear stress, the tumor cells displayed "pseudoexpression" of CD61 and high-level MHC class I at the cell surface in all cases (Fig. 1A). The physiologic relevance of platelet coating of cancer cells that have entered the blood stream was confirmed by analysis of peripheral blood of patients with metastatic colon and breast cancer involving the bone marrow and, therefore, presenting with large quantities of circulating tumor cells. Platelet-coated circulating tumor cells in peripheral blood were identified based on expression of CEA or cytokeratin and the platelet marker Glycoprotein IIb (CD41a). FACS analysis revealed different amounts of leukocyte–platelet aggregates (CD41a+/CEA− or CD41a−/cytokeratin−) in the peripheral blood of the patients. In line with findings of previous analyses (24, 25), patient PBMCs contained CEA+ or cytokeratin+ tumor cell populations with varying degrees of CD41a positivity, reflecting coexpression of platelet integrin α2 (Fig. 1B). Together, these data showed that tumor cells are rapidly coated in the presence of platelets in vitro and in vivo, which results in expression of platelet molecules by the tumor cells.

**Enhanced MHC class I levels on tumor cells after coating comprise platelet-derived MHC class I**

Next, we utilized flow cytometry to study tumor cell coating by platelets in greater detail. Resting platelets displayed high levels of CD41a and MHC class I, whereas only negligible levels of the platelet activation marker P-selectin (CD62P) were detected. Tumor cells alone were negative for CD41a and, in line with the results from immunofluorescent staining, expressed MHC class I at varying levels. When small amounts of tumor cells were coincubated with platelets, platelet adhesion onto the tumor cell surface in the absence of tumor cell–induced platelet aggregation was observed (not shown) and resulted in "pseudoexpression" of CD41a as well as CD62P on the tumor cell surface. This showed that coating of tumor cells lead to activation of the platelets and was consistent with previous findings by us and others regarding the activated phenotype of tumor-adherent platelets (19, 26, 27). Moreover, coincubation of platelets with NCCIT and SK-BR-3 cells, which constitutively express no/low MHC class I, resulted in substantial MHC class I "pseudoexpression". However, no increase of MHC class I upon platelet coating was detectable with PC3 cells. This was most likely due to the strong constitutive MHC class I expression on these tumor cells, which may have prevented detection of additional MHC class I with the pan-HLA-specific antibody used in these experiments. To distinguish transfer of platelet MHC class I to tumor cells from upregulation of the tumor cell’s own MHC class I, we employed an anti-HLA-A’2–specific antibody and used platelets of an HLA-A’2–positive donor. PC3 and NCCIT cells were negative for HLA-A’2, whereas SK-BR-3 cells displayed a weak staining (in line with the results of genotyping, not shown). After incubation with platelets substantial expression/upregulation of the platelet-specific HLA-A’2 was observed with all 3 tumor cell lines (Fig. 2A). This confirmed that in fact platelet-derived MHC class I is present on tumor cells, and increased MHC class I expression is not caused by induction of tumor-derived MHC class I upon interaction with platelets.

Expression of MHC class I on platelets, but not on NCCIT tumor cells, was also observed by confocal microscopy. These analyses confirmed further that MHC class I becomes visible on the tumor cell surface after coincubation with platelets (Fig. 2B and Supplementary Fig. S1). In addition, we coincubated live platelets and tumor cells on slides after staining platelet membranes in red (Dil) and tumor cell membranes and cytoplasm in green (DiO, Calcein). Confocal microscopy pictures were captured over 5 minutes, every 10 seconds, to trace platelet–tumor cell interactions over time. The data presented in Fig. 2C and the Supplementary Video reveal repetitive fusions (yellow) of platelet and tumor cell membranes, which provides a structural correlate for the exchange of membrane components between platelets and tumor cells (Fig. 2C and Supplementary Video).

