frontiers in Immunology

MINI REVIEW
published: 29 January 2020
doi: 10.3389/fimmu.2020.00073

Tumor Microenvironment-Associated Extracellular Matrix Components Regulate NK Cell Function

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The tumor microenvironment (TME) is composed of multiple infiltrating host cells (e.g., endothelial cells, fibroblasts, lymphocytes, and myeloid cells), extracellular matrix, and various secreted or cell membrane-presented molecules. Group 1 innate lymphoid cells (ILCs), which includes natural killer (NK) cells and ILC1, contribute to protecting the host against cancer and infection. Both subsets are able to quickly produce cytokines such as interferon gamma (IFN-γ), chemokines, and other growth factors in response to activating signals. However, the TME provides many molecules that can prevent the potential effector function of these cells, thereby protecting the tumor. For example, TME-derived tumor growth factor (TGF)-β and associated members of the superfamily downregulate NK cell cytotoxicity, cytokine secretion, metabolism, proliferation, and induce effector NK cells to upregulate ILC1-like characteristics. In concert, a family of carbohydrate-binding proteins called galectins, which can be produced by different cells composing the TME, can downregulate NK cell function. Matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase (ADAM) are also enzymes that can remodel the extracellular matrix and shred receptors from the tumor cell surface, impairing the activation of NK cells and leading to less effective effector functions. Gaining a better understanding of the characteristics of the TME and its associated factors, such as infiltrating cells and extracellular matrix, could lead to tailoring of new personalized immunotherapy approaches. This review provides an overview of our current knowledge on the impact of the TME and extracellular matrix-associated components on differentiation, impairment, and function of NK cells.

Keywords: NK cells, tumor microenvironment, galectin, MMP, ADAM

OPEN ACCESS

Edited by:
Nicolas Jacquelot, Walter and Eliza Hall Institute of Medical Research, Australia

Reviewed by:
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Jacques Zimmer, Luxembourg Institute of Health (LIH), Luxembourg

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Specialty section:
This article was submitted to NK and Innate Lymphoid Cell Biology, a section of the journal Frontiers in Immunology

Received: *10 November 2019*
Accepted: *13 January 2020*
Published: *29 January 2020*

Citation:
Rossi GR, Trindade ES and Souza-Fonseca-Guimaraes F (2020) Tumor Microenvironment-Associated Extracellular Matrix Components Regulate NK Cell Function. Front. Immunol. 11:73. doi: 10.3389/fimmu.2020.00073

INTRODUCTION

Innate lymphoid cells (ILCs) are lymphocytes derived from a common lymphoid precursor. Unlike T and B lymphocytes, ILCs do not express adaptive antigen receptors, instead being activated through cytokine receptors (1). Natural killer (NK) cells are classified as group 1 ILCs together with ILC1 (2), previously known as tissue resident NK cells (3), due to their shared dependence on the transcription factor T-bet, production of specific cytokines (e.g., interferon-gamma, IFN-γ), and surface receptor expression (e.g., NK1.1, NKp46 in mice, and NKp30 in humans) (1, 4). During development in the bone marrow, both mouse and human NK cells appear dependent on

the transcription factor Eomesdermin (Eomes) (5), then during maturation they repress Eomes and increase T-bet production (4). However, in humans, mature liver ILC1s can express Eomes (6). Although ILC1 are tissue resident and unlikely to migrate to other tissues (7–9), their function in cancer is poorly understood. Recent studies have revealed that transforming growth factor-beta (TGF-β) signaling (either by TGF-β itself or indirectly by Activin-A) can suppress cellular metabolism and effector functions (10–12). This suppressive signaling drives the upregulation of ILC1-related markers in circulating mouse or human NK cells, suggesting the possibility of intercellular plasticity which could be important within the tumor microenvironment (TME) (11, 13, 14). NK cell cytotoxicity can be controlled by many stimulatory (NKp30, NKp44, NKp46, CD16) and inhibitory (PD1, TIM3, TIGIT, KLRG1) surface receptors (15). Even with their ability to kill transformed cells, NK cell immunosurveillance can be evaded by tumor cells due to their ability to manipulate the TME in favor of immune equilibrium and escape, allowing tumor survival and the possibility of further metastatic spread (16–18). Once established, the TME is composed of different immune and non-immune cell subsets recruited by the tumor (e.g., fibroblasts, pericytes, endothelial cells, macrophages, lymphocytes, etc.) (19), bioactive products, such as extracellular matrix (ECM) proteins, cytokines, and growth factors (20), and specific glycosylation pattern (21, 22). In this review we will discuss some of the molecules present in the TME (summarized on **Table 1**), with a focus on their potential impact on NK cell functions.

