Conclusion: We have developed a mice model of severe cGVHD. Interestingly, rapamycin prevented death from cGVHD in that model, perhaps through in vivo expansion of Treg.

Depletion of Naïve T Cells From Peripheral Blood Stem Cell Grafts for GVHD Prevention

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Graft-versus-host disease (GVHD) frequently causes morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). In HLA-identical HCT, GVHD results from donor T cell recognition of minor histocompatibility (H) antigens on recipient tissues. Complete T cell depletion (TCD) of donor hematopoietic cell products is more effective than pharmacologic immunosuppression for preventing GVHD, but is complicated by delayed immune reconstitution and consequent life-threatening infections. Approaches to TCD at HCT that preferentially deplete T cells responsible for GVHD and preserve pathogen-specific T cells may improve outcomes. Mature CD3+CD8+ and CD3+CD4+ T cells can be classified into CD45RA+CD62L+ naïve (TN) and CD45RO+ memory (TM) subsets, the latter of which includes effector memory (TEM) and central memory (TCM) T cells. Murine studies in MHC-matched and –mismatched models demonstrated that transplanting TN cells causes severe GVHD, purified TEM causes mild GVHD, and TCM do not cause GVHD. In vitro studies have similarly demonstrated that human donor CD8+ T cell specific for recipient minor H antigens are found predominantly within the TN cell subset. In sum, these data suggest that selective TN cell depletion may alter the incidence or severity of GVHD in human HCT.

We developed an effective process for engineering human peripheral blood stem cell (PBSC) grafts that depletes CD45RA+TN and retains CD34+ stem cells and functional CD45RO+TN specific for diverse opportunistic pathogens. We initiated a clinical trial to evaluate selective depletion of TN cells from allogeneic PBSC for the prevention of GVHD in patients with acute leukemia. Each of the first 22 patients has engrafted (median day 12), regimen-related toxicity has been acceptable, T-cell numbers recover faster than reported for TCD HCT (median 412 CD3+ T cells/μl on day 28), and there is no increase in the rate of relapse, opportunistic infections, or EBV reactivation compared to patients treated with T cell replete PBSC grafts. Early onset gastrointestinal symptoms that are compatible with mild acute GVHD occur frequently, but rapidly respond to therapy, and most patients have successfully tapered immunosuppression. T cell responses to pathogens recover early after HCT. At a median of 14 months follow-up, overall and disease free survival are 80% and 75% respectively, and the frequency and severity of chronic GVHD is substantially reduced compared to recipients of T cell replete PBSC grafts.

Introduction: Acute graft versus host disease (aGVHD) is a common (20-50% of all HSCT recipients) and potentially lethal complication after allogeneic hematopoietic stem cell transplantation (HSCT). Risk factors for aGVHD include donor source, preparative regimen and the degree of HLA-mismatching. Currently, there is increasing evidence that (reactivation of) viral infection is a risk factor for aGVHD. We hypothesized that the presence of viruses in the gastrointestinal tract, including AdV, triggers the initiation phase of intestinal GVHD. Therefore we investigated the association between viral PCR-positivity in stool prior to HSCT and the occurrence of intestinal aGVHD.

Methods: We prospectively evaluated 27 consecutive pediatric allogeneic HSCT patients from January ’09 until October ’10. Primary endpoint was the development of intestinal aGVHD diagnosed according to Glucksbergs criteria and confirmed by histopathology. Follow-up ranged from 100 to 376 days or until death. Stool specimens were taken peri-HSCT and analyzed for entero-, -noro-, -astro-, -parecho- and adenovirus, by real-time PCR. The association between fecal PCR-positivity and intestinal aGVHD was analyzed using Fisher’s exact tests.

Results: Of the 27 patients that were evaluated, 6 (22%) developed intestinal aGVHD after a median of 64 days (range, 38-74). Four (15%) patients died due to transplant related complications or disease progression/relapse after 22-61 days. All patients with stool specimens positive for AdV (4/27, 15%) developed intestinal aGVHD (versus 2/23 (9%) patients without AdV in stool, p = .001, positive predictive value = 100%, negative predictive value = 91%). Four patients were positive for other viruses but none of these developed aGVHD. Interestingly, one patient became positive for AdV at 327 days post-SCT and developed chronic intestinal GVHD after 476 days. AdV persisted in patient stool for more than 140 days, and preceded systemic infection: AdV was first detected in plasma on day 409 and loads raised from 482 copies/ml to 1.4x10^4 copies/ml on day 500.

Conclusion: AdV in stool prior to HSCT was associated with intestinal acute GVHD. It supports the hypothesis that virally induced tissue damage leads to influx of inflammatory mediators and ultimately activation and influx of activated cytotoxic T-cells involved in GvHD. Currently we perform a prospective follow-up study. These results may impact monitoring and treatment (preventive and curative) guideline/protocols.

Allogeneic T Cells up-Regulate Fatty Acid Metabolism and Can Be Targeted Through Metabolic Inhibition of Fatty Acid Oxidation

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Recent research has increased our understanding of lymphocyte metabolism in vitro, but the metabolism of lymphocytes activated in vivo remains poorly understood. To evaluate this important issue further, we explored the metabolism of proliferating, donor T lymphocytes seven days after the initiation of graft versus-host disease (GVHD) in an acute model of GVHD (B6 into B6D2F1). Donor T cells up-regulated mRNA for fatty acid (FA) transport proteins (e.g.