**Analysis of MHC class I expression on the ultrastructural level**

Next, we employed electron microscopy to investigate MHC class I “pseudoexpression” at an ultrastructural level. Again, tumor cells were incubated with platelets at a ratio of 1:1,000 which resulted in efficient coating of the tumor cells by platelets. Beyond confirming tumor cell coating, electron microscopy revealed that the coating platelets displayed a degranulated phenotype (Fig. 3A), which is in line with the findings by us and others that activated platelets release a variety of soluble factors after interaction with tumor cells (19, 26, 27). Tumor cells and coating platelets displayed close membrane contact, including formation of tumor cell pseudopodia around the platelets (Fig. 3B). Immunogold staining
Figure 1. Expression of platelet surface molecules by tumor cells upon platelet coating. A, single-cell suspensions of the indicated tumor cell lines underwent immunofluorescent staining after incubation with or without platelets. Whereas all malignant cells expressed cytokeratin (green), platelets were positive for glycoprotein IIIa (CD61, red) and MHC class I (yellow). Note that after coincubation with platelets, tumor cells acquire positivity for MHC class I, as documented by merged immunofluorescence for cytokeratin and MHC class I (right column). Pan-cytokeratin-Alexa488 (green), CD61-PeCy3 (red), and MHC class I-PeCy5 (yellow) antibodies were used. Nuclei were counterstained with DAPI (blue). Absolute magnification 400×. B, flow cytometric analysis of peripheral blood after red cell lysis from 3 exemplary female patients, who presented with bone marrow involvement of colon (top) and breast cancer (middle and bottom). Circulating tumor cells were identified by their positivity for CEA or cytokeratin. Note that circulating tumor cells coexpress the platelet marker CD41a, indicating in vivo coating of cancer cells. The gating strategies are shown in forward and side scatter dot plots; isotype controls were included to rule out nonspecific antibody binding.
for MHC class I revealed substantial MHC class I levels at such tumor cell pseudopodia areas. The observed membrane fusions further indicated transmembraneous integration of platelet-derived MHC class I (Fig. 3B). These results provide a morphologic correlate for previous findings by us and others that coating of tumor cells by platelets leads to activation and degranulation of the platelets and may further result in transfer of platelet-specific molecules onto the tumor cell. Indeed, the above described tumor cell processes forming upon coincubation with platelets may actively contribute to this process.

**Cancer cell "pseudoself" impairs NK cell reactivity**

Next, we studied the functional relevance of MHC class I pseudoexpression for NK antitumor reactivity. As tumor cell coating leads to platelet activation and degranulation and because platelets can release a variety of factors capable of influencing NK reactivity (4, 19), it was important...
to dissect the contribution of soluble and membrane-bound molecules. To this end, we incubated the tumor cells in the absence or presence of platelets, followed by further extensive wash steps to remove platelet releasate as well as surplus platelets. Compared with uncoated controls, significantly ($P < 0.05$, Student $t$ test) reduced cytotoxicity by NK cells of the platelet donor was observed with platelet-coated tumor cells. NK reactivity could be restored in great part by blocking MHC class I (Fig. 4A). Of note, the blocking F(ab')$_2$ fragments did not alter NK reactivity against uncoated tumor cells, regardless whether the targets (allogenic to the NK/platelet donor) expressed MHC class I or not. This showed that the constitutive expression of tumor-specific MHC class I had no relevant influence in our experiments due to tumor–NK cell KIR (killer immunoglobulin-like receptors) mismatch, and inhibition of NK reactivity upon platelet coating was due to the inhibitory influence of platelet-specific MHC class I. Next, we studied NK cell IFN-γ production in cultures with platelet-coated/uncoated tumor targets. Presence of PC3 and NCCIT cells induced substantial IFN-γ release by NK cells, which peaked between 12 to 18 hours of incubation. Platelet coating significantly ($P < 0.05$ between 3 and 24 hours of incubation, Student $t$ test) reduced IFN-γ production with the inhibition of NK cytokine release being most pronounced at 9 to 18 hours of incubation (Fig. 4B). Next, we used our blocking MHC class I F(ab')$_2$ fragments to determine the contribution of platelet-derived MHC class I. Although cytokine levels in cultures with untreated tumor cells were not altered, MHC class I blockade partially restored IFN-γ production in cultures with platelet-coated tumor cells (Fig. 4C). This effect was statistically clearly significant ($P < 0.05$ Student $t$ test), albeit recovery of IFN-γ production was less pronounced as compared with the effect of MHC class I blockade on restoring NK cytotoxicity. A potential explanation for the differing efficacy in the analyses of cytotoxicity and cytokine production is provided by the fact that different technical settings were employed for analysis of the 2 NK effector functions (among others, 2-hour vs. 12-hour assay time in analyses of cytotoxicity and cytokine production, respectively). It seems possible that contamination with low levels of platelet releasate, which mediates inhibitory effects, for example, by NKG2D downregulation requiring several hours to occur (19), may have contributed to inhibition of NK cytokine production while not affecting cytotoxicity. In addition, cytotoxicity and cytokine production of NK cells are governed by at least partially differing mechanisms/signaling pathways (28–31), which may account for differential effects of platelets on these 2 NK cell effector functions.

