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Beyond immune checkpoint: First-in-Class antibody targeting soluble NKG2D ligand sMIC for cancer immunotherapy

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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 gδ T cells. Theoretically, engagement of NKG2D by tumor cell surface MIC is deemed to signal and provoke the immune system to eliminate transformed cells. Clinically, 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. Tumor-derived sMIC is known to be highly immune suppressive and profoundly insults the immune system by downregulating receptor NKG2D expression on effector NK and T cells, driving the expansion of tumor-favoring myeloid suppression cells, skewing macrophages into alternatively activated phenotypes,and perturbing NK cell peripheral maintenance. 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 mice lack homologues to human MIC, this concept was not proven until our recent studies. Using a "humanized" MIC-transgenic spontaneous mouse model which recapitulates the NKG2D-mediatedonco-immune dynamics of human cancer patients,we show that neutralizing circulating sMIC with a first-in-field non-blocking antibody B10 that does not block the interaction of MIC with NKG2D revamps endogenous innate and antigen-specific CD8 T cell responses. We show that therapy with the non-blocking sMIC-neutralizing antibody results in effectively debulk of primary tumor and elimination of metastasis, with no observed toxicity.Furthermore, we show that clearing sMIC with the first-in-class neutralizing antibody B10 also enhanced the efficacy of other cancer immunotherapeutic modalities, such as immune checkpoint blockade or adoptive cell-based therapy pre-clinically. Our study has launched a new avenue of cancer immunotherapy which can be readily translated into clinical trials.

Biography:

Dr. Jennifer Wu received her Ph. D from the University of British Columbia and post-doc training at the Fred Hutchinson Cancer Research Center. Later Dr. Wu joined the Faculty of Medicine at the University of Washington and tenured as an Associate Professor. In 2011, she accepted the faculty appointment at the Medical University of South Carolina and became a member of Hollings Cancer Center Cancer Immunology Program. Dr. Wu's research focuses on understanding how cancer cells disable the immune system with the ultimate goal to develop effective immunotherapy of cancer. Her work was the first to shown that tumors shed NKG2D ligand sMIC to perturb the maintenance of tumor-killing NK cells and to facilitate tumor metastasis. Her research team then developed a first-in-class sMIC-neutralizing immunostimulatory antibody and subsequently demonstrated that antibody targeting sMIC refuels and revamps endogenous innate and adoptive anti-tumor responses. Her findings were extensively published in Nature, Journal of Clinical investigations, Clinical Cancer Research, Oncotarget, OncoImmunology etc. Dr. Wu's research team has continuously received research support from NIH, DOD, and the first-in-field cancer immunology challenge award from Prostate Cancer Foundation. Dr. Wu has served as the elected Chair of Cancer Immunology in the Federation of Clinical Immunology Society, editorial board of an array of cancer immunology-related Journals, and grant review Study Sections at NIH and DOD.