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Effect of Immunostimulatory CpG-oligonucleotides in chronic lymphocytic leukemia B cells

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Bacterial DNA and phosphothioate oligonucleotides containing a CpG motif (CpG-ODN) can activate cells of the immune system such as monocytes, dendritic cells and B cells. Protective immune responses against pathogens and tumor cells were observed in murine models when mice were treated with CpG-ODN. Recent results have demonstrated strong activation of human immune cells as well. Apart from stimulating cells of the immune system, CpG ODN have many direct effects on B-CLL cells such as cell cycle entry, cytokine production and upregulation of potential target antigens for antibody therapy. In our studies, we demonstrated that B-CLL cells activated with the CpG-ODN DSP30 upregulate important costimulatory molecules such as CD80 and CD86. This effect was further enhanced upon costimulation with CD40ligand or IL-2. Resting B-CLL cells are poor stimulators of autologous or allogeneic T cells but we demonstrated autologous and allogeneic immune recognition of B-CLL cells stimulated with CpG-ODN in mixed lymphocyte reactions.

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Attempts to eradicate cancer by adoptive T cell transfer have been limited due to the difficulty of generating T cells with defined antigen specificity. The current study focuses on the generation of cytotoxic T lymphocytes (CTL) and T helper (Th) lymphocytes against the tumor-associated antigen HER2 using autologous dendritic cells (DC). Human dendritic progenitor cells were transduced with a retrovirus encoding the HER2 gene and then further matured into CD83+ DC. HER2-expressing DC were used as antigen presenting cells for stimulating autologous T cells in vitro. HER2-transduced DC elicited HER2-specific CD8+ CTL that lysed HER2-overexpressing tumor cells in context of distinct HLA class I alleles. Simultaneously, retrovirally transduced DC induced HER2-specific CD4+ Th1 cells that released IFN-gamma upon stimulation with DC pulsed with the recombinant protein of HER2. This method of stimulating HER2-specific CD8+ and CD4+ T cells was successfully implemented for generating HER2-specific CTL and Th1 clones from a patient with HER2-overexpressing breast cancer. These data indicate that retrovirally transduced DC expressing the HER2 molecule present multiple peptide epitopes and subsequently elicit HER2-specific CTL and Th1 cells. The ability to generate HER2-specific, HLA-restricted CTL and Th1 clones facilitates the development of adoptive T cell therapy for patients with HER2-overexpressing tumors.