Enhanced anti-tumor effects by a combination approach of interferon-γ producing recombinant *Bifidobacterium* and anti-mPD-1 antibody in syngeneic mouse model

Anaeropharma Science

Abstract #2631

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ABSTRACT

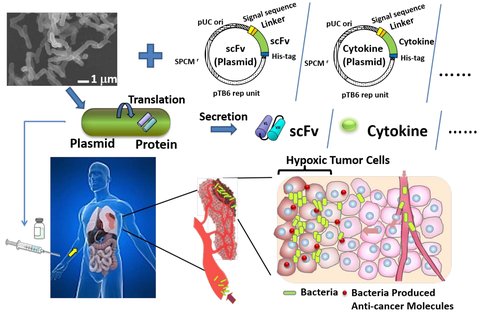
Interferon-γ is a cytokine having antitumor activity and has been developed as an anticancer drug in multiple cancer indications but failed due to its limited efficacy and severe adverse events. In several publications, IFN-γ has been clarified to induce PD-L1 expression in tumors. Upregulation of PD-L1 renders tumor resistance to cytotoxic T cell and it may cause the limited efficacy of the IFN-γ treatment.

Here in the present report, in an aim of decreasing adverse events, we have created recombinant *Bifidobacterium*, which is a non-pathogenic anaerobic bacterium modified to secrete IFN-γ specifically inside solid tumor. Both human and murine IFN-γ have growth inhibitory activities against tumor cells and CXCL10 inducing activity for T cells. On the other hand, IFN-γ induced immune suppressive molecule PD-L1 on tumor cell surface. For overcoming the immunosuppressive situation by PD-L1 expression, combination of IFN-γ producing *Bifidobacterium* and anti-murine PD-1 antibody is investigated. This combination significantly suppresses tumor growth whereas each single treatment moderately contributes to tumor suppression in a CT26 bearing syngeneic mouse model. In addition, ELISA assay indicated that there are substantial IFN-γ detected in tumor tissue but none of them are detectable in blood and other organs. All in together, combination treatment with IFN-γ producing *Bifidobacterium* and anti-PD-1 antibody offers a promising anti-tumor approach.

BACKGROUND

How does our platform technology work?

***In situ* Delivery and Production System (*i*-DPS)**

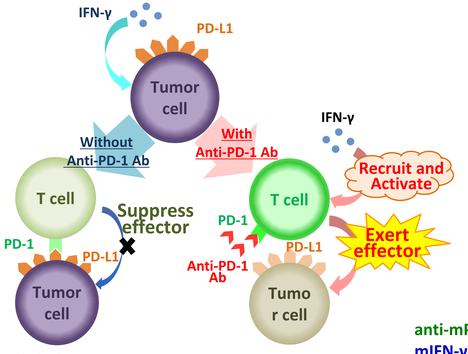


***Bifidobacterium longum*: The host cell for *i*-DPS**

- Derived from human intestinal gut flora
- Nonpathogenic obligate anaerobe
- Alive and grow at hypoxic environment
- Dead at the normoxic conditions (blood, organs)

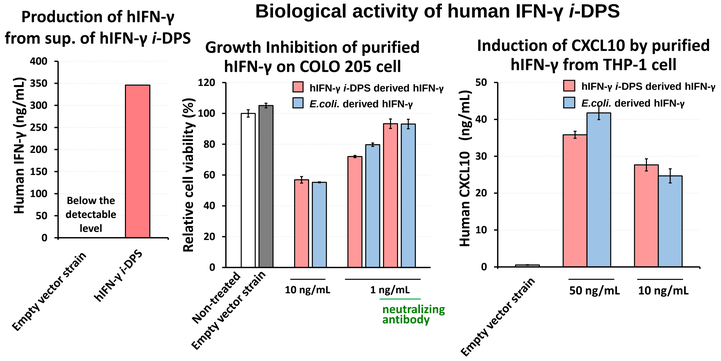
IFN-γ: A double-edged sword in anti-tumor regulation signals

- IFN-γ participates activation, proliferation and differentiation of T cells. However, IFN-γ also induces PD-L1 on tumor cell surface for immune evasion.
- Anti-PD-1 antibody would be a good partner with IFN-γ for exerting anti-tumor effect.

