Targeted STAT3 degradation leads to remodeling of an immunosuppressive tumor microenvironment and subsequent sensitization to immune checkpoint therapy

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**Background** Signal Transducer and Activator of Transcription 3 (STAT3), a multifaceted transcription factor, is aberrantly activated across a variety of malignancies; however, its selective targeting has to-date remained a therapeutic challenge. STAT3 plays a pivotal role in shaping the tumor immune landscape through cancer cell-intrinsic mechanisms, direct regulation of immune cell function and via cancer cell-tumor microenvironment (TME) crosstalk, that collectively result in an immunosuppressive TME. Targeted protein degradation represents a novel therapeutic modality enabling direct targeting of previously undruggable oncoproteins. We have developed potent and selective STAT3 heterobifunctional degraders demonstrating activity across diverse tumor and immune cell types.

**Methods** We investigated the immunomodulatory impact of STAT3 degradation on tumorigenesis in syngeneic mouse models representing cancers with heterogeneous immune milieus. Methods included in vivo pharmacological approaches, immunophenotyping and gene expression profiling.

**Results** Treatment of CT-26 (colorectal cancer) and A20 (B-cell lymphoma) tumor-bearing mice with a STAT3 degrader resulted in significant tumor growth inhibition compared to controls, with loss of STAT3 protein in both tumor cells and TME. This was accompanied by a decrease in M2 polarized macrophages and concomitant increases in M1 polarized macrophages and tumor infiltrating lymphocytes. The anti-tumor responses were abrogated by antibody mediated CD8+ T cell depletion or by using immunodeficient host-strains implicating the observed efficacy to be predominantly driven by immune-directed mechanisms. Gene expression profiling of STAT3 degrader-treated CT-26 tumors showed marked increases in proinflammatory genes including T cell and M1 macrophage activation markers, compared to controls. Notably, induction of an Ifnγ-responsive gene signature (Ifnγ, Stat1, Cxcl9, Cxcl10, Ido1) suggested that STAT3 degradation results in a T-cell inflamed phenotype associated with responsiveness to immune checkpoint therapy (ICT). Furthermore, on-treatment tumors showed an upregulation of genes such as Pdl1, Cda4, Lag3 which reflect T cell activation as well as counterregulatory mechanisms. Therefore, we evaluated STAT3 degradation in combination with anti-PD1 in these models which are poorly responsive to anti-PD1 monotherapy. Robust synergy was observed in the CT-26 model with 60% complete responses and development of immunological memory as confirmed by tumor re-challenge studies. Studies are underway to ascertain the applicability of this combination therapy in different tumor-immune contexts and indications, and to elucidate the mechanistic basis of synergy.

**Conclusions** STAT3 degradation remodels an immunosuppressed TME activating anti-tumor immunity as monotherapy and effectively combines with anti-PD1. These data provide a rationale for selectively degrading STAT3 as a strategy to sensitize cancers with relevant immune contexts to ICT in the clinic.

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