DECTIN-2, A NOVEL TARGET FOR TUMOR MACROPHAGE REPROGRAMMING IN CANCER IMMUNOTHERAPY

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Background Tumor-associated macrophages (TAMs) are an abundant immune cell population in most cancers that support tumor progression through their immunosuppressive effects. We discovered that TAMs express the pattern recognition receptor Dectin-2 (Clec4n/CLEC6A), an activating C-type lectin receptor (CLR) that binds to high-mannose glycans on fungi and other microbes and induces protective immune responses against infectious disease. Dectin-2 is selectively expressed by myeloid cells, and upon ligation mediates enhanced phagocytosis, antigen processing and presentation, and proinflammatory cytokine production. Given these properties, we evaluated the therapeutic potential of targeting Dectin-2 using naturally derived ligands. We also generated human Dectin-2-targeted agonistic antibodies capable of robustly activating immunosuppressive "M2" or TAM-like macrophages.

Methods Dectin-2 expression was assessed by flow cytometry, immunohistochemistry, and using public databases. Mouse and human monocytes were differentiated into macrophages using recombinant cytokines or tumor-conditioned media, and stimulation was measured following overnight incubation with Dectin-2 ligands or antibodies. Mouse tumor cell lines were implanted into syngeneic hosts and mice were treated with mannan derived from *S. cerevisiae* via IT or IV administration.

Results Dectin-2 gene expression is minimal in normal human tissues but elevated across many tumor types, including breast, colon, lung, and kidney cancers. Dectin-2 is strongly expressed by macrophages differentiated in vitro and on primary TAMs. The fungal Dectin-2 ligand mannan stimulated proinflammatory cytokine production (e.g. TNFalpha) and costimulatory molecule expression (e.g. CD86) by macrophages in a Dectin-2-dependent manner. Treatment of tumor-bearing mice with mannan mediated tumor regression in multiple syngeneic tumor models, with high rates of tumor clearance in the MB49 bladder cancer model. These effects were Dectin-2 dependent, as efficacy was not observed when a Dectin-2-blocking antibody was co-administered or in knockout mice lacking Dectin-2 signaling components. Furthermore, depletion of either macrophages or T cells impaired efficacy, suggesting that Dectin-2-stimulated TAMs augment anti-tumor T cell responses. Based on these data, we developed novel Dectin-2 targeted agonist antibodies capable of activating human "M2" or TAM-like macrophages in vitro to produce an array of proinflammatory cytokines and chemokines akin to tumor-destructive "M1" macrophages.

Conclusions The data presented demonstrate the therapeutic potential of targeting Dectin-2 using natural ligands or agonistic antibodies as a novel pan-cancer approach for myeloid cell-directed tumor immunotherapy.

Ethics Approval All animal studies were performed in accordance with Institutional Animal Care and Use Committee (IACUC)-approved protocols.

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