STING Activation as an Immunotherapeutic Strategy for Soft Tissue Sarcoma
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Background
There remain few systemic therapies effective against non-RMS soft tissue sarcomas (STS). Immunotherapies have revolutionized cancer care, however this line of therapy remains ineffective against most sarcoma types. Although histologically diverse, the tumour immune microenvironment of most sarcomas is characterized by a paucity of lymphocytes and dense, immune suppressive macrophage infiltrates.

We hypothesize that immunologic stimulation of the innate immune fraction within sarcomas will induce anti-tumour immune responses in sarcomas.

Methods

1. Immune profile murine UPS tumours using FACS, proteomics and NanoString® immune transcriptome analyses.
2. Ex-vivo characterization of UPS tumours treated with intra-tumoural mSTING agonist, DMXAA (FACS, NanoString)
3. Longitudinal survival studies: - Single, multiple doses of DMXAA - Combination therapy: STING + anti-PD1/anti-CTLA-4
4. UPS tumour rechallenge (leg or lung) in DMXAA survivors
5. DMXAA experiments in lymphocyte deficient (Rag 2 KO) mice

Experiments

Results – UPS mouse model

Results – intra-tumoural DMXAA

Discussion

• STING therapy induces durable cure in murine UPS
• STING activation recruits CD8+ lymphocytes into the sarcoma TME
• The therapeutic effects of STING are mediated by the adaptive immune system
• Cured mice are immunized against subsequent UPS rechallenge
• These effects are synergistic with immune checkpoint blockade

Future Directions:
• STING agonist therapies in additional immune competent STS models
• Role of macrophages in STING activation
• Testing human STING agonists
• Exploring synergy with radiation therapy
• Novel immune therapy combinations for STS using STING
• Clinical trials in relapsed/advanced STS patients

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