Receptor binding of a novel bifunctional TGF-β1/PD-L1 fusion protein elicited a down-regulated immune signature

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Statement of the Problem: There are more than 80 clinical distinct types of autoimmune diseases (AID) and their collective global prevalence rate have increased to >10%. Until now, treatment regimen has relied heavily on the use of drugs (i.e. NSAIDs, glucocorticoids and DMARDs) that down-regulate the entire body's immune response. High-dose and long-term medication with these drugs have been found to correlate with susceptibility to infections and tumorigenesis. Preclinical studies targeting the receptors of transforming growth factor superfamily such as TGF-β1 has implicated possible use of this molecule in AID management and treatment. However, researchers have reported several drawbacks of targeting TGF-β1 signaling, as they found its involvement in prevention but not reversal of AID. Another group of immune checkpoint protein, the PD-1/PD-L1 axis, has been found to down-regulate immune response and have clinical implications for treatment of the disease. This study aims to utilize the combinatorial immune-downregulating activities of TGF-β1 and PD-L1 by generating a fusion product which has never been described before.

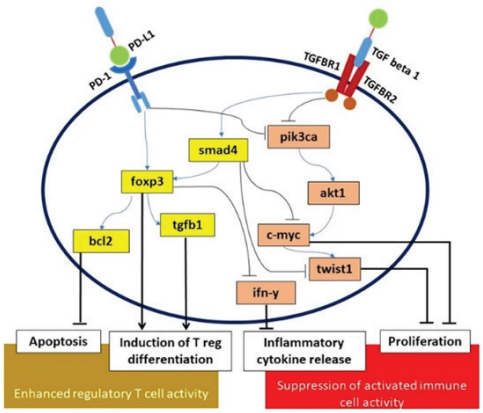

Figure 1. Down-regulated immune signature elicited by TGF-β1/PD-L1 fusion protein in AMLK cell line model as revelaed by pathway analysis using qRT-PCR.

Methodology: We were able to previously successfully clone and generate a fusion gene construct of TGF-β1 and PD-L, validated by DNA sequencing. The study focused next on characterizing the bifunctional binding of the proteins with their respective receptors by co-immunoprecipitation (co-IP) and reverse co-IP experiments coupled with pathway analysis by qRT-PCR.

Findings and Results: A 70 kDa TGF-β1/PD-L1 fusion protein was demonstrated to bind TGF-β1 receptors such as TGF-β receptor 1 and PD-L1 target receptor, PD-1, in co-IP and reverse co-IP experiments. Gene expression analysis showed that these interactions are functional and elicit gene expression signature that is seen in suppressed immunity using a cell line model.

Conclusion and Significance: TGF-β1/PD-L1 fusion protein may represent a new class of immunotherapy for treatment and management of autoimmune diseases in the future.

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