INTRODUCTION

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 promotes protective immune responses against infective disease. Dectin-2 is selectively expressed by myeloid cells, and upon ligand binding, mediates enhanced phagocytosis, antigen presentation, and pro-inflammatory cytokine production. Given these properties, we evaluated the immunopotent 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.

RESULTS

Dectin-2 agonist activity is CD8 T cell dependent and elicits immunological memory

Anti-tumor efficacy requires Dectin-2 signaling components

Fc-engineered agonist mAb potently activates human macrophages

CONCLUSIONS

- Dectin-2 is a novel target expressed by tumor-associated macrophages (TAMs)
- Agonism of Dectin-2 on TAMs elicits secretion of pro-inflammatory cytokines and chemokines to stimulate a productive antitumor immune response
- Dectin-2 agonists mediate tumor efficacy in a CD8 T cell-dependent manner and elicits immunological memory
- Discovery and lead optimization identified a potent agonist antibody targeting Dectin-2 with an enhanced Fc domain
- Bolt Biotherapeutics’ antibody has the potential to reprogram tumor-supportive macrophages into tumor-destructive macrophages as a novel antitumor immunotherapy

Figure 1: Schematic of proposed mechanism of action driving Dectin-2-mediated anti-tumor activity.

Figure 2: Dectin-2 gene expression is elevated across tumor types

Figure 3: Dectin-2 is selectively expressed by TAMs in a range of human tumors

Figure 4: Dectin-2 agonist activates murine TAMs in vitro and in vivo

Figure 5: Dectin-2 agonist activity is CD8 T cell dependent and elicits immunological memory

Figure 6: Dectin-2 agonist activity requires Dectin-2 signaling components

Figure 7: Dectin-2 agonist mAb 1 (Fc variant) elicits proinflammatory cytokine and chemokine production by human macrophages.