Anti-CTLA-4 antibody scFv producing recombinant Bifidobacterium secretes CTLA-4 blocker specifically inside hypoxic tumor and suppresses tumor growth in syngeneic mice model

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BACKGROUND

How does our platform technology work?

In situ Delivery and Production System (i-DPS)

Bifidobacterium longum: The host cell for i-DPS
- Derived from human intestinal gut flora
- Nonpathogenic obligate anaerobe
- Alive and grow at hypoxic environment
- Dead at the normoxic conditions (blood, organs)

B. longum is a good drug delivery carrier because:
- Selectively colonize and proliferate in hypoxic tumor after systemic injection in vivo
- Be engineered with genes coding various biologically active molecules in plasmid (antibodies, cytokines, etc.)

Roles of i-DPS in immunotherapy

To produce antibody scFv against immune checkpoints inside tumor

Immune checkpoint blockade leads anti-cancer drug development. However, off-target effects and severe immune related adverse events such as autoimmune diseases still need to be addressed.

i-DPS offers unique delivery system to allow immune checkpoint blockers to be generated inside the tumor.

RESULTS

Establishment of his tagged anti-hCTLA-4 scFv secretion B. longum

Anti-tumor effects of anti-murine CTLA4 scFv i-DPS (mcF1) against CT26 in Balb/c mice

SUCCESS of immune checkpoint antibody drugs has provided broad perspective in cancer immunotherapy. Anti-PD-1 antibody and anti-CTLA-4 antibody showed notable efficacy and the combination complementarily enhanced antitumor benefit. Nevertheless, either single-agent therapy or combination therapy is faced with non-specific adverse events (irAEs), which are major cause of treatment discontinuation. Also, still large fraction of cancer patients doesn’t respond to the antibody immunotherapy. Since non-specific systemic activation of normal immune system by the therapy is one of major reasons to cause the above problems, approaches to target the hypoxic condition of tumors may help increasing the drug’s tumor-targeting specificity, which results in minimizing the irAEs and improving the response rate in patients.

In an aim to improve efficiency of anti-cancer drug delivery, we have been developing in situ Delivery and Production System (i-DPS) by modifying a non-pathogenic anaerobic bacteria and proliferates only in the hypoxic environment like solid tumors after I.V. administration, produces anticancer proteins, enzymes or other pharmacologically active molecules selectively at the tumor site.

Here we present anti-CTLA-4 antibody scFv producing i-DPS in cancer immunotherapy, which could specifically delivered to and amplified only at the hypoxic sites of solid tumors. Anti-murine CTLA4 scFv producing Bifidobacterium as surrogate systemically administered to the syngeneic mice model demonstrated significant tumor growth inhibition. Moreover, the combination of anti-mCTLA-4 scFv producing Bifidobacterium and anti-murine PD-1 antibody was more effective than each of monotherapy. It is noteworthy that scFv was only detected in tumor tissue but not in blood proved by immunoprecipitation assay. Altogether, i-DPS for anti-CTLA-4 antibody provide a new promising immune-therapeutic modality to target hypoxic solid tumors and also provide a unique insight for antibody drug delivery in cancer immunotherapy.

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Conclusion & Perspectives

- Anti-murine CTLA4 scFv i-DPS was designed to produce anti-CTLA4 scFv specifically inside tumor. We have demonstrated its tumor suppression effects in syngeneic mice model. Furthermore, we found that anti-CTLA4 scFv was secreted inside tumor but not in blood.
- Application of i-DPS in cancer immunotherapy provides promising perspectives to reduce AEs and enhance patient response rate. Proceeding anti-CTLA4 scFv i-DPS therapy to clinic may prove the above notion and contribute to patient benefit.

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