J Proteomics Bioinform 2017, 10:10 (Suppl)
DOI: 10.4172/0974-276X-C1-104

Beyond immune checkpoint: Targeting soluble NKG2D ligands for cancer immunotherapy

Jennifer Wu
Medical University of South Carolina, USA

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 serves as the ligands for 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 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 down regulating 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 non-blocking antibody 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 effectively debulked primary tumor and eliminated metastasis. Clearing sMIC with the neutralizing antibody also enhanced the efficacy of other cancer immunotherapeutic modalities, such as immune checkpoint blockade therapy. Our study has launched a new avenue of cancer immunotherapy which can be readily translated into clinical trials.

wujjd@musc.edu