HLA-DP specific responses in allogeneic stem cell transplantation

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6 Summary and General Discussion

Summary

Following allogeneic hematopoietic stem cell transplantation (SCT), donor derived T-cells recognizing mismatched antigens on residual malignant cells can induce strong graft versus leukemia (GVL) reactions. Treatment of patients with relapsed leukemia, lymphoma or multiple myeloma with allogeneic hematopoietic SCT followed by donor lymphocyte infusion (DLI) can result in long lasting complete remissions.[1-4] Unfortunately, the beneficial GVL-effects of DLI are often accompanied by graft versus host disease (GVHD). To reduce the risk of GVHD, patient and donor are preferably matched for HLA-A, -B and -C, -DRB1 or also HLA-DQB1 (8/8 or 10/10 match).[5-7]

HLA-DPB1 is not taken into consideration in donor selection, since mismatching for HLA-DPB1 is not associated with decreased survival. HLA-DPB1 mismatched allo-SCT is however associated with an increased risk of graft versus host disease and a decreased risk of disease relapse compared to HLA-DPB1 matched SCT.[6;8] In T-cell depleted allo-SCT, mismatching of HLA-DPB1 was not associated with an increased risk of severe GVHD, whereas a significant decreased risk of disease relapse was still observed, suggesting a selective GVL-effect.[9] In this thesis we investigated whether HLA-DP could be used as a relatively specific target for anti-leukemia reactivity following HLA-DPB1 mismatched T-cell depleted allo-SCT.

To investigate whether HLA-DP specific T-cells could mediate GVL-reactivity following HLA-DPB1 mismatched URD-SCT and DLI we analyzed in ***chapter 2*** the immune response in a patient with a refractory chronic B cell leukemia responding to DLI after HLA-DPB1 mismatched SCT. Patient and donor were fully matched for HLA-A, -B, -C, -DRB1 and –DQB1. The patient was typed HLA-DPB1*02:01,03:01 and the donor HLA-DPB1*04:02,05:01. We observed a profound GVL-effect with minimal skin GVHD resulting in a persistent complete remission of the disease. By ELISPOT analysis we identified the antileukemic CD4+ T-cell response starting 6 weeks after DLI. Following clonal isolation of these leukemia reactive CD4+ T-cells, blocking studies, panel studies and retroviral transduction experiments of the mismatched HLA-DPB1 alleles, identified both mismatched HLA-DPB1*02:01 and HLA-DPB1*03:01 as the targets of this immune response. The GVL-effect was caused by a polyclonal immune response comprising both T-helper and cytotoxic CD4+ T-cells. Since the emergence and kinetics of the leukemia-reactive CD4+ T-cells corresponded to the disappearance of the malignant cells, these HLA-DP specific CD4+ T-cells were likely to have mediated the anti-leukemic effect. Furthermore, the isolated HLA-DP specific CD4+ T-cells were capable of recognizing and lysing several HLA-DP-expressing myeloid and lymphoid hematological malignant cells. Recognition of non-hematopoietic cells was analyzed by testing for recognition of fibroblasts, renal cell carcinoma cell lines or breast cell carcinoma cell lines. Expression of HLA-DP was absent on most of these resting non-hematopoietic cells. Incubation with IFN-γ resulted in upregulated expression of HLA-DP and specific HLA-DP restricted recognition. These results illustrated that HLA-DP may

represent a relatively specific target for GVL-reactivity and that HLA-DPB1 mismatched allo-SCT may be preferable over a fully matched SCT for HLA-class II expressing hematological malignancies, making use of HLA-DP as a target for immunotherapy.

Some studies showed, in mostly T-cell repleted transplant regimens, that specific HLA-DPB1 mismatches were associated with poor clinical outcome.[10-14] It was suggested that this unfavorable effect was caused by a difference in immunogenicity between various HLA-DPB1 alleles. An algorithm defining permissive and non-permissive HLA-DPB1 mismatches was developed based on cross-reactive T-cell recognition patterns. It was suggested that permissive mismatches would not result in T-cell responses, whereas strong T-cell responses were expected to be generated against non-permissive mismatches.[10;13]

