Minor histocompatibility antigen specific cytotoxic and regulatory immune responses in health and disease

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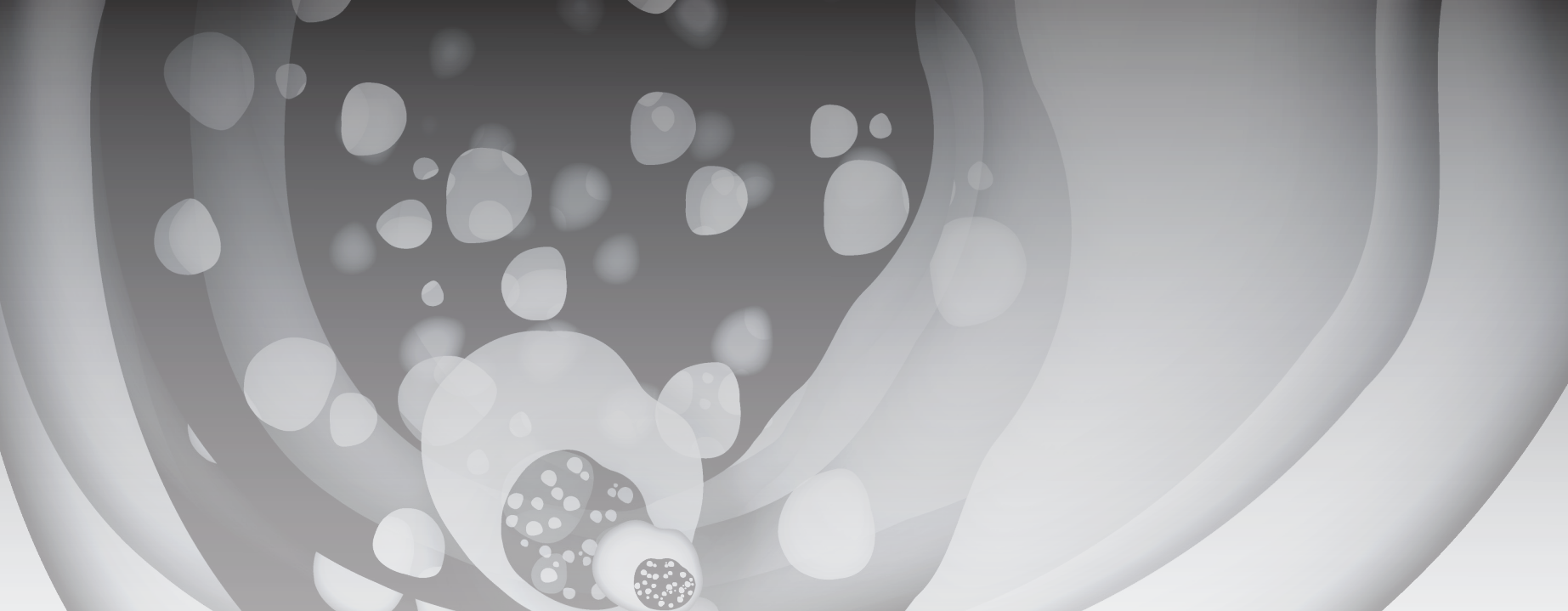

CHAPTER I

Introduction

1. Allogeneic hematopoietic stem cell transplantation

In 1957 the first human bone marrow transplantation for the treatment of a hematological malignancy was performed[1, 2]. The results of the first series of bone marrow transplantation were very poor. This was improved by the introduction of matching of the patient and its donor for the Human Leukocyte Antigen (HLA)[3-6], better pre-transplant conditioning and immunosuppression[7-10]. To date many patients are transplanted for various hematological malignancies[11], some solid tumors[12], hematological or immunological deficits[13-15] and other non-malignant diseases, like metabolic disorders[16, 17]. The number of performed transplantations increases every year and transplantation indication and transplant source are changing.

Although the results of transplantation improved enormously over the years, severe complications after hematopoietic stem cell transplantation (HSCT) including Graft versus Host Disease (GvHD)[18, 19], infections and transplant related toxicity still occur. Furthermore a significant number of patients experience relapse after transplantation for hematological malignancies[20]. The curative effect of HSCT in hematological malignancies and solid tumors, needing high dose chemotherapy and/or lethal irradiation, is partially due to graft versus leukemia or graft versus tumor responses[21, 22]. These responses can be enhanced by donor lymphocyte infusion (DLI)[23-25], which will be further discussed in paragraph 2.1.

1.1 Hematopoietic stem cell transplantation graft source

Depending of several factors like underlying disease, patient age, and transplant availability, patients receive either a bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT) or umbilical cord blood transplantation (UCBT). The use of BMT has decreased over the years. In the most recent survey of the European Group for Blood and Marrow Transplantation (EBMT) 23% of hematopoietic transplants were BMT and 72% of patients received a PBSCT[10, 26]. BMT was merely performed in patients with non-malignant diseases, especially in HLA-identical sibling transplantations and pediatric transplantations.

