Effective immunotherapeutic regimen with combinations of TLR agonists and immune check point blockade against mouse 4T1 breast carcinoma

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Abstract:
Emerging evidence on resistance to immune checkpoint blockade therapy has spurred the development of novel combinations of drugs to treat certain types of highly resistant carcinoma, including those with no/low infiltration of T cells. In this study, we developed a combinational immunotherapeutic regimen to eradicate established mouse 4T1 tumors by modulating the immune system. Intratumoral administration of combination of dendritic cell activating TLR4 agonist HMGN1 and TLR2/6 agonist fibroblast-stimulating lipopeptide (FSL-1) coupled with intraperitoneal administration of immune checkpoint inhibitor anti-CTLA4 antibody significantly regressed the growth of established 4T1 mouse breast carcinoma, however, curative effect was not observed. We screened and found that TLR7/8 agonist R848 could cooperate with HMGN1 and FSL-1 to induce the maturation of both mouse and human dendritic cells. Intratumoral delivery of HMGN1, FSL-1, R848 plus intraperitoneal administration of anti-CTLA4 antibody exhibited even better immunotherapeutic effect, evidenced by significantly improved inhibition of tumor growth, prolonged survival, and reduced lung metastasis. This immunotherapeutic regimen increased the generation of CD8+ cytotoxic T cells in draining lymph node (dLN) and their infiltration in the tumor tissue. Thus, we have developed an effective immunotherapeutic regimen dubbed ‘TheraVac plus’ consisting of HMGN1, FSL-1, R848, plus a checkpoint inhibitor, that can, without administering exogenous tumor associated antigen(s), effectively treat the highly aggressive and metastatic 4T1 tumor, a mouse model of human triple negative breast carcinoma.