To analyze whether permissive HLA-DPB1 specific immune responses occur in vivo, we analyzed in ***chapter 3*** immune responses in 2 patients responding to donor lymphocyte infusion (DLI) after HLA-A, -B, -C, -DRB1, -DQB1 matched, HLA-DPB1 mismatched SCT. One of the patients received a permissive HLA-DPB1 mismatched SCT, the other patient a non-permissive HLA-DPB1 mismatched SCT. CD4+ T-cells were isolated from peripheral blood obtained during the clinical immune response to DLI, and stimulated with HLA-class II negative HeLa cells transduced with the specific HLA-DP molecules derived from patient or donor. In both patients, HLA-DP specific CD4+ T-cells were demonstrated by CD137 up-regulation in response to stimulation with HeLa cells transduced with patient and not donor HLA-DP molecules. Clonal isolation of these CD4+ T-cells confirmed specific recognition of the mismatched patient HLA-DPB1 molecules. Furthermore, we demonstrated in vitro for 4 additional individuals that permissive and non-permissive HLA-DPB1 responses were equally effective generated, illustrating immunogenicity of both permissive and non-permissive mismatches.

In ***chapter 4*** we further analyzed whether immunogenicity of HLA-DPB1 mismatches could be predicted based on the presence or absence of specific amino acid sequences. We developed a model to generate allo-HLA-DP responses in vitro and tested in total 48 different stimulator/responder combinations by stimulating CD4+ T-cells from 5 HLA-DPB1 homozygous individuals with the same antigen presenting cells transduced with different allo-HLA-DP molecules. HLA-DPB1 molecules used for stimulation comprised 76-99% of HLA-DPB1 molecules present in different ethnic populations. We showed that all HLA-DPB1 mismatches as defined by allele typing resulted in high frequency immune responses. Furthermore, we demonstrated that cross-recognition of different HLA-DPB1 molecules by HLA-DP specific CD4+ T-cell clones was a common observation. Individual CD4+ T-cell clones directed against the same HLA-DPB1 molecule exhibited different patterns in cross-recognition demonstrating that these CD4+ T-cell clones were specific for different epitopes. We confirmed previously described patterns in cross-recognition but also demonstrated cross-recognition patterns which did not correspond to the proposed algorithm. Overall, the data illustrated that frequently observed cross-recognition patterns

between specific HLA-DPB1 molecules did not preclude allo-HLA-DP responses between individuals expressing these HLA-DPB1 molecules. Together the data demonstrate that a high degree in similarity between HLA-DPB1 alleles is predictive for cross-reactivity but not for immunogenicity and illustrate that T-cell recognition patterns may not predict allo-reactivity.

To investigate whether patient HLA-DP specific immune responses were frequently induced following T-cell depleted HLA-DPB1 mismatched allo-SCT and DLI, we developed in ***chapter 5*** a method to screen for the presence of HLA-DP specific CD4+ T-cells. Using HeLa cells transduced with various genes encoding relevant molecules for appropriate HLA-class II processing in conjunction with different HLA-DP molecules as stimulator cells, we were able to measure the emergence of patient HLA-DP specific CD4+ T-cells in peripheral blood in a simple and effective manner. We demonstrated that patient HLA-DP specific CD4+ T-cell responses were frequently found following T-cell depleted HLA-DPB1 mismatched SCT and DLI (14 of 24 patients: 58%). The presence of HLA-DP specific CD4+ T-cells seemed to correlate with clinical responses to DLI, since patient HLA-DP specific CD4+ T-cells were measured in 13 (72%) out of 18 patients with clinical responses to DLI, and in only one (17%) out of 6 patients without clinical responses. HLA-DP specific CD4+ T-cells were most dominantly found in patients who developed GVHD following HLA-DPB1 mismatched T-cell depleted SCT and DLI. However, patient HLA-DP specific CD4+ T-cells were also found in a significant number of patients who developed beneficial clinical responses after DLI without GVHD. HLA-DP specific CD4+ T-cell responses were induced in patients suffering from a variety of hematological malignancies, including multiple myeloma, B-cell malignancies and myeloid leukemias.

