TOLL-LIKE RECEPTOR LIGANDS DELAY ACUTE LYMPHOBLASTIC LEUKEMIA ONSET VIA DEPLETION OF PRE-LEUKEMIC CELLS

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Onset of pediatric acute lymphoblastic leukemia (ALL) depends on the long-term survival and evolution of a pre-leukemic cell population that arises during in-utero. Detection of chromosomal translocations indicates that about 1% of all newborns harbor early-occurring abnormal cells; however, only 1 in 100 of these infants will progress to leukemia. This reveals that progression to leukemia is not the inevitable fate of these early-occurring abnormal cells.

Infection has been postulated to play a role in the development of pediatric ALL. While epidemiologic studies have implicated exposure to infection as a protective factor, the impact of immune modulation during the pre-leukemic phase has not been reported. In this study, we use the B cell precursor (BCP) leukemia-prone Emu-RET transgenic mouse to investigate whether exposure to infection associated danger signals influences disease progression via changes in pre-leukemic cell survival.

Using splenocyte cultures from pre-leukemic mice, we observed significant depletion of pre-leukemic cells following incubation with a panel of ligands for infection-related pattern recognition receptors. The strongest activity was observed with ligands for Toll-like receptors 7/8 (R848), and 9 (CpG) with >75% reduction in pre-leukemic cell number ($p<0.01$).

We were able to determine that this mechanism works primarily through indirect pathways, and is mediated almost exclusively by soluble factors produced by responding immune effector cells.

Consistent with these in vitro results, we have previously shown that administration of CpG to leukemia-prone mice early in life reduced the size of the pre-leukemic cell population and significantly delayed disease onset ($p<0.0001$).

Our results are the first to demonstrate that exposure to infection-related danger signals alters leukemia progression through the reduction in pre-leukemic cell viability. These findings provide mechanistic support for the protective effects of early-life infections and suggest novel strategies to eliminate the early-occurring abnormal cells that can give rise to initial disease and relapse.