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Novel antibody for cancer immunotherapy: Beyond and synergistic with immune checkpoint blockade therapy

During tumorigenesis, 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 γδ T cells. Theoretically, engagement of NKG2D by tumor cell surface MIC 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-mediated onco-immune dynamics of human cancer patients, we show that neutralizing circulating sMIC with a first-in-field monoclonal antibody B10G5 alleviates the immune suppressive effect of sMIC and revamps endogenous anti-tumor immune responses. Therapy with B10G5 results in effective debulking of primary tumor and elimination of metastasis, with no observed toxicity. Furthermore, we show that clearing sMIC with B10G5 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

Jennifer Wu has received her PhD from the University of British Columbia and Post doctorate training at the Fred Hutchinson Cancer Research Center. She has joined the Faculty of Medicine at the University of Washington and tenured as an Associate Professor. In 2011, she has accepted the faculty appointment at the Medical University of South Carolina and became a Member of Hollings Cancer Center Cancer Immunology Program. Her 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 is the first to demonstrate 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, Oncoimmunology. She has served as the elected Committee Chair of Cancer in the Federation of Clinical Immunology Society and Editorial Board of many cancer immunology related Journals.

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