In summary, HLA-DPB1 mismatched allo-SCT followed by DLI late after transplantation can result in selective GVL-reactivity. Furthermore, all HLA-DPB1 mismatches as defined by allele typing are immunogenic and resulted in vitro in high frequency immune responses. In a cohort of 24 patients transplanted for various hematological malignancies with a 10 out 10 matched HLA-DPB1 mismatched SCT followed by DLI, HLA-DP specific immune responses were frequently found. The presence of HLA-DP specific CD4+ T-cells correlated with clinical immune responses including both selective GVL-reactivity and GVHD. It is likely that in each individual local environmental circumstances possibly in combination with the induction of other immune responses may finally determine the balance between GVHD and GVL-reactivity.

General Discussion

In this thesis we demonstrated that HLA-DPB1 mismatched SCT followed by DLI late after transplantation can result in selective GVL-reactivity. Furthermore, we showed that all HLA-DPB1 mismatches are immunogenic and that HLA-DPB1 mismatched SCT followed by DLI frequently resulted in an HLA-DP specific immune response. The presence of patient HLA-DP specific CD4+ T-cells correlated with clinical immune responses. However, in the analyzed patient cohort not only selective GVL-reactivity was observed but a significant number of patients also developed GVHD.

Of the 24 patients analyzed, 8 patients developed clinical significant GVHD. This included both patients who received DLI early after SCT and patients who received DLI later after SCT. GVHD was observed in patients receiving DLI for various indications including both persistent- and progressive disease and mixed chimerism. Furthermore, patients who developed GVHD suffered from various diseases, including multiple myeloma, B-cell malignancies and myeloid leukemia. Although this patient cohort was rather diverse en small, no clear correlation between clinical circumstances and development of GVHD was found. The results indicated that it is not easily predictable in which patients GVHD can be expected to develop.

Balance between GVL-reactivity and GVHD in HLA-class II restricted immune responses

In a fully HLA-matched setting, it has been shown that in patients with selective GVL-reactivity relatively limited immune responses directed against a few MiHAs were found. In contrast, in patients with GVHD, higher frequencies of multiple different MiHA specific T-cells have been found.[15;16] These data suggest that the development of a broader immune response may be correlated with the development of GVHD. In an HLA-matched setting, MiHA specific T-cells recognize non-self polymorphic peptides in the context of self-HLA molecules. During thymic development, T-cells are positively selected for recognition of self-HLA-molecules, followed by deletion of T-cells specific for a self-peptide in a self-HLA-molecule. This selection process results in a T-cell repertoire recognizing only non-self-peptides in self-HLA.[17] In allo-HLA-reactivity, T-cells recognize a peptide in the context of non-self HLA molecules. Allo-HLA-reactivity is therefore due to cross-reactivity of T-cells educated in the thymus to recognize a non-self peptide in the context of self-HLA. Any T-cell may by chance be cross-reactive with a peptide presented in a non-self HLA-molecule. Since there is no thymic selection for non-self HLA-molecules, no selection for cross-recognition of allo-HLA molecules occurs. The frequencies of T-cells directed against allo-HLA molecules can therefore be expected to be much higher than the frequencies of allo-reactive T-cells in a HLA-matched setting. Frequencies of allo-reactive T-cells in an HLA-

mismatched setting have been demonstrated to be a 1000 fold higher than the frequencies of allo-reactive T-cells in HLA-identical setting.[18;19] Following HLA-mismatched allo-SCT and DLI a broad immune response is therefore likely to develop, possibly increasing the risk for GVHD. Furthermore, in adult donors the T-cell compartment consists of both naïve and memory T-cells. Since any T-cell can exhibit reactivity against a peptide in the context of non-self HLA, allo-HLA-reactive T-cells may reside both in the naïve and in the memory repertoire.[18] An allo-HLA-DP specific CD4+ T-cell in the naïve T-cell repertoire requires professional antigen presenting cells (APC) for priming and has a relatively high threshold of activation.[20] In contrast, memory T-cells have a low threshold of activation and do not require professional APCs for priming of the immune response.[21] If by chance, T-cells specific for a peptide/allo-HLA-DP-molecule are present in the memory compartment of the donor, a vigorous immune response may be expected to be generated following HLA-DPB1 mismatched allo-SCT, whereas an allo-HLA-DP specific CD4+ T-cell from the naïve repertoire may result in a more limited immune responses.

