**Prophylactic treatment with attenuated Salmonella LVR01 helps to control tumour growth: role of trained immunity.**
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Attenuated Salmonella immunotherapy has been successfully evaluated as a therapeutic option for cancer. Its potential is attributed to a direct effect, by invading and killing tumour cells, and an indirect one, by stimulating the immune system, particularly at the tumour microenvironment. In this work, we explore the potential of an attenuated Salmonella Typhymurium (LVR01, aroC-) as a prophylactic approach for the treatment of cancer in two preclinical models (B16F10 melanoma and A20 non-Hodgkin lymphoma). Intraperitoneal pre-treatment with 1x106 CFU of LVR01, applied one week before tumour implantation, resulted in a retarded tumour growth and hence a prolonged animal survival, in both tumour models. This effect was not directly ascribed to Salmonella, as pretreatment with LVR01 30 days before tumour implantation also revealed anti-cancer activity, in the absence of circulating bacteria. Thus, the anti-tumour effect ought to be immune-mediated. However, no differences in percentage of CD8+ T lymphocytes, NK cells nor myeloid CD11b+ cells were found between LVR01-pre-treated and control mice, in both models. These results suggest that the antitumour activity is independent of tumour-infiltrating immune cell numbers, but still dependent on cell functionality. In this regard, splenocytes from LVR01-pre-treated melanoma-bearing mice produced higher amounts of IL-6 and TNF-α upon stimulation with an unrelated stimulus (Candida albicans), a mechanism associated to trained immunity. Actually, LVR01 reached bone marrow after intraperitoneal administration and boosted proinflammatory cytokines levels in serum after a challenge with a second stimulus. In addition, pre-treatment with heat-killed LVR01 resulted in loss of anti-tumour effect in B16F10 melanoma model. Altogether, these results suggest that Salmonella induces central trained immunity, which could help to control tumour growth and extend animal survival. Further studies are currently undergoing to confirm this hypothesis.