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TLR5 agonist rflagellin: A novel agent that reduces GvHD while protects allo-HSCT recipients from CMV infection

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The major causes of mortality in cancer patients treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) are graft vs. host disease (GvHD), opportunistic infections and disease relapse. Clinically, approximately 30-40% and 50-60% of long-term survivors of allo-HSCT develop acute GvHD and chronic GvHD, respectively. GvHD is caused by donor T cells and initiated by inflammatory cytokines. Prophylactic pharmacological immunosuppression can limit the incidence and severity of GvHD, but increases the risks of opportunistic infection and relapse. A long-standing goal has been to develop novel therapies that protect allo-HSCT recipients from GvHD without global immuno-suppression. Toward this end, we have tested the effect of flagellin, a TLR5 agonist extracted from bacterial flagella, on GvHD in murine allo-HSCT models. We observed that flagellin administration (3 hours before irradiation and 24 hours after allo-HSCT) protected recipients from GvHD while preserving complete donor T cell chimerism and anti-viral immunity. The proliferation and activation of donor T cells, and serum pro-inflammatory cytokines were reduced significantly in flagellin-treated recipients compared with PBS-treated recipients. Using allo-HSCT radiation chimeras previously engrafted with TLR5 knockout hematopoietic cells, we have shown that interaction between flagellin and TLR5 expressed on both host hematopoietic and epithelial cells is required to maximum reduction of GvHD. Recombinant flagellin (rflagellin) has been tested as vaccine adjuvant in a number of clinical trials against influenza infection and diarrhea and has been found to be safe for use in humans. A cGMP grade recombinant flagellin variant CBLB502 (rflagellin) is exceptionally stable and less toxic than native flagellin also protected allo-HSCT recipients from GvHD while preserving donor T cell chimerism and anti-viral immunity. These data indicate that rflagellin can be used as a novel drug to control GvHD without global immuno-suppression, and thereby will enhance post-transplant immune reconstitution to prevent tumor relapse and opportunistic infections.

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