T-cell responses directed against ubiquitously expressed antigens may be involved in both GVL-reactivity and GVHD, whereas T-cell responses directed against antigens specifically expressed on hematopoietic cells, including malignant cells may induce GVL-reactivity without severe GVHD. Immune responses directed against HLA-class II restricted MiHAs may also result in selective GVL-reactivity since expression of HLA-class II molecules is relatively restricted to hematopoietic cells. Indeed, T-cell responses directed against several HLA-class II restricted MiHAs encoded by broadly expressed genes have been identified in patients with GVL-reactivity accompanied by only mild GVHD.[22;23] This is further supported by the observation from clinical studies showing that CD8+ T-cell depletion reduces the incidence of GVHD associated with DLI without adversely affecting conversion to donor hematopoiesis.[24;25] However, HLA-class II expression can be induced on non-hematopoietic cells by pro-inflammatory cytokines.[26;27] HLA-class II restricted CD4+ T-cell responses may therefore contribute to development of GVHD when high levels of pro-inflammatory cytokines are released as a consequence of conditioning regimens or high pathogenic loads early after transplantation. High frequencies of MiHA-specific CD4+ T-cells have indeed been shown in several studies to precede and closely correlate with the onset of clinical GVHD.[28;29] Furthermore, allo-HLA-DP specific CD4+ T-cells have been isolated from skin biopsies of patients suffering from GVHD.[30-32] These data suggest that when a broad HLA-class II specific immune response is generated local circumstances at the time of DLI may influence the balance between GVL-reactivity and GVHD.

HLA-class II expression on non-hematopoietic tissues

We hypothesized that mismatched HLA-class II molecules may be used as a relatively specific target for cellular immunotherapy since most leukemic cells are expected to express HLA-class II molecules. In chapter 2 we demonstrated the expression of HLA-DP

on various leukemic cells. B-ALL and CLL cells showed high expression of HLA-DP whereas more variable expression of HLA-DP was found on myeloid leukemic cells. Furthermore, we demonstrated that various leukemic cells were recognized and lysed by HLA-DP specific CD4+ T-cell clones. Under normal conditions HLA-class II expression on non-hematopoietic tissues is anticipated to be restricted to antigen presenting cells. However, upon exposure to pro-inflammatory cytokines HLA-class II expression on non-hematopoietic cells may be upregulated[26;27] and thereby become a target for GVHD. We demonstrated that HLA-DP expression was not found on resting non-hematopoietic cells including fibroblasts and renal- or breast-cell carcinoma cell-lines, and showed that co-incubation with IFN-γ can result in upregulation of HLA-DP and specific recognition by HLA-DP specific CD4+ T-cell clones.

HLA-class II expression on non-hematopoietic tissues following conditioning regimens or in the presence of immune responses against pathogens has been described to result from a local release of cytokines which induce upregulation of co-stimulatory molecules and HLA-class II molecules on APC. These APC then induce activation and proliferation of T-cells, resulting in a further release of pro-inflammatory cytokines and more upregulation of HLA-class II molecules. In the end this cascade may result in cell damage or tissue destruction.[33;34]

To further support the hypothesis that mismatched HLA-class II molecules might be used as a relatively specific target for cellular immunotherapy in hematological malignancies we analyzed the expression of HLA-class II molecules on non-hematopoietic tissues at various moments during the course of SCT. Skin biopsies were collected after conditioning regimen at the time of SCT and during GVHD and stained for HLA-class II expression. In normal skin biopsies, HLA-class II expression was only found on dendritic cells in the epidermis. In the dermis clumps of HLA-class II expressing cells, possibly close to vessel structures were found. No upregulation of HLA-class II compared to normal skin biopsies was found following conditioning regimens at time of SCT. However, three months after SCT upregulation of HLA-class II molecules was found. In patients with GVHD also increased expression of HLA-class II molecules was demonstrated in the dermis. We did not find increased expression of HLA-class II molecules on keratinocytes in the epidermis. The results may indicate that not the conditioning regimen itself but possibly repair mechanisms or lymphopenia-induced homeostatic proliferation of donor T-cells induced upregulation of HLA-class II molecules on non-hematopoietic tissues found prior to the development of GVHD. Possibly the inflammatory status in the patient at time of DLI infusion greatly influences the outcome of GVHD. (unpublished data)

