DKK1 IS A BIOMARKER AND IMMUNOTHERAPEUTIC TARGET FOR BONE METASTASES IN MALIGNANT CANCERS

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Background Malignant tumors with bone metastases seriously threaten the survival of cancer patients. However, the understanding of bone-tumor microenvironment remains poor, and currently, there is no effective therapeutic target for bone metastases.

Methods Serum Dickkopf-1 (DKK1) expression from healthy donors and gastric cancer (GC) patients were detected. Mouse GC and breast cancer bone metastasis model was established by intro-caudal artery (CA) GC cell injection, and in vivo efficacy of DKK1 blockade with murine DKK1 antibody (mDKN-01) was evaluated by micro-CT, MRI and IHC staining modalities. The bone-tumor immune microenvironment (bone-TIME) was analyzed via flow cytometry and immunofluorescence.

Results Serum DKK1 expressions were increased in GC patients (n=63) than in healthy donors (n=25), and stage IV GC patients (n=42) had higher serum DKK1 levels than stage II-III patients (n=21), with bone-metastatic patients (n=22) displaying the highest DKK1 level. Also, serum DKK1 levels are increased in patients with progressive disease (PD), while decreased in patients who had complete response (CR)/partial response (PR) to treatments. DKK1 blockade by mDKN-01 obviously reduced the tumor burden of bone metastases, and significantly inhibited osteoclast activation and alleviates bone destruction in different bone metastasis models. Moreover, the bone-TIME was improved after DKK1 blockade, with increased proportions of CD8+ T cells, M1-like macrophages, and activated dendritic cells (DCs).

Conclusions Our study suggests DKK1 as a potential predictor to bone metastasis and progressive disease in cancer patients. Blockade of DKK1 brings an improved bone-TIME, therefore, DKK1 could be considered as a novel and promising immunotherapeutic target for bone metastases.