TABLE 1 | TME molecules and the effect on NK cells.

TME molecule	Effect on NK cells	Cancer type	References
Hyaluronan	Impair access to tumor and ADCC	Breast and ovarian caner	(23)
Heparanase	Decrease recognition of target cells	Breast cancer	(24)
Galectin-1	Impair cytotoxicity	Glioma	(25)
Galectin-3	Galectin-$3^{-/-}$ mice have more effective cytotoxic $CD27^{high}CD11b^{high}$ NK cells	Melanoma	(26)
	Increase of galectin-3 impair NK cells cytotoxicity	Adenocarcinoma, cervix cancer	(27)
Galectin-9	Increase of NK cells infiltration	Melanoma	(28)
	Downregulation of stimulatory genes (LTB, KLRF1, FCGR3A) and impair cytotoxicity against K562 cells	Leukemia	(29)
	Galectin-9 binds to TIM-3 leading to NK cells exhaustion	Gastrointestinal tumors	(30)
Sialic acid	Low sialylation of tumor cells increases NK cell cytotoxicity	Melanoma	(31)
Siglec-7/9	Membrane inhibitory receptor on NK cells that recognize sialic acid	Melanoma, basal cell carcinoma, squamous cell carcinoma, and cutaneous T cell lymphoma	(32)
MMP-9	Cleaves MIC-A, MIC-B and ULBP-2 from tumor cells membrane avoiding killing by NK cells	Human gastric cancer, lung adenocarcinoma and osteosarcoma	(33–35)
ADAM-10/17	Cleave MIC-B, ULBP-2 and B7-H6 from tumor cells membrane avoiding killing by NK cells	Human pancreatic adenocarcinoma, melanoma, cervical, breast, hepatocellular carcinomas and glioblastoma	(36–38)

GLYCOSAMINOGLYCANS AND PROTEOGLYCANS

Glycosaminoglycans (GAGs) are a family of linear polysaccharides composed of repeating disaccharide units. Depending on the disaccharide composition, GAGs can be classified as: keratan, chondroitin, dermatan or heparan sulfate (HS), heparin, or hyaluronan (39). Except for hyaluronan, all GAGs can be linked to proteins, forming proteoglycans (PGs) (40).

Hyaluronan is the only non-sulfated GAG, first isolated and characterized from bovine vitreous humor in 1934 (41). It is produced and secreted to the ECM by the transmembrane hyaluronan synthase (42), which is encoded by three conserved genes in both mice (*Has1, Has2,* and *Has3*) and humans (*HAS1, HAS2,* and *HAS3*) (43, 44). In cancer, hyaluronan is associated with tumor cell proliferation, angiogenesis, and evasion of immune responses and apoptosis (45–50). The presence of hyaluronan in the TME appears to be detrimental to NK cell function against cancer cells; hyaluronan rich tumors can inhibit both NK cell access to tumor cells and antibody-dependent cell-mediated cytotoxicity (ADCC) (23). Although hyaluronan does not form PGs, it can bind to PGs by linking proteins (51). Our group recently identified a poor prognostic association between the *HAPLN3* gene (Hyaluronan and Proteoglycan Link Protein 3) and a low NK cell infiltration in malignant melanoma patients, suggesting a potential inhibition of anti-tumor immune functions by *HAPLN3* and identifying this gene as a potential target for immunotherapy (52).