CD4+ DLI resulting in selective GVL-reactivity or GVHD

In allo-SCT, T-cell depletion of the graft has shown to reduce the risk of severe GVHD. However, in these protocols post-transplantation anti-viral and anti-tumor immunity is

also significantly impaired. To accelerate immune reconstitution for viral antigens and prevent relapse of malignancies, after T-cell depleted allo-SCT, prophylactic DLI can be administered. However, early intervention is associated with a risk of GVHD. CD8+ T-cells are known to be potent effector cells in both anti-tumor and anti-viral immunity, but they also play an essential role in GVHD. Although CD4+ T-cells are generally regarded as helper cells in induction and maintenance of CD8+ T-cell immunity, direct cytolytic activity in anti-tumor and viral responses has been shown. Administration of CD4+ DLI may reduce the risk of severe GVHD while preserving anti-tumor and antiviral activity.[24;25]

At this moment in our center a phase II open label single center randomized clinical study is ongoing in which immunologic effects of prophylactic infusion of purified donor CD4+ T-cells early after T-cell depleted allo-SCT for various hematological malignancies are evaluated. In patients receiving DLI from a matched related donor, no increase in GVHD was observed. Three patients received prophylactic CD4+ DLI from a 10/10 matched unrelated donor. Two of these patients suffered from AML and received a graft from a fully HLA-A, -B, -C, -DRB1 and -DQB1 matched, HLA-DPB1 mismatched donor. Three months after SCT, both patients received CD4+ DLI for mixed chimerism. This resulted in an increase in donor chimerism, which coincided with initially limited acute GVHD of the skin requiring only topical corticosteroid treatment. Subsequently, three to 8 weeks later, both patients developed grade 3/4 acute GVHD of the colon that was successfully treated with systemic immune suppression. At 15 months after alloSCT, both patients were still in CR. The clinical course and specificity of the T-cell immune response was analyzed in detail in these patients. Both patients experienced an episode of cytomegalovirus (CMV) reactivation early after alloSCT and were shown to contain significant numbers of patient-derived CMV specific T-cells with an activated phenotype as reflected by expression of HLA-class II at the time of prophylactic CD4+ DLI. A profound polyclonal CD4+ T-cell immune responses directed against mismatched HLA-DPB1 alleles in both patients was found. Allo-reactive HLA-DP specific CD4+ T-cells were shown to recognize HLA-class II expressing patient hematopoietic cells as well as skin-derived fibroblasts of the patients cultured with pro-inflammatory cytokines. In addition, colonic biopsies of both patients at the time of GVHD showed predominant infiltration with CD4+ T-cells and colonic epithelial cells displayed expression of HLA-class II. CMV specific T-cells may have contributed to the upregulation of HLA-class II expression on patient hematopoietic as well as non-hematopoietic cells. As a consequence, HLA-class II expressing residual patient-derived T-cells and non-hematopoietic tissues became targets for allo-reactive HLA-DP specific CD4+ T-cells. HLA-class II expression may have been particularly upregulated on non-hematopoietic cells in CMV-infected tissues due to a strong local inflammatory response mediated by CMV specific T-cells and activated inflammatory cells. The subsequent recognition of HLA-class II expressing non-hematopoietic cells by HLA-DP specific CD4+ T-cells may have resulted in local exacerbation of GVHD. These data support the hypothesis that active viral infection at

the time of HLA-DPB1 mismatched T-cell infusion may trigger HLA-DP specific CD4+ T-cells to mediate both a beneficial GVL-reactivity and detrimental GVHD.[35]

CD4+ T-cells as helper cells in GVL-reactivity

CD4+ T-cells are known as helper cells for the induction and maintenance of CD8+ T-cell immune responses. Naïve CD8+ T-cells require priming by activated APCs to proliferate and differentiate in effector cells. APCs can be activated by inflammatory signals derived from pathogens. Alternatively, in the absence of inflammatory signals, CD4+ T-cells can activate APCs by CD40-CD40Ligand interaction and cytokine production.[36-38] In patients successfully treated with DLI for relapsed hematological malignancies after allo-SCT, both MiHA specific CD4+ T-cells and CD8+ T-cells have been isolated suggesting that the MiHA specific CD4+ T-cells may have provided help for the induction of CD8+ T-cell responses.[22;23;39] Animal models have shown that in the absence of tissue damage or infection, CD8+ T-cell mediated GVL-reactivity following DLI administration required priming of CD4+ T helper cells by host APCs.[40]

