OncoImmunology

ISSN: (Print) 2162-402X (Online) Journal homepage: http://www.tandfonline.com/loi/koni20

Antibody targeting soluble NKG2D ligand sMIC refuels and invigorates the endogenous immune system to fight cancer

Jennifer Wu

To cite this article: Jennifer Wu (2016) Antibody targeting soluble NKG2D ligand sMIC refuels and invigorates the endogenous immune system to fight cancer, OncoImmunology, 5:3, e1095434, DOI: 10.1080/2162402X.2015.1095434

To link to this article: http://dx.doi.org/10.1080/2162402X.2015.1095434

Accepted author version posted online: 29 Oct 2015.

ONCOIMMUNOLOGY
2016, VOL. 5, NO. 3, e1095434 (3 pages)
http://dx.doi.org/10.1080/2162402X.2015.1095434

Taylor & Francis
Taylor & Francis Group

AUTHOR'S VIEW

Antibody targeting soluble NKG2D ligand sMIC refuels and invigorates the endogenous immune system to fight cancer

Jennifer Wu[a,b,c]

[a]Department of Microbiology and Immunology, Medical University of South Carolina, Charleston, SC, USA; [b]Cancer Immunology Program, Hollings Cancer Center, Charleston, SC, USA; [c]Department of Medicine, University of Washington, Seattle, WA, USA

ABSTRACT
Human tumor-derived soluble NKG2D sMIC paralyzes the immune system through multiple pathways. Targeting soluble MIC with a nonblocking sMIC-neutralizing anti-MIC antibody effectuated and revamped endogenous innate and adoptive antitumor responses. Therapy induced regression of primary tumors and eliminated metastasis in preclinical models.

ARTICLE HISTORY
Received 14 September 2015
Accepted 14 September 2015

KEYWORDS
Cancer immunotherapy; NKG2D ligands; nonblocking sMIC-neutralizing anti-MIC antibody; soluble MIC

In response to oncogenic insult, human cells were induced to express a family of MHC I chain-related molecules A and B (MICA and MICB, generally termed MIC) on the surface which serve as the ligands for the activating immune receptor NKG2D expressed by all human NK, $CD8^+$ T, NKT, and subsets of $\gamma\delta$ T cells.[1-3] Theoretically, engagement of NKG2D by tumor cell surface MIC is deemed to signal and provoke the immune system to eliminate transformed cells. The significance of NKG2D signaling in eradicating tumors was well proven in experimental animal models decades ago and re-enforced in recent studies.[4,5] Paradoxically, most, if not all, advanced solid tumors express high levels of MIC, suggesting a dominant immune evasion mechanism that allows tumor cells to ignore the NKG2D-mediated immune surveillance and progress.

Clinical evidence revealed that almost all advanced tumors in cancer patients produce soluble MIC through proteolytic shedding mediated by metalloproteases, or by release in exosomes derived from the cell membrane.[3,6] Tumor-derived sMIC is known to be highly immune suppressive (Fig. 1) and profoundly insults the immune system by downregulating receptor NKG2D expression on effector NK and T cells,[1,3] driving the expansion of tumor-favoring myeloid suppression cells, skewing macrophages into alternatively activated phenotypes,[7] and perturbing NK cell peripheral maintenance.[5] High levels of serum sMIC significantly correlate with advanced diseases of many types of cancer. These observations clearly endorse sMIC to be a cancer immune therapeutic target. However, due to potential biological limitations, therapeutic effect of antibody targeting soluble MIC was not determined until our recent studies.[8] First, there was no preclinical mouse model for therapeutic validation since rodents do not express MIC ortholog and mouse NKG2D ligands present different physiobiology from human MIC.[9] Second, a given anti-sMIC mAb may also block the interaction of NKG2D with tumor cell-surface MIC since sMIC shares the same NKG2D-binding ectodomain as cell-bound MIC.[9] This biology poses a therapeutic dichotomy.

