TOLL-LIKE RECEPTOR-BASED THERAPY FOR CHILDHOOD ACUTE LEUKEMIA

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Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children. Despite advances in the treatment, relapsed ALL remain an ongoing clinical challenge. Conventional chemotherapy is often insufficient to provide long-term cures in these challenging patients. Previously, we reported the ability of immunostimulatory DNA (CpG ODN) treatment both to enhance the immunogenicity of ALL blasts and to stimulate significant anti-ALL immune activity resulting in T cell-mediated protection against leukemia progression. To further explore the potential for toll-like receptor signaling to amplify immune responses against ALL, we investigated the ability of ligands for TLR2/1 (Pam3), TLR3 (poly I:C), and TLR7/8 (R848) to induce anti-ALL activity in comparison to CpG ODN.

Stimulation with Pam3 up-regulated CD40 expression on primary ALL cells, which were harvested from Emu-RET transgenic mice with spontaneous ALL, even higher than with CpG ODN stimulation *in vitro* ($p < 0.0001$). Furthermore, Pam3 induced the strongest lymphocyte-mediated cytotoxicity against ALL cells in a dose-dependent manner. In contrast to its *in vitro* efficacy, our syngeneic adoptive transfer studies showed that Pam3 treatment fail to inhibit the expansion of ALL cells providing no survival benefits. Both CpG ODN and poly I:C treatments significantly depleted the ALL cells in the recipients by day 21 post- leukemia challenge; however, only CpG ODN treatment conferred survival advantages. These results suggest that although its ability to initiate anti-ALL activity, the protective effect of poly I:C may be transient due to lack of T cell-mediated immune responses that is required for durable control over leukemia progression. Taken together, CpG ODN shows the most promising TLR-based therapy to eradicate residual disease after chemotherapy. Work is ongoing to understand the underlying mechanism of CpG ODN-induced anti-ALL immune responses by identifying key immune mediators.