

## Reduced immunogenicity of chromatin modifying agents expanded human cord blood grafts

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The limited number of hematopoietic stem cells (HSC) within a single unit of cord blood (CB) currently limits its use as an alternate graft source. Using chromatin modifying agents (CMA), including 5aza-2-deoxycytidine (5azaD) and trichostatin A (TSA), we have developed a culture strategy which allows for 7- to 10-fold expansion of transplantable HSC. Here we have assessed the allostimulatory capacity of CMA-expanded CB grafts. The co-expression of immunophenotypic markers of dendritic cells (DC) such as HLA-DR/CD86 and HLA-DR/CD11c, were significantly reduced in 5azaD/TSA-expanded grafts compared to control. In addition, the allostimulatory capacity of CMA-expanded grafts, as measured by mixed lymphocyte culture, was dramatically reduced compared to control. We hypothesized that the reduction in allostimulatory capacity of CMA expanded grafts is due to inhibition of DC differentiation or promotion of apoptosis in culture. It has been previously shown that STAT3 is indispensable in the commitment of HSC into DC. 5azaD/TSA-expanded cells express more STAT3 transcripts than control, but the expression of two inhibitors of STAT3, p21 and GATA1, are also increased significantly. LINE-1 assay, as surrogate of global methylation, shows that 5azaD/TSA-expanded cells are hypomethylated, and specifically the promoters of GATA1 but not STAT3 nor p21. However, both STAT3 protein and phosphorylation are shown to be increased in CMA expanded grafts. When expanded CB cells are grown in conditions which are permissive to DC generation, 5azaD/TSA-expanded cells produce fewer net numbers of DC than control. However, when normalized to the number of CD14+ cells at the end of expansion culture the efficiency of DC generation by 5azaD/TSA expanded graft was comparable to control cultures. Taken together, our studies indicate that the reduced allostimulatory capacity of 5azaD/TSA-expanded cells is likely due to reversible inhibition of an early stage of DC differentiation.

### Biography

Nadim Mahmud received his medical degree from the University of Chittagong with the highest distinction and completed his internal medicine residency at the same institution and at the Institute of Post Graduate Medicine and Research in Dhaka, Bangladesh. He then received his doctoral degree in stem cell biology from the Mie University School of Medicine in Mie, Japan and also completed a post-doctoral fellowship awarded by the Japan Society for the Promotion of Science. Currently Mahmud is serving as an Associate Professor in the section of Hematology/Oncology and the Director of Clinical Stem Cell Laboratory for the University of Illinois Blood & Marrow Transplant Program.

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