Immunostimulatory CpG-DNA and PSA-peptide vaccination elicits profound cytotoxic T cell responses.

Abstract:

Novel strategies for the treatment of advanced prostate cancer (CaP), including immunotherapy or gene therapy, are currently under evaluation with Sipuleucel-T as first FDA-approved immunotherapeutic. Here, we examine cytosine-phosphorothioate-guanine (CpG)-DNA oligonucleotides (ODN) to boost cytokine responses and costimulatory molecule expression on murine bone marrow-derived dendritic cells (mBMDC). Furthermore, we evaluate the potency of a PSA-peptide based vaccine in combination with CpG-DNA to elicit specific cytotoxic T cell (CTL) responses. mBMDC were stimulated with CpG-DNA (1668: 5'-TCCATGACGTTCCTGATGCT-3') or non-stimulatory control-ODN (1720: 5'-TCCATGAGCTTCCTGATGCT-3'). Subsequently, expression of the costimulatory molecules CD40 and CD86 and induction of proinflammatory cytokines (interleukin (IL)-6 and IL-12) were analyzed. For induction of PSA-peptide specific CTL, female C57BL6 mice were immunized with PSA-peptide 65-73 (HCIRNKSVI) alone or in combination with 1668 or 1720-ODN. In vivo cytotoxicity assay determined PSA-peptide specific cytotoxicity 1 week after vaccination. Treatment of mBMDC with stimulatory CpG-DNA ODN resulted in pronounced up-regulation of costimulatory molecule expression on mBMDC in a dose-dependent manner. CpG-ODN significantly increased
production of IL-6 and IL-12 in mBMDC (P< 0.001). Induction of PSA-peptide specific CTL responses in mice immunized with PSA-peptide and CpG-DNA were significantly greater than those of PSA-peptide and control-ODN immunized mice or PSA-peptide only vaccination. CpG-DNA acts as potent adjuvant for vaccination therapies and elicits profound PSA-peptide specific CTL responses in combination with an immunodominant PSA-peptide. CpG-ODN mediated immunotherapy represents a potentially inexpensive, safe, easy-to-produce, and easy-to-handle treatment alternative. Therefore, further evaluation of CpG-DNA in immunization therapies against CaP is warranted.