Characterization and Therapeutic Application of the ICOS Receptor To Treat Peripheral T-Cell Lymphoma

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Peripheral T-cell lymphoma (PTCL) is a rare and aggressive non-Hodgkin lymphoma resulting from clonal proliferation of mature post-thymic T-cells. The mechanisms behind PTCL development and progression remains incompletely understood, which explains the lack of successful targeted immunotherapies. The inducible T-cell co-stimulator (ICOS), a member of the CD28 superfamily, has shown to be upregulated in PTCL, which makes it a worthy target of further investigation. This study investigated the role of ICOS in regulating the mechanisms of PTCL by examining cytokine release, cellular proliferation, and ICOS expression in two cutaneous T-cell lymphoma (CTCL) cell lines upon induced ICOS activation. The results highlight that ICOS activation independent of T-cell receptor co-engagement induces potent secretion of IFNγ, and that ICOS activation directly inhibits CTCL cell proliferation in vitro. Additionally, this study validated ICOS as an effective therapeutic candidate for an antibody-drug conjugate (ADC) by demonstrating the internalization capability of the ICOS receptor upon activation via flow cytometry. Lastly, this study validated the efficacy of an anti-ICOS ADC in vitro; an ADC targeting ICOS potentiated killing of 40% of CTCL tumor volume over a 3-day period. These findings indicate that an anti-ICOS ADC could be highly effective at killing malignant PTCL cells that express ICOS. Anti-ICOS monoclonal antibodies by themselves may also inhibit tumor growth in CTCL. Ultimately, this study elucidates the vital role ICOS plays in regulating PTCL tumor growth and signaling, and provides rationale for an immunotherapy which could markedly enhance antitumor efficacy in ICOS-positive PTCLs.