M-CSF induced myeloid and NK cell differentiation cascade protects from CMV viremia during hematopoietic stem cell transplantation

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Immune-deficiency after hematopoietic stem and progenitor cell (HS/PC) transplantation results in increased susceptibility to infection. Cytomegalovirus (CMV) infection is the largest clinical challenge to HS/PC transplantation (HCT) and a significant cause of post transplantation morbidity and mortality. Current treatments are focused on inhibition of viral replication. Common anti-viral drugs like ganciclovir, however, are problematic due to significant bone marrow toxicity that impedes the success of donor cell engraftment and the reconstitution of a functional immune and hematopoietic system. They are therefore limited to pre-emptive applications, although prophylactic treatments stimulating patients' antiviral defenses would be highly desirable. We have previously shown that macrophage colony-stimulating factor (M-CSF/CSF-1) directly instructed myeloid commitment in HSC and that this effect had therapeutic benefit in improving protection against bacterial and fungal pathogens after HCT. Here we report that in a preclinical model of HCT treatment with M-CSF promotes rapid reconstitution of antiviral activity and protects the graft recipient from CMV infection. M-CSF treatment resulted in an increased survival of recipient mice infected with lethal doses of CMV. The increased survival advantage correlated with decreased viral load in several tissues. We observed that this effect depended on the accelerated development and increased activity of NK cells. The M-CSF stimulated generation of myeloid progenitors (GMP) was sufficient to induce increased production and activity of NK via higher production and presentation of the cytokine IL-15, a regulatory loop that was further enhanced by IFN-I production in myeloid cells. IL-15 production by M-CSF induced myeloid cells lead to increased NK cell differentiation and activity that protected graft recipients from CMV viremia. Together our experiments establish cell types and cytokine mediated cross talk involved in M-CSF induced protection against viral infection after HCT. Our results thus encourage potential clinical applications of M-CSF to prevent severe viral infections following HCT

Keywords : Infection models, HSC transplantation, Cytokine therapy, Immune recovery, Protection from infection
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