484 BLOCKADE OF THE MYELOID CLEC-1 CHECKPOINT ENHANCES ANTITUMOR RESPONSES AND TUMOR ANTIGEN CROSS-PRESENTATION

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Background Myeloid cells represent one of the most abundant immune cell types in solid tumors that impede antitumor immune responses. We previously reported that the orphan CLR CLEC-1 is expressed by dendritic cells (DCs) and macrophages (MPs). Single cell transcriptional analysis of the tumor microenvironment (TME) confirms the expression by myeloids especially cDC1, best professional antigen presenting cells and tumor-associated macrophages (TAM).

Methods Damaged CLEC-1 ligand expressing tumor cells were used to identify the ligand of CLEC-1 by co-immunoprecipitation. CLEC-1 mechanism deciphering was performed with Clec1a deficient mice, notably by isolating dendritic cells. Human CLEC-1 knock-in animals were challenged for antitumor responses, administered with antagonistic anti-human CLEC-1 monoclonal antibodies in hepatocellular carcinoma (Hepa1.6) and in colorectal cancer (MC38) preclinical models.

Results Furthermore, we showed that the CLEC-1 senses dead cells induced by programmed necrosis and identified this CLEC-1 protein ligand (CLEC-1 ligand) over-expressed in cancers. Mechanistically, we identified CLEC-1 as a sensor of tissue-damage which increases the cross-presentation of dead-cell tumor associated antigens by cDC1 without breaking established tolerance against natural antigens. Interestingly, we observed that CLEC-1 blockade as a monotherapy or combined with chemotherapy prolongs mice overall survival in hepatocellular and colon carcinoma models. We revealed that loss of CLEC-1 reduced the accumulation of immunosuppressive myeloid cells in tumors and invigorated the activation state of dendritic cells (DCs), thereby increasing T cell activation & response. Importantly, we generated anti-human CLEC-1 antagonist antibodies able to enhance anti-tumor immunity in CLEC-1 humanized mice.

Conclusions Altogether, our results demonstrate that CLEC-1 acts as an immune checkpoint in myeloid cells and support CLEC-1 as a novel target for cancer immunotherapy.

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