Heparan sulfate proteoglycans (HSPGs) can be found on the cell surface (glypicans and syndecans families) or in the ECM (perlecan, agrin, collagen XVIII) (53). Many types of tumors overexpress HSPGs, which is associated with increased angiogenesis in hepatocellular and colon carcinomas, breast and pancreatic cancers, and melanoma (54–58). HSPGs are also associated with invasion and metastasis in melanoma and breast cancer (59–61). Some reports have suggested that HS chains can be ligands for NKp30 (62, 63), NKp44 (63, 64), NKp46 (62, 63, 65), and for the NKG2D and CD94 complex (66). This tumor production of HSPG is not sufficient to stimulate NK cell cytotoxicity, and there are two potential hypotheses for this observation:

i) Tumor cells present altered expression of many enzymes related to the HSPG modifications, such as sulfatase 2 and heparan sulfate 6-O- sulfotransferase 2 (67–69), leading to production of PGs containing distinctly sulfated HS chains (70, 71). Differences in sulfation pattern could impair the recognition of HS chains by NKp30, NKp44, and NKp46 (62, 63, 65).
ii) Melanomas, multiple myeloma, bladder, prostate, breast, colon and liver cancers overexpress heparanase (72–76), which is an endo β-D-glucuronidase that cleaves specific regions of HS into small fragments (77, 78), decreasing NK cells ability to recognize target cells (24). However, a previous study showed that heparanase produced by NK cells is also unexpectedly important for the host tumor surveillance by allowing NK cell navigation through the ECM (79).

GALECTINS

Galectins are a group of proteins with two main features: β-galactoside binding sites and conserved carbohydrate recognition domains (CRDs) (80). The first galectin was isolated in 1975 from an electric fish (*Electrophorus electricus*) and named electrolectin (81). Just in 1994, the name galectin was given to this family of lectins and all members were numbered in order of discovery (80). Galectins are divided into three groups: prototype have one CRD domain (galectins 1, 2, 7, 10, 11, 13, 14, and 15); tandem-repeat type have two CDR domains (galectins 4, 8, 9, and 12); chimera-type have a single CRD domain and an amino-terminal polypeptide rich in proline, glycine, and tyrosine residues (galectin-3) (82).

Galectins are expressed in many different mammalian tissues (83, 84) and are involved in early development, tissue regeneration, immune homeostasis, and some pathologies (e.g., cancer, obesity, type II diabetes) (85). In some types of cancer, galectins may be associated with angiogenesis, cancer cell survival, invasion, metastasis, and avoiding immunosurveillance (86). Here we will discuss and revisit the potential contribution of different galectins for the TME, NK cell function, and anti-cancer responses.

Galectin-1 is important for maturation of B cells in the bone marrow (87, 88) and T cells homeostasis (89–91). It is overexpressed in some types of cancer such as ovarian, breast, myeloma, and melanoma (92–95), and can contribute to tumor survival by inhibition of NK cells (25). Glioma cells deficient for galectin-1 showed reduced tumor growth, increased intra-tumor NK cell infiltration, and elevated expression of granzyme B when implanted into the striatum of *Rag1*$^{-/-}$ mice (which develop NK, but not T or B cells) when compared to *Rag1*$^{-/-}$ mice injected with wild-type cells (25). In the same study, galectin-1 deficient glioma cells were injected into NGS (T, B, and NK cells deficient) or C57BL/6 immunocompetent mice treated with anti-asialo GM1, which depletes NK cells. Enhanced tumor growth was observed in both models, proving the inhibitory effect galectin-1 has on NK cell anti-tumor function (25).

Galectin-3 was initially discovered in macrophages and named Mac-2 (96). It starts to be expressed in many normal tissues during embryogenesis (in both mice and humans) (97) and is involved in angiogenesis (98) and migration of monocytes and macrophages (99). In cancer, galectin-3 overexpression in the TME is associated with angiogenesis (98), tumor progression (97), and immune escape by inducing T cell apoptosis (100, 101). Some reports have also shown the impact of galectin-3 on NK cells. For example, galetin-3-deficient mice are resistant to lung metastasis development by B16-F1 melanoma cells, potentially due to an increase of CD27^{high} CD11b^{high} NK cells in their spleen compared with the wild type (26), suggesting an inhibitory effect of galectin-3 on NK cell immunosurveillance. Additionally, HeLa cells overexpressing galectin-3 are more resistant to human NK cell-mediated death; yet when galectin-3 is knocked out the killing capacity of NK cells is restored in a mechanism mainly mediated by NKp30 (27). Considering the potential for galectins as cancer treatment targets, clinical trials using galectin inhibitors have already started for both galectins 1 (ClinicalTrials.gov identifier: NCT01724320—for advanced solid tumors; NCT00054977—for advanced solid tumors in combination or not with 5-Fluorouracil) and 3 (NCT02575404—for advanced melanoma, non-small cell lung cancer, and head and neck squamous cell cancer in combination with Pembrolizumab; NCT02117362—for advanced melanoma in combination with Ipilimumab).