For BMT, cells are harvested from the donors iliac crest under local or general anesthesia, whereas for PBSCT hematopoietic stem cells are derived from peripheral blood in which the release of stem cells from the bone marrow has been increased by treatment of the donor with granulocyte colony stimulating factor (G-CSF)[27]. This makes the latter procedure much more donor friendly. Depending of the patient's underlying disease, donor characteristics and local hospital protocols the either way obtained stem cell product is infused into the patient with or without T cell depletion[28].

In the last two decades umbilical cord blood (UCB) as stem cell source is used more frequently[29-31]. UCB is harvested from the placenta directly after birth, therewith

being the most donor friendly procedure. Cord blood in general is less antigen experienced than adult blood[32, 33]. Therefore HLA matching is not as stringent as for other transplant sources[34], nevertheless still important[35, 36]. Since the number of nucleated cells derived from cord blood is limited, UCBT was initially performed in pediatric patients only[37, 38]. More recently double cord blood transplantation with good clinical results is performed in adults as well[31, 39-41]. Since the many benefits of umbilical cord blood compared to bone marrow or peripheral blood stem cells, like lower incidence of Graft versus Host disease, fast availability and less stringent HLA-matching, it is believed that the use of UCBT will only increase in the coming years[42].

2. Minor Histocompatibility antigens

Minor Histocompatibility (H) antigens were discovered shortly after the unraveling of the human leukocyte antigen (HLA)[43, 44]. As mentioned above, matching for HLA, as observed in HLA-identical (sibling) and HLA-matched (unrelated) transplantations, increased survival and reduced morbidity enormously. Nevertheless even in HLA-identical transplantation adverse effects like GvHD and graft rejection occur[18, 19, 43-45.] In GvHD, immune responses of the graft against host tissue result in severe damage of the skin, intestine and/or liver[45]. This leads to severe morbidity and mortality, in which minor H antigens play an important role. The first described and still one of the most studied antigen, HY, is derived from the Y-chromosome and is involved in gender mismatched transplantation[43, 44, 46, 47].

Since the molecular identification of minor H antigens it has become clear that these antigens are polymorphic self-proteins presented in the context of HLA class I or HLA class II molecules[48-50]. To date the identification of new minor H antigens is quickly increasing[51-55]. By now 24 autosomaly encoded and 12 Y chromosome encoded relevant minor H antigens have been described (table 1 and 2). Minor H antigens can be broadly expressed on different cell types or are restricted to the hematopoietic system. Some of the hematopoietic restricted minor H antigens are expressed at tumor cells as well56. These different expression patterns, broad versus restricted, can lead to both beneficial and adverse effects after HSCT[43, 44, 57-59]. Hematopoietic restricted minor H antigen mismatches between a HLA-identical patient and donor have important anti-tumor or anti-leukemia (GvT or GvL) effects[60-63]. Whereas mismatches in broadly expressed antigens can lead to GvT or GvL responses[59], but can especially lead to severe GvHD[57, 64, 65].

2.1 Minor H antigens in hematopoietic stem cell transplantation

It is known that minor H antigens have both positive and negative effects after HSCT.

Table 1. Autosomaly encoded minor H antigens

Minor H antigen	Restriction molecule	Tissue distribution	Ref
HA-1/A2	HLA-A*0201	Restricted: hematopoietic/solid tumor cells	50
HA-1/B60	HLA-B60	Restricted: hematopoietic cells	66
HA-2	HLA-A2	Restricted: hematopoietic cells	49
HA-3	HLA-A1	Broad	67
HA-8	HLA-A2	Broad	68
HB-1	HLA-B44	Restricted: hematopoietic cells	69
ACC-1	HLA-A24	Restricted: hematopoietic/solid tumor cells	70
ACC-2	HLA-B44	Restricted: hematopoietic/solid tumor cells	70
UGT2B17/A29	HLA-A29	Restricted: hematopoietic cells	71
UGT2B17/B44	HLA-B44	Restricted: hematopoietic cells	71
LRH-1	HLA-B7	Restricted: hematopoietic/solid tumor cells	72
SP110/ HwA9	HLA-A3	Restricted: hematopoietic cells	73
PANE1/ HwA10	HLA-A3	Restricted: hematopoietic cells	74
C19Orf48/ HwA11	HLA-A2	Restricted: solid tumor cells	75
LB-ECGF-1	HLA-B7	Restricted: solid tumor cells	76
CTSH/A31	HLA-A31	Restricted: hematopoietic cells	77
CTSH/A33	HLA-A33	Restricted: hematopoietic cells	77
LB-ADIR	HLA-A2	Restricted: hematopoietic/solid tumor cells	78
ACC-6	HLA-B44	Broad	79
CD19	HLA-DQA1*05/B1*02	Restricted: hematopoietic/solid tumor cells	80
UTA2-1	HLA-A2	Restricted: hematopoietic cells	81
ZAPHIR	HLA-B7	Restricted: solid tumor cells	82
LB-SWAP70-1Q	HLA-B*40:01	Restricted: hematopoietic cells	83
UTDP4-1	HLA-DP4	Restricted: hematopoietic cells	55