It has been suggested that efficacy of DLI to induce an anti-tumor response may depend on the capacity of leukemic cells to become APC in vivo. Recently it was shown that cross-talk between CD4+ T-cells and leukemic cells in vivo can change leukemic cells into an APC phenotype. In this study, leukemic cells in mice treated with DLI acquired an APC phenotype in vivo, whereas leukemic cells from non-treated mice remained unchanged. In vitro experiments confirmed that co-culture of primary leukemic cells with leukemia-reactive CD4+ T-cells induced an APC-phenotype on leukemic cells, whereas this was not observed from non-specific CD4+ T-cells. In this study allo-reactive CD4+ T-cells fulfilled a dual role in the anti-tumor response. First, as effector cells by directly eliminating leukemic cells, and secondly, as helper cells by producing cytokines with induced an APC-phenotype on leukemic cells. This cross-talk between leukemic cells and leukemia specific CD4+ T-cells may have had a significant role in the overall magnitude of the antitumor response.[41]

CD4+ T-cells as effector cells

Although CD4+ T-cells have mostly been studied in their role as helper cells for CD8+ T-cell immunity, in several studies CD4+ T-cells with direct cytolytic activity have been isolated from patients with GVL-responses after allo-SCT.[22;23;42;43] These CD4+ T-cells have been suggested to be involved in mediating direct anti-tumor responses as effector cells. This is supported by both murine and human studies showing that CD4+ DLI mediated GVL-reactivity.[25;44] Direct evidence that CD4+ T-cells can mediate an anti-tumor response in a mouse model was provided by Stevanovic et al. Anti-tumor effect of CD4+ T-cells was investigated by administering highly purified CD4+ DLI, obtained after positive isolation of CD4+CD8- T-cells by flowcytometry. The CD4+ DLI did not contain contaminating CD8+ T-cells and in vivo no expansion of CD8+ T-cells was observed. Since the emergence

and kinetics of activated CD4+ T-cells corresponded to the disappearance of leukemic cells, conclusive evidence was provided that CD4+ T-cells are capable of mediating GVL-reactivity.[41] In chapter 2, we demonstrated using ex vivo ELISOT analysis the presence of only CD4+ and not CD8+ leukemia reactive T-cells in both peripheral blood and bone marrow indicating that CD4+ T-cells can elicit a profound anti-leukemia response in the absence of leukemia-reactive CD8+ T-cells. In these studies both CD4+ T-cells producing high levels of IFN-γ without cytolytic activity and CD4+ T-cells which were capable of direct lysis of leukemic cells were found. The results demonstrated that CD4+ T helper cells and CD4+ cytotoxic CD4+ T-cells are sufficient for direct effector function in GVL-reactivity in patients.

In conclusion

In chapter 5, it was shown that following HLA-DPB1 mismatched allo-SCT and DLI a variety of responses can occur. In a few patients no response was observed, whereas in other patients GVL-reactivity in the presence or absence of GVHD was observed. From these data it could not be easily predicted in which patient population a selective GVL-effect may be expected. We demonstrated in chapter 3 that allo-HLA-DP specific immune responses can be generated from all HLA-DPB1 mismatch combinations. Therefore, we hypothesize that not only the T-cell repertoire of the donor, but possibly more importantly local circumstances in the host determines the balance between GVL-reactivity and GVHD. Expression of HLA-class II in different target tissues influenced by inflammatory conditions may determine the magnitude and diversity of immune responses. To further support this hypothesis research analyzing local circumstances in the host like expression of HLA-class II molecules, adhesion and co-stimulatory molecules and their relation to GVHD is essential.

As long as it is not possible to predict which patients are especially at risk to develop GVHD following HLA-DPB1 mismatched SCT and DLI, it may be preferable to use HLA-DPB1 matched SCT over HLA-DPB1 mismatched SCT in low-grade disease, in order to reduce the risk for GVHD as much as possible. However, in high risk patients, in whom a strong anti-tumor response is required, an HLA-DPB1 mismatched donor may be favorable over an HLA-DPB1 matched donor to provoke a GVL-effect while accepting a risk for concurrent GVHD.

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