studied. In vivo experiments of treatment with of Nc tachyzoites[2] administered locally (intra and peri tumoral) or remotely (subcutaneous) in a murine thymoma EG7 tumor and in human Merkel cell carcinoma (MCC).

Results We demonstrated that the treatment of thymoma EG7 by Nc strongly inhibited tumor development. Analysis of immune responses and interactions between Nc and tumor cells showed that Nc had the ability to lyze infected cancer cells, reactivated immune competence within the Tumor Microenvironment (TME), and activated the systemic immune system by promoting the recruitment of immune cells to the site of tumor. We also established in a NOD/SCID mouse model that Nc was able to induce a strong regression of human MCC. Recently, to further enhance oncotherapeutic effect, we engineered an Nc strain to secrete human IL-15 (cross reactive with mouse cells), associated with alpha subunit of IL-15 receptor, increasing its stability.[3] This strain induced proliferation of human PBMCs and their secretion of IFN-γ. In the EG7 model, human IL-15 secreting Nc showed greater protection against tumor development, confirming enhancement of immunotherapy by engineering Nc to deliver/secrete IL-15.

Conclusions These results highlight Neospora caninum as a potentially extremely efficient, and non-toxic anti-cancer agent, capable of being engineered to express at its surface or to secrete bio-drugs, like human IL-15 cytokine. Our work has identified the broad clinical possibilities of using N. caninum as an oncolytic protozoan in human medicine capable of vectoring molecular therapy, overcoming TME defenses.

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847 INFLAMMASOME ACTIVATION IN M2 MACROPHAGE RESTRAIN THE IMMUNE SUPPRESSIVE FUNCTION

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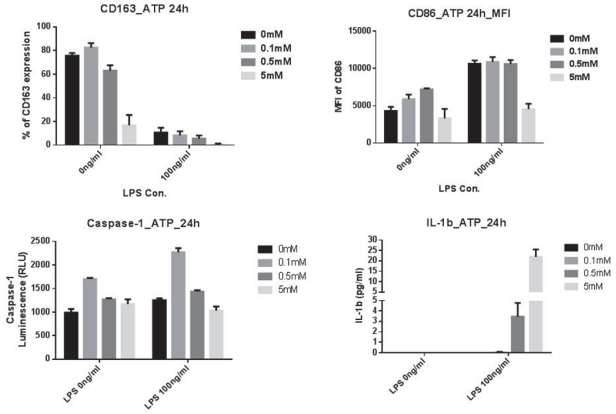
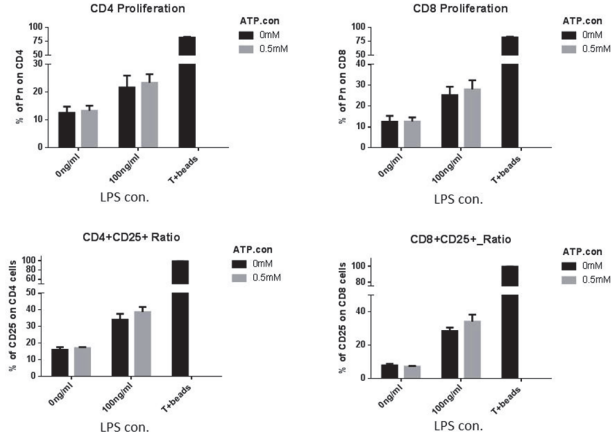
Background Macrophage is an important component in tumor microenvironment (TME) and plays multiple roles in tumor initiation, progression and metastases. In response to various stimuli within TME, macrophage exhibits high level of functional heterogeneity. There are two distinct groups of macrophages: M1 macrophage exhibits pro-inflammatory phenotype with high levels of TNF-a, IL-6, and IL-1ß, while M2 macrophage displays immune suppressive phenotype with high levels of anti-inflammatory cytokines such as IL-10 and TGF-ß. In response to the M2 cytokines, myeloid cells within the TME further acquire higher expression of PD-L1 and thus inactivate T cells. M2 cytokines can also directly inhibit T cell activation. As a result, re-polarizing M2 macrophages becomes a key concept for cancer immunotherapy. The NLRP3 inflammasome is acquired by macrophages to fight against endogenous danger signals. Macrophage NLRP3 activation has been observed in several tumor models, but the function of NLRP3 on macrophage polarity remains controversial. Inflammasome activation with IL-1ß/IL-18 secretion was reported to promote M1 polarization. However, NLRP3 activation was also reported to promote M2 polarity through up-regulation of IL4 in asthma model

Methods Here, we have established an in vitro human macrophage NLRP3 activation system (figure 1), coupled with M2 macrophage polarization assay, to dissect the role of NLRP3 in macrophage phenotype.

Results Our results indicate that NLRP3 activation restrained M2 phenotype and further enhanced T cell activation in an M2/T cell co-culture system (figure 2).



Abstract 847 Figure 1 Inflammasome activation polarize M2 macrophage int
Use LPS/ATP to stimulate NLRP3 in M2 macrophage and demonstrate NLRP3 activation could reduce CD163 and increase CD86



Abstract 847 Figure 2 Inflammasome in M2 rescue T cell activation establish M2/T co-culture system in vitro to demonstrate M2 could suppress T activation while Inflammatory M2 could partial rescue the suppressive phenotype

Conclusions Inflammasome could be the potential target for cancer by modulating T cell activation through macrophage polarization regulation

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