Inhibition of NK reactivity was also observed when NK cells were cultured in the presence of carefully washed platelets from the same donor and IFN-γ production was induced by addition of the activating cytokine IL-15 in the absence of tumor targets. Although only low levels of IFN-γ were detectable without IL-15, substantial IFN-γ production that peaked at about 12 hours of culture was observed upon cytokine stimulation. In the presence of platelets, IFN-γ

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**Figure 3.** Platelet-derived MHC class I integrates into tumor cell membranes. A, structural interaction of tumor cell–platelet aggregates was assessed by transmission electron microscopy. Note the “empty”, degranulated (open arrow) versus granulated appearance of tumor-coating platelets and platelets without intimate tumor contact, respectively. B, MHC class I on platelet-coated tumor cells was stained with postembedding immunogold labeling using 10 nm gold particles (red dots). Gold particles densely accumulating on the platelet surface as well as at sites of focal intimate contacts of platelet (left) and tumor cell (right) membranes are indicated by arrows. Bars represent 500 nm.
release was significantly reduced ($P < 0.05$ between 3 and 18 hours, Student $t$ test) and required 24 hours to reach the levels produced by NK cells in the absence of platelets (Fig. 4D). MHC class I blockade significantly ($P < 0.05$, Student $t$ test), but only partially, restored NK IFN-$\gamma$ release in the presence of platelets (Fig. 4E). Although this indicates that other, yet unidentified molecules contribute to inhibition of NK reactivity by platelets, these results confirmed the NK-inhibitory effect of platelet-expressed MHC class I and, notably, also excluded that merely direct effects of the platelets on the tumor cells were responsible for the impaired NK reactivity observed in antecedent analyses.

**Discussion**

Recognition of MHC class I by inhibitory KIR is considered a predominant mechanism responsible for NK cell tolerance to self (9, 11, 12). Although counterintuitive from the "missing self" principle of NK cell activation (11, 12), tumor cells often downregulate MHC class I, likely to evade T-cell-mediated immunosurveillance (32). In this study, we provide evidence that circulating/metastasizing tumor cells rapidly get coated in the presence of platelets. This causes transfer of platelet-derived MHC class I onto the tumor cells and results in impaired NK antitumor reactivity. We suggest that this molecular mimicry may contribute to evasion of cancer cells from immunosurveillance as it allows reduction of tumor antigen presentation via MHC to T cells by MHC class I downregulation, while disturbing missing self-recognition and thus antitumor reactivity of NK cells.

Already in 1968 Gasic and coworkers showed the impact of platelets on the formation of metastasis, as platelet depletion reduced the number of pulmonary metastases after tail-vein injection of tumor cells in mice (16). Anticoagulant drugs also attenuated metastasis in the same model. About 15 years later Gorelik and colleagues reported that interfering with the hemostatic system prevents metastasis by a NK cell–dependent mechanism (33). Although fibrinogen and factor XIII, components of the plasmatic coagulation system, were found to reduce NK cell reactivity (13, 15), the available data point to a more prominent role of platelets for inhibiting NK cell reactivity in metastasis (8). Utilizing Gøq-deficient (Gøq$^{-/-}$) mice, Palumbo and colleagues showed that platelet activation, which is associated with both adhesion to tumor cells and release of platelet granule contents, is crucial for their metastasis-facilitating effect (13). Importantly, adhesion may be more important for metastasis than aggregation, which is mainly associated with release of granule contents (34). Considering that platelets and the plasmatic coagulation system may promote metastasis on multiple different levels (4), it is obvious that delineation of specific mechanisms is close to impossible in animal models. Even mouse models with functional, rather than quantitative platelet defects, such as in the diligent work of Palumbo and coworkers, can only partially help to distinguish tumor-promoting effects of platelets mediated by NK cell inhibition and NK-independent mechanisms. Thus, a detailed dissection of NK-evasion mechanisms

