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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-1α. 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-γR1 inducing proliferation and IFN-γR2 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-γR1 and IFN-γR2 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-γR2 than tumor associated $Pmel^{Ag+IL\text{-}12}$.

Conclusions

These results suggest that the enhanced anti-tumor activity of $Pmel^{Ag+IL\text{-}12}$ 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-γR2 expression on T cells may represent a novel mechanism by which IL-12 enhances anti-tumor activity.

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