Dexamethasone turns tumor antigen-presenting cells into tolerogenic dendritic cells with T cell inhibitory functions

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Background: Dendritic cells (DCs) are usually immunogenic, but they are also capable of inducing tolerance under anti-inflammatory conditions. Immunotherapy based on autologous DCs loaded with an allogeneic melanoma cell lysate (TRIMEL/DCs) induces immunological responses and increases melanoma patient survival. Glucocorticoids can suppress DC maturation and function, leading to a DC-mediated inhibition of T cell responses. Methods: The effect of dexamethasone, a glucocorticoid extensively used in cancer therapies, on TRIMEL/DCs phenotype and immunogenicity was examined. Results: Dexamethasone induced a semi-mature phenotype on TRIMEL/DC with low maturation surface marker expressions, decreased pro-inflammatory cytokine induction (IL-1? and IL-12) and increased release of regulatory cytokines (IL-10 and TGF-?). Dexamethasone-treated

TRIMEL/DCs inhibited allogeneic CD4+ T cell proliferation and cytokine release (IFN?, TNF-? and IL-17). Co-culturing melanoma-specific memory tumor-infiltrating lymphocytes with dexamethasone-treated TRIMEL/DC inhibited proliferation and effector T cell activities, including cytokine secretion and anti-melanoma cytotoxicity. Conclusions: These findings suggest that dexamethasone repressed melanoma cell lysate-mediated DC maturation, generating a potent tolerogenic-like DC phenotype that inhibited melanoma-specific effector T cell activities. These results suggest that dexamethasone-induced immunosuppression may interfere with the clinical efficacy of DC-based melanoma vaccines, and must be taken into account for optimal design of cellular therapy against cancer.