Aus dem Institut für medizinische Immunologie
der Medizinischen Fakultät der Charité – Universitätsmedizin Berlin

DISSERTATION

CC chemokine receptor 2 is relevant for CD8-induced graft-versus-host disease but not for graft-versus-tumor activity

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät der Charité –
Universitätsmedizin Berlin

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Datum der Promotion: 11. September 2006

Summary

Allogeneic hematopoietic stem cell transplantation (HSCT) is a well-established therapy for a variety of malignant and non-malignant disorders of the hematopoietic system and for certain solid tumors. One of the major complications limiting the success and wider application of allogeneic HSCT is the occurrence of acute graft-versus-host disease (GVHD), which is a rapidly progressive illness with epithelial damage of gut, liver, skin, and lung, immunosuppression and cachexia. GVHD is mediated by alloreactive donor T cells contained in the graft and can be prevented by depletion of these T cells prior to transfer. However, alloreactive donor T cells also mediate the so-called graft-versus-tumor (GVT) effect, which is increasingly being recognized as an important component of the overall anti-tumor effect of an allogeneic HSCT. Therefore, a major focus of current research is to ameliorate GVHD without reducing GVT activity. Recent murine bone marrow transplantation studies suggest that interfering with T cell migration represents an attractive therapeutic approach towards this goal.

Three families of migration molecules (selectins, chemokines, integrins, and their respective ligands and receptors) control T cell migration in homeostasis and inflammation, and members of all three families have been identified as important players during GVHD. Recently, especially chemokines and chemokine receptors have been evaluated as possible new targets for GVHD therapy.

In the present study, the role of the inflammatory chemokine receptor CCR2 for donor $CD8^+$ T cell migration during GVHD was analyzed in well-established murine bone marrow transplantation models. It was found that recipients of CCR2-deficient ($CCR2^{-/-}$) $CD8^+$ T cells develop significantly less GVHD morbidity and mortality than recipients of wild type $CD8^+$ T cells and that this correlates with reduced target organ damage to the gut and liver. A competitive *in vivo* migration assay revealed that $CCR2^{-/-}$ $CD8^+$ T cells have an intrinsic migratory defect to the gut and liver, which was previously unknown. Other causes for the reduction in GVHD could be excluded, as alloreactive proliferation, activation, IFN-γ production and *in vitro* cytotoxicity of $CCR2^{-/-}$ $CD8^+$ T cells were intact. Importantly, the GVT effect of $CCR2^{-/-}$ $CD8^+$ T cells against murine P815 mastocytoma and A20 B cell lymphoma was preserved, which demonstrates that interference with T cell migration by blockade of CCR2 signaling can separate GVHD from GVT activity. These data provide first evidence for a critical role of CCR2 for the control of $CD8^+$ T cell migration in a pre-clinical disease model and establish the rationale for the use of CCR2 antagonists possibly in combination with other chemokine receptor antagonists as novel therapeutic tools in GVHD.

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