Galectin-9 was first described in mouse embryos and later discovered during homeostasis in many adult organs such as liver, kidney, spleen, and lungs (102). In some cancers, galectin-9 is related with a good prognosis (103). In breast, pancreatic cancer and melanoma, expression of galectin-9 correlates with good prognosis for those patients (28, 104, 105). Galectin-9 appears to promote patient survival in part through NK cell modulation (106). C57BL/6 mice that had B16-F10 melanoma injected into their peritoneal cavity followed by galectin-9 treatment showed prolonged survival compared with untreated controls, which also correlated with increased NK cell infiltration into the peritoneal cavity; however, when NK cells were depleted by anti-asialo GM1, those positive effects were lost, suggesting a stimulatory effect of galectin-9 on NK cells (106). Despite these findings, the role of galectin-9 may be ambiguous, as inhibitory effects over NK cells have also been demonstrated (29). Human NK cells exposed to galectin-9 downregulate many NK cell stimulatory genes (e.g., LTB, KLRF1, FCGR3A), resulting in less efficient killing of target leukemia K562 cells (29). A possible explanation for galectin-9 mediated inhibition of NK cells could be its interaction with and activation of TIM-3 (T cell immunoglobulin and mucin domain 3) (107), which is a transmembrane receptor associated with NK cell exhaustion (108, 109). Additionally, a positive correlation was found between galectin-9 expression on human gastrointestinal stromal tumor and TIM-3^{+} expression on infiltrating NK cells (30). This study suggests that targeting galectin-9 or preventing its interaction with TIM-3 could potentially act as a novel immunotherapy approach to enhance NK cell functions against cancer (30).

SIALIC ACID AND MUCINS

Sialic acids (Sia) are a family of carbohydrates composed of *N*-acetylneuraminic acids (110) linked to many proteins, lipids,

and other polysaccharides on the cell surface. The most common Sia are *N*-acetylneuraminic (Neu5Ac) and *N*-glycolylneuraminic (Neu5Gc) acids (111). Humans only express Neu5Ac, due to the lack of an enzyme called cytidine monophospho-*N*-acetylneuraminic acid hydroxylase, which converts Neu5Ac to Neu5Gc (112). Sia are associated with many biological processes, but an important function is recognizing self and non-self (113). Many types of cancer, including breast cancer and cervix squamous cell carcinoma, are hypersialyated (114, 115) due to the overexpression of Sia synthesis enzymes (116, 117). This hypersialytion is associated with increased metastasis (117) and immune system evasion (118). A study using "Sia low" B16-F10 cells demonstrated that after their subcutaneous injection into C57BL/6 mice, tumors grew more slowly and exhibited increased NK cell infiltration when compared with standard B16-F10 cells (31). Additionally, after NK cell depletion (using anti-NK1.1) "low Sia" tumors grew at a similar rate to the control group, highlighting the importance of NK cells during the defense against sialyated tumors (31).

The interactions between cells and Sia are mediated by transmembrane proteins called Siglecs (sialic acid-binding immunoglobulin-type lectins) (119). Siglecs are expressed in all immune cells and are divided into two broad groups: CD33 and CD33-related Siglecs, which have high homology with CD33 in their extracellular domains, and CD33-unrelated Siglecs which have high homology between human, rodents and other vertebrates (120). Both groups consist of both activating and inhibitory receptors, where the inhibitory Siglecs contain the intracellular immune receptor tyrosine-based inhibition motifs (ITIM), leading to tyrosine phosphorylation and tyrosine phosphatases SHP-1 and SHP-2 (121) (and as exemplified in **Figure 1A**). ITIMs are associated with NK cell inhibition and

