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SEMLIKI FOREST VIRUS VECTOR PRODUCING IFN-GAMMA INHIBITS INTRATUMORAL INFILTRATION OF MACROPHAGES IN MOUSE MODEL

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Tumour microenvironment (TME) and tumour associated immune cells, like tumour associated macrophages (TAM), play essential role in cancer development. TAM can be polarized by specific cytokines into various phenotypes with different properties generally classified as M1 (TAM with strong tumoricidal abilities) and M2 (tumour supportive phenotype).

In this study we investigated the role of macrophages in tumour progression and evaluated the therapeutic potential of transient intratumoral expression of IFNgamma delivered by Semliki forest virus vector.

The influence of co-injection of M1 and M0 bone marrow derived macrophages (BMDMs) with 4T1 breast cancer cells on tumour growth inhibition in vivo was studied. BMDMs were polarised to M1 *in vitro* with IFNgamma and co-injected with 4T1/Luc2 cells orthotopically in mouse fat pad. As 4T1 cell express Luc2 gene – the tumour growth dynamics were monitored using in vivo imaging system. Co-injection of tumour cells with M1 TAM showed significant tumour growth inhibition. FACS analysis of tumour tissues showed changes in immune cell composition. We observed that the presence of M1 in tumours lead to the increase of amount of macrophage population highly positive with nitric oxide synthase (iNOs) and MHCII as a strong anti-tumoral markers. FACS analysis showed increase of CD8+ cytotoxic and CD4+ helper cells in M1 and M0 mice groups, comparing to the control group received 4T1 cells only. Furthermore, we observed the migration of BMDMs into 4T1 tumours. The fluorescently labelled BMDMs were i.v. injected into 4T1 tumour bearing mice. The fluorescent signal of BMDMs was detected in tumours next day and within 5 days post injection. Importantly, the intratumoral injection of recombinant Semliki forest virus, expressing mouse IFNgamma (SFV/IFNgamma), inhibited the infiltration of BMDMs into the tumour, confirmed by fluorescent in vivo imaging. The FACS analysis of tumour immune cells showed the decrease of general CD11b cell population and significant increase of iNOs positive cells in SFV/IFNgamma received group. We concluded that SFV/IFNgamma vector inhibits intratumoral infiltration of BMDMs and promotes the activation of macrophages to M1 tumoricidal phenotype. Therefore, the high potential of SFV-based delivery of IFNgamma for therapeutic programming of tumour macrophages was demonstrated.

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