Treatment with peptide-conjugated antisense to c-FLIP promotes transplant acceptance of a minor histoincompatible antigen.

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The cellular protein c-FLIP regulates Fas-mediated activation-induced cell death (AICD) in T cells. To examine if blocking c-FLIP would sensitize T cells to antigen-mediated AICD and permit transplant acceptance, we inhibited translation of the c-FLIP protein using an antisense morpholino oligomer conjugated to an arginine-rich peptide. We observed *in vitro* that this conjugate is taken up by activated T cells and not resting naïve cells. Induction of antigen-mediated AICD in KJ26+ cells was observed when DO11.10 splenocytes were treated with c-FLIP conjugate and co-cultured with ovalbumin-pulsed DCs. To determine if c-FLIP antisense treatment would augment AICD to a transplantation antigen and thus promote transplant survival in the mouse, we transferred male DO11.10 cells into female BALB/c recipients who received a course of c-FLIP antisense treatment over 14 days. Enumeration of male donor cells persisting in recipients showed that c-FLIP antisense treated mice retained significantly more functional KJ26+ CD4+ cells compared to controls. To our knowledge, this is the first demonstration of differential uptake of an antisense molecule into activated versus naïve T cells. Collectively these results suggest this particular peptide-facilitated delivery of c-FLIP antisense could serve as a therapeutic treatment for transplantation rejection.