

POSTER PRESENTATION

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Ex vivo conditioning with IL-12 decreases T cell sensitivity to intratumoral INF- γ -induced apoptosis following adoptive transfer

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Background

In order to induce significant tumor regression T cells must effectively recognize and kill target cells. Secretion of IFN- γ is considered a key effector function of activated CD8⁺ T cells via induction of apoptosis. Thus programming T cells to secrete high levels of IFN- γ after adoptive transfer could represent a therapeutically effective anti-cancer intervention.

Methods

We previously demonstrated that naïve CD8⁺ T cells exposed to IL-12 during antigenic priming (Pmel^{Ag+12}) provided superior anti-tumor activity after transfer when compared to cells activated in the presence of antigen alone (Pmel^{Ag}). In this setting, tumor regression was associated with sustained levels of intra-tumoral IFN- γ . Expression analysis using total tumor RNA showed elevated expression of IFN- γ responsive genes such as IP-10, MCP-1, MIG, and MIP-1 α . Even without IL-12 stimulation during *ex vivo* antigenic priming, Pmel cells were able to initially reach the tumor and secrete high levels of IFN- γ . However, by day 7 after adoptive transfer tumors in mice that received Pmel^{Ag} were significantly larger than those in mice injected with Pmel^{Ag+12}. Failure to maintain intra-tumoral levels of IFN- γ was associated with a decrease in the frequency of tumor infiltrating Pmel^{Ag}. We hypothesized that high levels of IFN- γ had a detrimental effect on Pmel^{Ag}, via induction of apoptosis. IFN- γ is a multifunctional cytokine that induces a variety of contrasting cell responses such as proliferation or cell death. The cellular response to an IFN- γ stimulus depends on the specific receptor being

activated, with IFN- γ R1 inducing proliferation and IFN- γ R2 inducing apoptosis.

Results

We tested the hypothesis that the ability of T cells to survive *in vivo* after adoptive transfer was dependent on their susceptibility to IFN- γ -induced apoptosis. Real time PCR revealed that the expression levels of IFN- γ R1 and IFN- γ R2 immediately following antigen or antigen+IL-12 priming were similar, though by 4d post adoptive transfer the tumor-infiltrating Pmel cells stimulated with antigen alone had 10 fold higher levels of IFN- γ R2 than tumor associated Pmel^{Ag+IL-12}.

Conclusions

These results suggest that the enhanced anti-tumor activity of Pmel^{Ag+IL-12} might be due to their decreased sensitivity to IFN- γ -induced apoptosis. Thus inhibiting IFN- γ -induced activation induced cell death (AICD) by down-regulating IFN- γ R2 expression on T cells may represent a novel mechanism by which IL-12 enhances anti-tumor activity.

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