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.

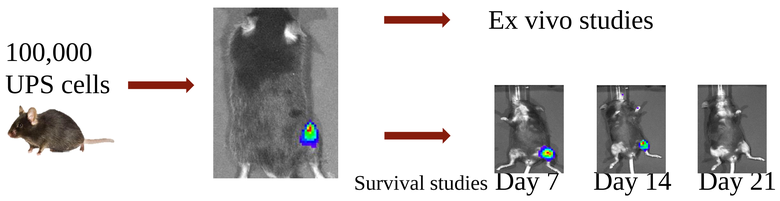
The STING (STimulator of INterferon Genes) pathway is a highly conserved DNA sensing apparatus of eukaryotic cells that potently activates both the innate and adaptive immune system in response to foreign DNA and DNA damage. DMXAA is a murine STING agonist (mSTING) and can induce potent Type I Interferon (Type I IFN) responses in solid tumours and stimulate anti-tumour adaptive immunity. STING activation immunotherapy has never been evaluated in sarcoma.

Objective

To evaluate the anti-tumour effects of intra-tumoural STING activation in an immune competent mouse model of undifferentiated pleomorphic sarcoma (UPS).

Experiments

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



Results – UPS mouse model

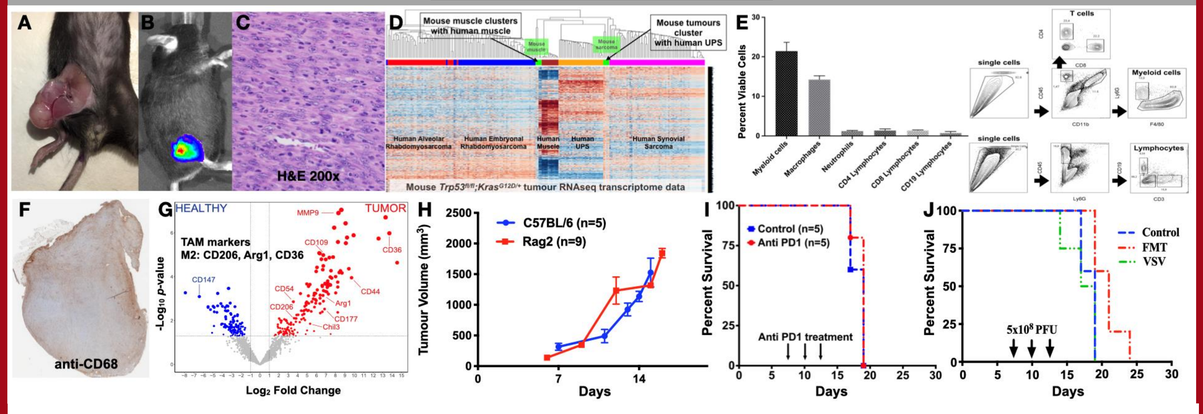


Figure 1. Murine model of UPS is lymphocyte poor and unresponsive to immunotherapies. Mutation of *Kras*^{G12D} and *Trp53* in the C57Bl/6 mouse hindlimb induces a STS with histologic and genomic features consistent with UPS (A-D). These tumours are void of lymphocytes, rich in macrophages (E-G), grow unaffected by lymphocytic immune pressure (H) and are resistant to immune therapy (I-J).
This UPS model is an excellent pre-clinical tool to evaluate new immunotherapies for STS.

Results – intra-tumoural DMXAA

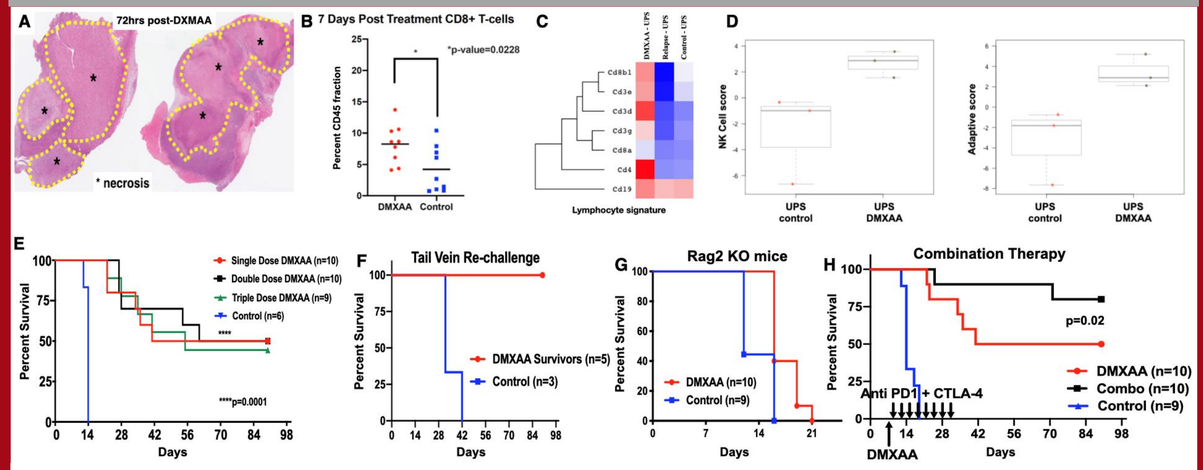


Figure 2. STING activation has dramatic anti-sarcoma effects in UPS-bearing mice. 72hrs post-injection, we observed 60-90% tumour necrosis (A). Increased CD8+ lymphocytes were observed in tumours 1wk post-injection (B). Transcriptomic immune profiling (NanoString®) demonstrates increased lymphocyte markers (C) and NK cell and adaptive immunity signatures (D). Longitudinal survival following a single intra-tumoural injection of DMXAA was 50% > 3 months (E). Surviving mice rejected repeat tumour challenge challenge in the lung (F) and contralateral leg. DMXAA therapy was ineffective in lymphocyte deficient mice (G). Combination STING therapy with immune checkpoint blockade increased long-term survival (> 3months) to 80% (H). **Collectively, these data support a strong therapeutic benefit of STING activation in UPS, which is mediated by an adaptive immunologic response.**

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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