In our recent studies, we demonstrated the antitumor efficacy of a nonblocking sMIC-neutralizing anti-MIC antibody B10G5 using a state-of-the-art MIC/TRAMP double transgenic mouse model, which was shown to closely recapitulate the oncoimmune dynamics of MIC^+ cancer patients.[5] B10G5 is an anti-MIC monoclonal antibody that can reduce serum sMIC but does not block the interaction of NKG2D with MIC or sMIC. On the contrary, B10G5 augments NK cell killing of MIC^+ tumor cells presumably through enhanced immune synapse formation. With an eight-week monotherapy of B10G5, TRAMP/MIC mice that had high levels of serum sMIC and advanced prostate carcinoma exhibited remarkable responses with significant regression of primary tumors and complete elimination of metastasis. Therapy obliterated the immune suppression induced by sMIC, exemplified as restoring peripheral NK cell homeostatic renewal and function and recovering NKG2D expression on NK and $CD8^+$ T cells. Therapy also remodeled tumor microenvironment by reducing MDSC and arginase I^+ cells and increasing infiltration of NK and $CD8^+$ T cells in tumor parenchyma. Furthermore, therapy nullified the inherent antigen-specific $CD8^+$ T cell immune tolerance in tumor host, enhanced the $CD44^{hi}$ memory phenotype of $CD8^+$ and $CD4^+$ T cells, primed $CD4^+$ T cells polarizing to IFNγ-producing Th1 phenotype, and enabled DC activation in tumor-draining lymph nodes. Remarkably, therapy elicited a systemic cytokine "storm" including multiple antitumor cytokines, however, presented no systemic autoimmune cytotoxicity. The therapeutic effect was recaptured in TRAMP/MIC mice that had less progressed carcinoma where MIC was

CONTACT Jennifer Wu wujjd@musc.edu

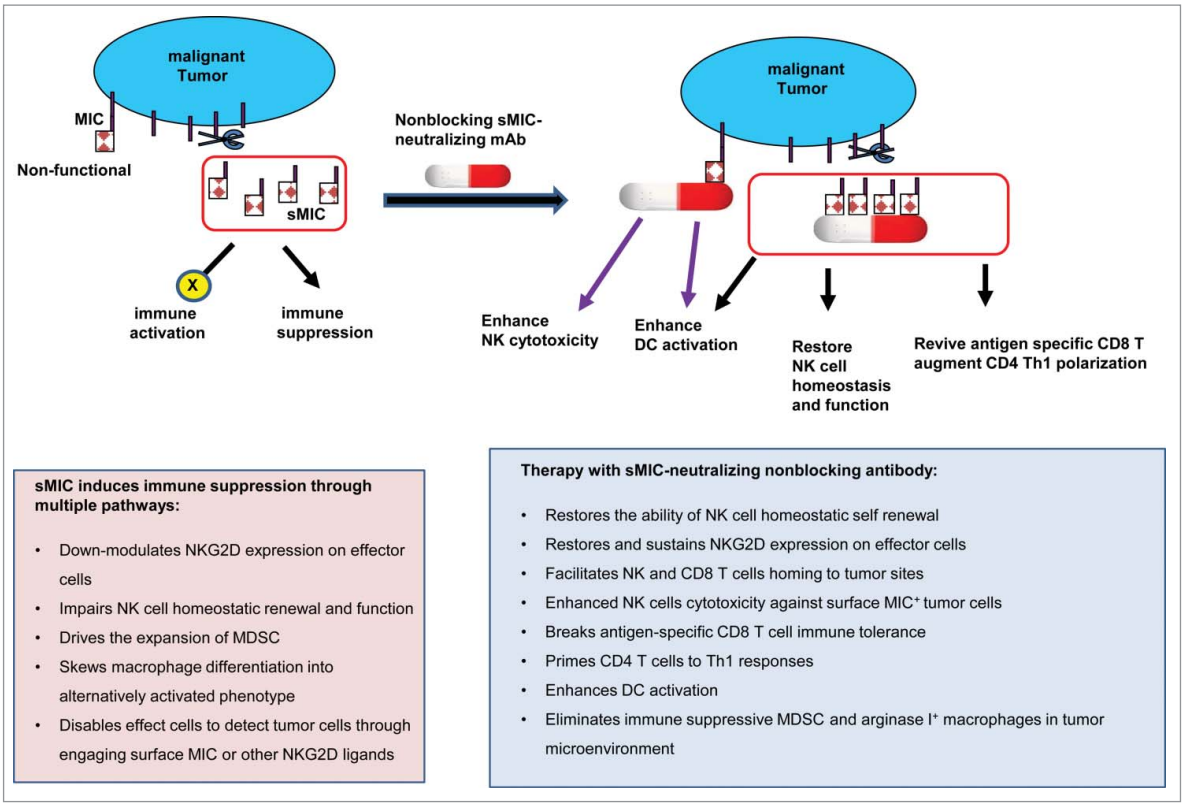

Figure 1. Proposed antitumor therapeutic effector mechanism of the non-blocking sMIC-neutralizing antibody. Malignant tumor cells shed soluble MIC (sMIC), which disarms host antitumor responses through multiple pathways. Therapy with a nonblocking sMIC-neutralizing antibody not only annuls sMIC-induced immune suppression, but also revamps the innate and adaptive immune responses.

predominantly retained on cell surface and in syngeneic transplantable model where tumor cells only express sMIC.

