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Engineered live attenuated bacteria producing 5- hydroxyindole remodels heterogeneous tumor microenvironment and promotes antitumor immunity

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The highly immunosuppressive tumor microenvironment (TME) stimulates cancer cells resistance to immunotherapy. We have previously shown that a live-attenuated *Brucella melitensis* Δ*vjbR* (BmΔ*vjbR*) bacterial strain, breaks cancer cell resistance to immunotherapy by remodeling the TME and facilitating infiltration of cytotoxic $CD8^+$ T cells (CTLs) into the tumor. As a result, there was shrinkage of tumor size and significant improvement in survival of these mice. However, BmΔ*vjbR* was efficient in only controlling colorectal tumors, but was rendered ineffective in B16 melanoma. In this study, we sought to improve the efficacy of BmΔ*vjbR* in controlling different cancers by engineering it to augment the production of 5-hydroxyindole (HI), i.e., BmΔ*vjbR*-HI. The effect of BmΔ*vjbR*-HI in modulating the function and activity of CTLs was assessed by flowcytometry in *in vitro* assays. The tumor modulating activity of the BmΔ*vjbR*-HI was also assessed by intravenous injection of this bacteria followed by adoptive CTL therapy in colon carcinoma, melanoma and pancreatic orthotropic murine tumors. We found that BmΔ*vjbR*-HI increased inflammatory cytokines in $CD8^+$ T cells. The granzyme-B production and cytotoxicity of $CD8^+$ T cells was also enhanced on treatment with the bacteria. BmΔ*vjbR*-HI remodeled the TME and ameliorated MC32-CEA colorectal cancer, B16-OVA melanoma and Panc-02 orthotropic pancreatic tumors. Moreover, the BmΔ*vjbR*-HI homed into the TME by uptake in myeloid derived suppressor cells. Overall, our findings demonstrate that BmΔ*vjbR*-HI remodels heterogeneous TMEs of different cancers to promote CTL-mediated antitumor immunity. These findings have significant translational potential in antitumor microbial immunotherapy.