**Figure 4.** Pseudoexpression of MHC class I on tumor cells impairs NK antitumor reactivity. A, PC3 and NCCIT tumor cells were incubated with or without platelets. Then cytotoxicity of NK cells of the platelet donor in the presence or absence of anti-MHC class I F(ab’)2 or isotype control (5 μg/mL each) was evaluated by 2-hour BATDA Europium assays. B, PC3 and NCCIT tumor cells were incubated with or without platelets and then cultured with NK cells of the platelet donor for the indicated times. IFN-γ production in the presence or absence of anti-MHC class I F(ab’)2 or isotype control (5 μg/mL each) was analyzed as described in B after 12 hours. Where indicated, anti-MHC class I F(ab’)2 or isotype control (5 μg/mL each) had been added to platelets. Exemplary data of at least 3 experiments with similar results are shown. Significant differences ($P < 0.05$, Student $t$ test) are indicated by *.

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Platelet MHC Class I Impairs NK Antitumor Reactivity

By such analyses, we recently showed that platelet-derived TGF-β, released upon tumor cell–platelet interaction, inhibits NK-mediated immunosurveillance through downregulation of the activating NK receptor NK2D and thus impaired "induced self" recognition (19). Although this provided evidence for a molecular mechanism accounting for the effect of platelet-derived soluble factors, the data presented here show that platelets can confer an immunophenotype of false pretenses—or "pseudoself"—to the tumor cell surface. Transfer of membrane fragments and immunoregulatory molecules has previously been described upon interaction of lymphocytes with antigen-presenting cells or tumor cells. This process was termed trogocytosis and, depending on the transferred molecules, the involved cell types, and the disease model utilized, results in enhanced or reduced immune responses (e.g., refs. 35, 36). Very recently, Wakim and Bevan reported that dendritic cells, upon contact with neighboring donor cells, can acquire MHC class I–peptide complexes capable to stimulate memory CD8 T-cell responses and confirmed the functional role of such "cross-dressed" dendritic cells in a mouse model of viral infection (37). Upon NK–tumor cell interaction, transfer of tumor-expressed HLA-G, a nonclassical MHC class I molecule with immunosuppressive properties, impairs NK effector functions and even causes HLA-G1–positive NK cells to behave as suppressor cells (38). Our data, provide, to our knowledge, the first evidence that transfer of immunoregulatory proteins may occur between platelets and tumor cells. Their interaction causes an MHC class I–positive phenotype (i.e., "pseudoself") of inherently MHC class I–negative/low cancer cells upon entering the blood stream, which may allow tumor cells to down-regulate MHC class I to evade T-cell–mediated immune responses without inducing a sufficient NK cell reaction. The platelet-derived MHC class I blocks NK cell reactivity and, presumably, presents "unsuspicious" self peptides which do not induce T-cell reactivity, as platelet MHC class I molecules present peptides reflecting the normal ligandome of the megakaryocyte lineage. In line, allogenic MHC class I molecules were found to be incapable to stimulate allogenic CD8 T-cell responses in vitro (23, 39).

Of note, Nieswandt and colleagues observed in mice that impaired NK cytotoxicity against YAC1 cells occurred with platelets from different allogenic as well as β2-microglobulin-deficient animals (8). This led the investigators to conclude that tumor protection by platelets may occur independently of HMC class I. However, although supernatants of platelets mediated NK inhibitory effects in their analyses, no measures to remove releasate were employed in this study. Therefore, MHC class I–mediated effects may have been masked by platelet-derived soluble factors. Because NK cell reactivity results of an integrative response emerging from multiple activating, inhibitory, and costimulatory signals, the results of Nieswandt and colleagues do not contradict our findings but rather support our notion that platelets may influence NK cell antitumor reactivity by various mechanisms, including disruption of "induced self" and "missing self" recognition.

Numerous attempts are presently made to introduce NK cells in the treatment of cancer by interventions that prevent suppression or stimulate the reactivity of autologous or allogenic NK cells (40). Our data not only elucidate a mechanism by which malignant cells may utilize platelets to impair the ability of NK cells to prevent metastasis, they also indicate that modulation of platelets as an underestimated third player should be incorporated in strategies aiming to enhance NK antitumor reactivity. A better understanding of the molecular mechanisms underlying platelet contribution to immune evasion of tumor cells holds promise to identify new antimetastatic therapies that ultimately may improve therapeutic options for cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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