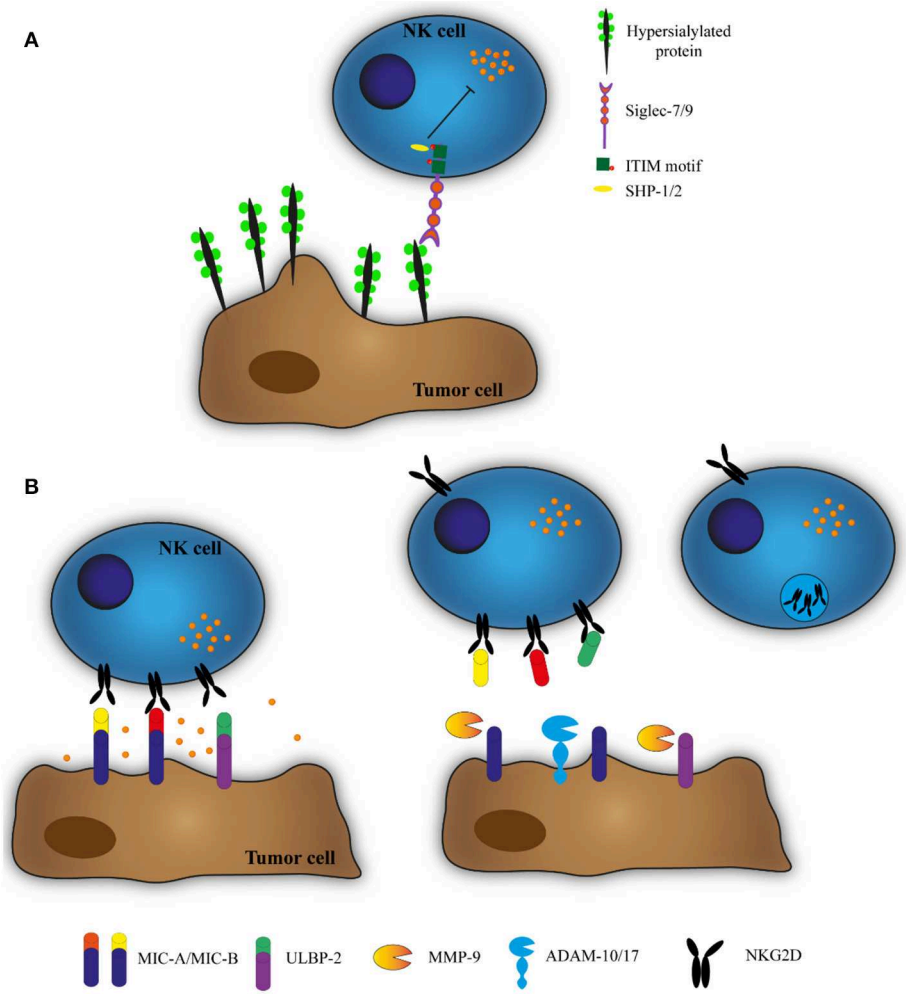

FIGURE 1 | (A) Hypersialysation of tumor cells inhibits NK cell cytotoxicity. To impair recognition by NK cells, tumor cells change their glycosylation pattern, expressing more sialic acid on the cell membrane. NK cells express membrane receptors that recognize this sialic acid (Siglecs). Siglecs have an intracellular immune receptor tyrosine-based inhibition motif (ITIM) that recruits tyrosine phosphatases SHP-1 and SHP-2 and inhibits NK cell cytotoxicity. **(B)** ADAMs and MMPs cleave MIC-A, MIC-B, and ULBP-2 and downregulate NKG2D expression. NK cells can recognize and kill target cells by the interaction between the stimulatory receptor NKG2D and the ligands MIC-A, MIC-B, and ULBP-2. However, the TME contains ADAMs and MMPs that cleave these ligands, allowing the soluble proteins to bind to NKG2D and stimulate its degradation.

are related to other inhibitory receptors (e.g., Ly-49 and NKG2-A) (122, 123). Human NK cells express Siglec-7 (also named as p75/AIRM1) (124, 125) and Siglec-9 (126) on the cell surface. Siglec-7 is expressed in all human NK cells (124, 125) whereas Siglec-9 is expressed selectively in a subset of $CD56^{dim}$ NK cells (32, 127). Jandus and colleagues demonstrated that various human tumor samples (melanoma, basal cell carcinoma, squamous cell carcinoma, and cutaneous T cell lymphoma) and tumor cell lines (e.g., A375, HeLa, SW1116, and K562) have ligands for both Siglec-7 and 9. They also found that NK cells displayed increased cytotoxicity against HeLa and K562 after enzymatic treatment to remove the Sia from the target cell surface (32). Cell lines of multiple myeloma (e.g., RPMI 8226 and H929) pre-treated with a sialyltransferase inhibitor were also more susceptible to NK cell-mediated killing (128). In a separate study, Balb/c mice injected with desialylated MCA-induced fibrosarcoma cells developed less lung metastasis, an effect which could be abolished when NK cells were depleted by antibodies (129). Besides inhibitors of sialytranferase and enzymes that cleave Sia, other strategies can be applied to avoid Sia-mediated inhibition of NK cells, and antagonists for Siglecs-7 and 9 could be an option (130). This has been demonstrated by Prescher and collaborators, who described a small molecule inhibitor of Siglec-7 which increased cytotoxicity of human NK cells toward Mel1106 melanoma target cells (130).