Induced expression of surface MIC during oncogenesis forms a systemic alarm to prevent tumor progression. However, during the oncoimmune dynamic interaction, tumors evolved to create a negative systemic immune checkpoint to favor disease progression by releasing sMIC. Our study provided the definite evidence and preclinical validation that neutralizing sMIC with a nonblocking anti-MIC antibody is a viable therapeutic approach for MIC^+ malignancies. Intriguingly, antibody targeting sMIC not only alleviated sMIC-induced immune suppression and revamped the endogenous NK immunity as expected, but also surprisingly heightened effector $CD8^+$ and $CD4^+$ T cell antitumor potential and enhanced DC activation in the tumor-draining lymph nodes (**Fig. 1**). It is evident that further investigations are required to gain full understandings of these therapeutic effects at the molecular and cellular level. The compelling question is how therapy can revamp and refuel the adaptive immune responses. With all due respect, our study has demonstrated that sustained NK cell function plays a significant role in heightening effector $CD8^+$ and $CD4^+$ T cell antitumor potentials.

Our study has launched a new avenue or at the very least raised a concern of current clinical practice of cancer immunotherapy. Most of cancer immune therapeutic modalities, such as checkpoint blockade or vaccine therapy, are dependent upon ongoing active or competent endogenous immune responses. Providing circulating sMIC can sabotage endogenous immune responses through multiple pathways, co-targeting sMIC with a neutralizing antibody should be considered to bolster the outcome of current immune therapeutic modalities in MIC^+ patients. In retrospect, clinical investigations in MIC^+ cancer patients have supported this concept, where patients who developed anti-MIC autoantibody during anti-CTLA4 or vaccine therapy demonstrated better clinical responses.[10]

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

1. Nausch N, Cerwenka A. NKG2D ligands in tumor immunity. Oncogene 2008; 27:5944-58; PMID:18836475; http://dx.doi.org/10.1038/onc.2008.272
2. Raulet DH. Roles of the NKG2D immunoreceptor and its ligands. Nat Rev Immunol 2003; 3:781-90; PMID:14523385; http://dx.doi.org/10.1038/nri1199
3. Zhang J, Basher F, Wu JD. NKG2D Ligands in Tumor Immunity: Two Sides of a Coin. Front Immunol 2015; 6:97; PMID:25788898; http://dx.doi.org/10.3389/fimmu.2015.00097.
4. Deng W, Gowen BG, Zhang L, Wang L, Lau S, Iannello A, Xu J, Rovis TL, Xiong N, Raulet DH. Antitumor immunity. A shed NKG2D ligand that promotes natural killer cell activation and tumor rejection. Science 2015; 348:136-9; PMID:25745066; http://dx.doi.org/10.1126/science.1258867
5. Liu G, Lu S, Wang X, Page ST, Higano CS, Plymate SR, Greenberg NM, Sun S, Li Z, Wu JD. Perturbation of NK cell peripheral homeostasis accelerates prostate carcinoma metastasis. J Clin Invest 2013; 123:4410-22; PMID:24018560; http://dx.doi.org/10.1172/JCI69369

6. Baragano Raneros A, Suarez-Alvarez B, Lopez-Larrea C. Secretory pathways generating immunosuppressive NKG2D ligands: New targets for therapeutic intervention. Oncoimmunology 2014; 3:e28497; PMID:25050215; http://dx.doi.org/10.4161/onci.28497
7. Xiao G, Wang X, Sheng J, Lu S, Yu X, Wu JD. Soluble NKG2D ligand promotes MDSC expansion and skews macrophage to the alternatively activated phenotype. J Hematol Oncol 2015; 8:13; PMID:25887583; http://dx.doi.org/10.1186/s13045-015-0110-z
8. Lu S, Zhang J, Liu D, Li G, Staveley-O'Carrol K, Li Z, Wu JD. Non-blocking monoclonal antibody targeting soluble MIC revamps endogenous innate and adaptive antitumor responses and eliminates primary and metastatic tumors. Clin Cancer Res. 2015 Nov 1; 21 (21):4819-30; http://dx.doi.org/10.1158/1078-0432.CCR-15-0845
9. Pardoll DM. Distinct mechanisms of tumor resistance to NK killing: of mice and men. Immunity 2015; 42:605-6; PMID:25902479; http://dx.doi.org/10.1016/j.immuni.2015.04.007
10. Jinushi M, Hodi FS, Dranoff G. Therapy-induced antibodies to MHC class I chain-related protein A antagonize immune suppression and stimulate antitumor cytotoxicity. Proc Natl Acad Sci U S A 2006; 103:9190-5; PMID:16754847; http://dx.doi.org/10.1073/pnas.060350-3103