The assessment of tumor suppressor immune gene therapy to reverse immunotherapy resistance

Background

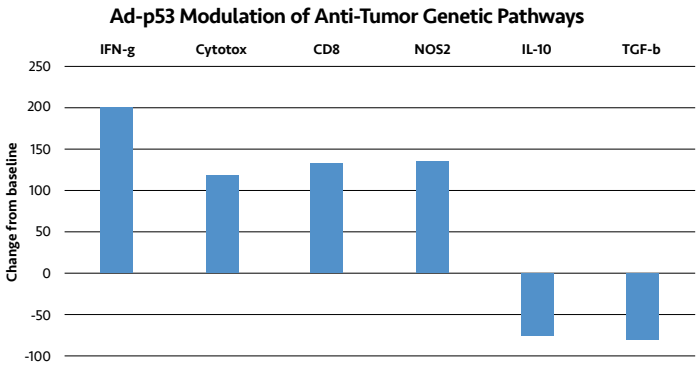
While immune checkpoint therapy has become standard of care for multiple primary and metastatic cancers, most patients to do not respond well or have recurrence after treatment with this form of immunotherapy.

Research Question

Can gene therapy targeting tumor suppressor genes (specifically Adenoviral gene therapy Ad-p53 + immune checkpoints) reverse IO therapy resistance?

Experimental Setup

Sample Type	Head & Neck Squamous Cell Carcinoma (HNSCC); human type 5 adenovirus (Ad5) vector expressing p53
Tissue Type	Human
Assay	PanCancer IO 360™ Panel
Analyte	RNA
Instrument	nCounter® Analysis System



"The NanoString IO 360 dataset was analyzed for genes substantially up- or down regulated as a result of p53 treatment defined by a greater than or less than tenfold change from baseline. A total of 23 strongly modulated genes out of the 770 gene set met these criteria."

-Chada et. al.

Figure 8. Concomitant upregulation of immune activating and downregulation of immune-suppressive/stromal gene pathways.
Ad-p53 treatment increased immunstimulatory interferon-gamma (IFN-g), Cytoxicity (Cytotox), CD8+T cells, and nitric oxide synthase 2 (NOS2) signatures while decreasing expression of immune inhibitory and stroma forming interleukin 10 (IL-10) and transforming growth factor-beta (TGF-b) signatures.

Results & Conclusions

- Gene expression profiling comparing pre and post Ad-p53 treatment HNSCC tumor biopsies showed strong upregulation of genetic pathways involved in anti-tumor immune responses. The nCounter and IO 360 panel are able to provide actionable data from clinical samples.
- Preclinical results led to the initiation of a human Phase I/2 clinical trial of combined Ad-p53 and anti-PD-1 therapy in patients with recurrent HNSCC (NCT03544723) that will include IO 360 profiling.
- Loco-regional Ad-p53 tumor suppressor gene therapy reversed resistance to both immune checkpoint inhibitor and selective CD122/CD32 agonist, IL2 and IL15 therapies demonstrating synergies with abscopal effects on distant tumors that were not treated with Ad-p53.
- Synergy to support further development of combination gene therapy + immune checkpoint combination treatment.

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