Siglec-9 can also interact with mucin-1 and 16 (127, 131), which are rich in Sia (132, 133). Mucins are proteins that have tandem repeat structures which are highly glycosylated and rich in proline, threonine, and serine (PTS domains) (134). They are normally expressed by epithelial cells, but are overexpressed in some types of cancer, particularly ovarian (135). Some reports have shown that murine ovarian cancer cells knocked down for mucin-16 are more susceptible for NK cell killing, showing that mucin-16 has an impact on NK cells (136, 137). While mucin-1 is also a ligand for Siglec-9, it has only been demonstrated to have a direct inhibition on macrophages (138). However, mucin-1 may have other effects on NK cells (139). In human metastatic bladder cancer, tumor cells overexpress the enzyme 2β-1,6-N-acetylglucosaminyltransferase (C2GnT) that adds a poly-N-acetyllactosamine on Mucin-1. The increased glycosylation of Mucin-1 raises its affinity for galectin-3 binding. Consequently, this Mucin-1/galectin-3 complex is suggested to generate a shield around tumor cells, which impairs recognition by NK cells (139).

MATRIX METALLOPROTEINASES (MMPs) AND A DISINTEGRIN AND METALLOPROTEINASES (ADAMs)

Matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinases (ADAMs) belong to a superfamily of zinc-dependent metalloproteinases known as metzincins, which process or degrade virtually all structural ECM proteins, growth factor–binding proteins, cell-cell adhesion molecules, and cell surface receptors (138, 139). MMPs are found either on the cell surface or soluble, and are involved in tissue remodeling and wound healing (140). ADAMs are single-pass membrane proteins that are important in shedding proteins and embryogenesis (141). In many types of cancer, MMPs and ADAMs are associated with tumor progression through angiogenesis, invasion, metastasis, and regulation of the immune response (142, 143).

MMPs and ADAMs can cleave NKG2D ligands from the tumor cell surface, including MHC class I chain-related A (MIC-A), MHC class I chain-related B (MIC-B), and UL16-binding protein (ULBP) (144, 145). The soluble forms of cleaved proteins from tumor cell membrane bind to NKG2D, inducing endocytosis and degradation of this receptor, resulting in the tumor evasion from the surveillance of this receptor (144, 146) (**Figure 1B**). This effect has been observed in multiple studies using different tumor cell lines, and in all of them the NK cell function returns to normal after using inhibitors for MMPs or ADAMs (33–37). *Ferrari de Andrade* and collaborators developed an antibody that binds to the MIC-A α3 domain, the site of proteolytic shedding, to avoid MIC-A cleavage, and demonstrated this could increase NK cell cytotoxicity toward human melanoma cells (147).

MMPs can also shed intercellular-adhesion molecule 1 (ICAM-1) from the tumor cell surface, a protein that is important for the adhesion of cytotoxic T lymphocytes and NK cells to target cells (148, 149). Interaction of NK cells with target cells expressing ICAM-1 leads to an expression of IFN-γ (150). Many types of cancers express ICAM-1 (151), however it is thought to be shed from the surface of tumor cells to avoid an immune response (152, 153). Indeed, when comparing the human breast cancer cell line MDA-MB435 ($ICAM\text{-}1^{+}$ and $MMP\text{-}9^{-}$) to transfected MDA-MB435 ($ICAM\text{-}1^{+}$ and $MMP\text{-}9^{+}$), the transfected cells had a higher concentration of soluble ICAM-1 in the supernatant and were more resistant to NK cells. This resistance was reversed when those cells were co-cultured in the presence of MMP-9 inhibitors (154).