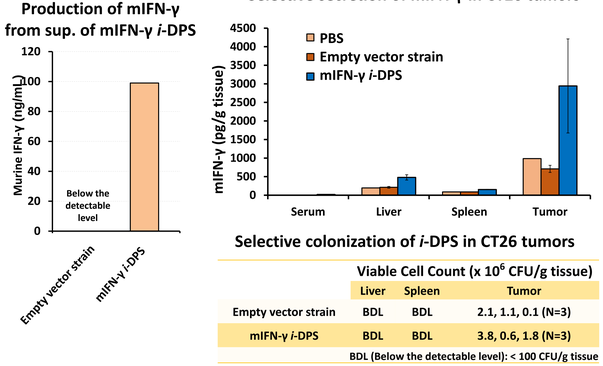


RESULTS

Establishment of human IFN-γ secreting *B. longum*



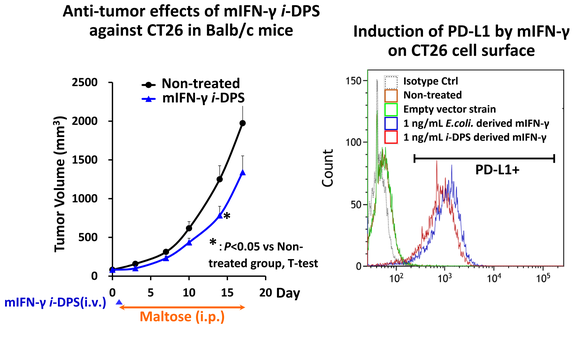
Establishment of murine IFN-γ secreting *B. longum*



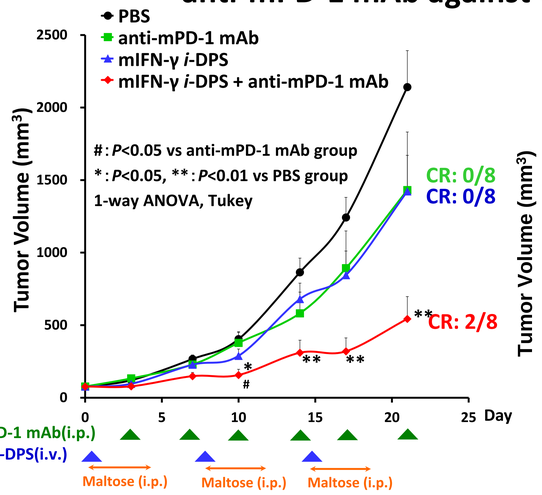
Selective colonization of *i*-DPS in CT26 tumors

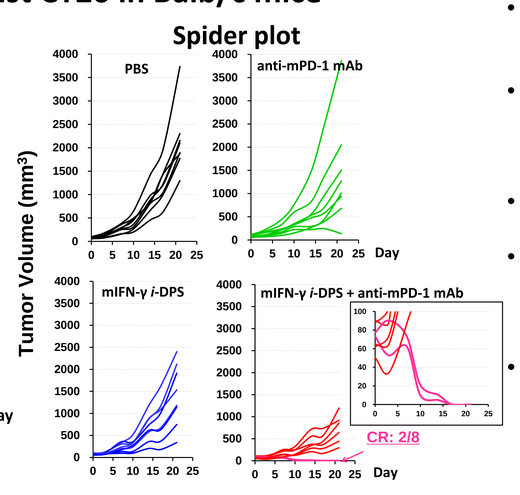
	Viable Cell Count (x 10^6 CFU/g tissue)		
	Liver	Spleen	Tumor
Empty vector strain	BDL	BDL	2.1, 1.1, 0.1 (N=3)
mIFN-γ *i*-DPS	BDL	BDL	3.8, 0.6, 1.8 (N=3)

BDL (Below the detectable level): < 100 CFU/g tissue



Anti-tumor effect of murine IFN-γ *i*-DPS combined with anti-mPD-1 mAb against CT26 in Balb/c mice





Conclusion

- We have established human IFN-γ *i*-DPS and murine IFN-γ *i*-DPS and confirmed secretion of IFN-γ from IFN-γ *i*-DPS and its biological activities.
- Administration of IFN-γ *i*-DPS to CT26 tumor bearing mice resulted in colonization of IFN-γ *i*-DPS and production of IFN-γ only in tumor but not in blood and other normal organs.
- In the IFN-γ treated CT26 cells, PD-L1 expression was enhanced at surface of tumor cells.
- Single treatment of IFN-γ *i*-DPS showed a modest tumor suppression fashion, whereas combination of IFN-γ *i*-DPS and immune checkpoint blocker, anti-mPD-1 mAb notably strengthened tumor suppression.
- All above evidence implied IFN-γ *i*-DPS is a worth-trying combination candidate for anti-PD-1 antibody.

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