ADAM-10 and 17 can also catalyze the cleavage of B7-H6, one of the ligands for NKp30 (both only expressed in human) (38). Using many different human tumor cell lines (pancreatic adenocarcinoma, melanoma, cervical, breast, and hepatocellular carcinomas), Schlecker and colleagues observed that these cells produced B7-H6 at the mRNA level; however they had a low abundance of this protein on the cell membrane compared to what was detectable in the culture supernatant, showing ADAM-10 and 17 cleaving activity (38). The high levels of soluble B7-H6 decreased the expression of NKp30 on the NK cell membrane, leading to a decrease of degranulation. However, in the presence of inhibitors or siRNA for ADAM-10 or 17, the levels of soluble B7-H6 decreased and the degranulation of NK cells was restored (38). Curiously, several reports have also described the effects of ADAM-17 in cleaving CD16 (FcgRIIIA), one of the most important activating receptors responsible for recognition of antibody-coated target cells and NK cell-mediated ADCC, suggesting the potential for inhibitors of ADAM17 as a novel therapeutic approach to increase NK cell anti-tumor potency during immunotherapy (155). As an alternative to prevent ADAM-17-mediated shedding of CD16, Jing and

colleagues showed that replacing the serine at position 197 of the cleavage site of CD16 with proline completely prevented ADAM-17-mediated cleavage of both CD16a and b, enhancing NK cell function to antibody-opsonized tumor cells (156). More recently, the same group provided evidence that amino acid replacement to generate uncleavable CD16 can be feasibly employed in induced human pluripotent stem cells (hiPSC), as a renewable and gene-editable source of off-the-shelf NK cell products with enhanced functionality (157).

Peng and collaborators showed that MMPs can also have a direct effect on NK cells, leading to their dysfunction. NK cells were co-cultured with a pancreatic cancer cell line (SW1990), and an increase of MMP-9 production was observed compared with NK cells co-cultured with a normal pancreatic cell line (hTERT-HPNE) (158). It was also observed that NK cells after been co-cultured with SW1990 presented a reduction in the percentage of cells positive for NKG2D, NKp30, NKp44, NKp46, DNAM-1, perforin, and granzyme B, and those cells were less cytotoxic against K563 (158). However, after incubation with an inhibitor for MMP-9 (TIMP-1) the levels of NKG2D, NKp30 and perforin were partially restored and the killing capacity was recovered (158). Additionally, in concert with our previous observations in murine NK cells (13), Bruno and colleagues described that infiltrating NK cells in human colorectal tumors display a "decidual" behavior by expression of CD49a (among other tissue resident-related markers) and MMP-9 (159). The same study also revealed MMP-9-expressing NK cells as important contributors of tumor angiogenesis, and that inhibition of MMP-9 with immunotherapy could help repolarize NK from pro-angiogenesis to anti-tumor effector cells (159). These recent findings reveal that MMPs might not only play a role in NK cell migration and *in vivo* positioning as previously believed (160), but also directly impact their anti-tumorigenic function and potentially be considered as novel inhibitory checkpoints in NK cell biology.

CONCLUSION

Many components of the TME can impair the cytotoxic activity of NK cells by changing or cleaving ligands that could lead the activation of NK cells, or by an increasing the availability of factors that can downregulate NK cells effector functions. There is an arising interest for identifying novel immune checkpoints for NK cells. Studies around the composition of the TME, such as ECM proteins, enzymes, and glycosylation patterns, are now a field of interest to understand how to overcome tumor inhibitory signals and discover new therapeutic targets.

AUTHOR CONTRIBUTIONS

GR and FS-F-G wrote the manuscript. ET and FS-F-G reviewed the manuscript and provided critical input.

FUNDING

FS-F-G was supported by a project grant from the National Health and Medical Research Council (NHMRC) of Australia (#1140406), and a grant #1158085 awarded through the Priority-driven Collaborative Cancer Research Scheme and funded by Cure Cancer Australia with the assistance of Cancer Australia. ET was supported by a project grant from Conselho Nacional de Desenvolvimento Científico e Tecnológico-Brazil (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brazil (CAPES) (Finance Code 001). GR was supported by CAPES (PDSE-88881.188501/2018-01) and CNPq (140637/2017-6) Ph.D. scholarships.

ACKNOWLEDGMENTS

We thank Timothy McCulloch for critical comments and editing support.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.