Table 2. HY encoded minor H antigens

Minor H antigen	Restriction molecule	Gene	Tissue distribution	Ref
A1/HY	HLA-A*0101	DFFRY	Broad	84, 85
A2/HY	HLA-A*0201	SMCY	Broad	86
A24/HY	HLA-A*2402	UTY	Broad	87
A33/HY	HLA-A*3303	TMSB4Y	Broad	88
B7/HY	HLA-B7	SMCY	Broad	46
B8/HY	HLA-B8	UTY	Restricted: hematopoietic cells	89
B52/HY	HLA-B*5201	RPS4Y	Restricted: hematopoietic/ solid tumor cells	90
B60/HY	HLA-B60	SMCY	Broad	91
DQ5/HY	HLA-DQ5	DBY	Broad	92
DRB1*1501/HY	HLA-DRB1*1501	DBY	Broad	93
DRB3*0301/HY	HLA-DRB3*0301	RPS4Y	Broad	94
DRB1*07:01HY	HLA-DR7	RPS4Y	Broad	95

The positive effects are leading in adoptive immunotherapy protocols. The mutual aim of these studies is to enhance GvL responses without the induction of GvHD. Before it was possible to specifically target minor H antigen specific responses, patients with severe hematological malignancies received donor lymphocyte infusion (DLI) to enhance the GvL effect after HSCT. Since these procedures were performed after HLA-identical sibling transplantation it was reasoned that minor H antigen mismatches were involved in the good clinical response of these patients[23, 96]. The anti-leukemic response was later found to be indeed associated with hematopoietic restricted minor H antigen mismatches[60, 97]. The drawback of these therapies is the increased risk of GvHD. Although there is evidence that the presence of GvHD might be needed or can be a surrogate marker for a good GvL response[63]. Nevertheless DLI is less popular as it was a decade ago, because of the increased risk of GvHD and more importantly the current use of new drugs like monoclonal antibodies, which specifically target malignant cells[25].
In the meantime minor H antigen specific targeted immunotherapies after HSCT are under study. Clinical trials (EudraCT number 2012-002435-28 and 2012-002879-34) have recently started in which patients are vaccinated with hematopoietic restricted minor H antigenic peptides in order to enhance the GvL response[98-100]. Another method to induce minor H antigen specific responses is to perform transfers of minor H antigenic specific T cell receptors to generate hematopoietic restricted minor H antigen specific T cells. Clinical implementation of transfusion of these generated antigen specific T cells is being prepared[101-105] (EudraCT number 2007-004334-16 and 2010-02462520).

2.2 Minor H antigens in solid organ transplantation

Whereas the clinical relevance of minor H antigens is well documented in HSCT[57, 106, 107], information on their impact in solid organ transplantation is scarce[108]. Similar to HSCT HLA matching is important, since rejection is much more common in HLA partially-matched or fully-mismatched donor-recipient combinations. However, rejection of renal transplants still occurs in HLA-identical sibling pairs in whom 10-year survival has hovered at 68-70% in the most recent multi-center analyses[109, 110]. It remains questionable whether minor H antigens play a role in solid organ transplantation. The impact of minor H antigen mismatches can be studied best in HLA-identical sibling transplantation. These studies, however, are hampered by the fairly low number of solid organ familial transplants and basically restrict itself to sib-sib renal transplantation. Nevertheless in recent years a number of studies have been executed in order to identify the role of minor H antigens in different settings of renal transplantation with conflicting results. The studies include mainly the effect of gender mismatches[111-114],

and some of a limited number of autosomally encoded minor H antigens both on acute and chronic rejection[115, 116]. Table 3 summarizes studies wherein the role of minor H antigens in renal transplantation is well investigated.

Table 3. Overview of literature describing clinical associations regarding minor H antigen mismatches in renal transplantation

Year	Minor H antigen	Important findings	Reference
1978	A2/HY	Reduced graft survival of male organs in female HLA-A2 recipients	117
1981	A2/HY	HY cytotoxicity in acute rejection in HLA-identical sibling transplantation	118
1994	HY	No effect of HY in completely HLA matched living donor transplantation	119
2004	A2/HA-1	HA-1 cytotoxic and regulator T cells are found in tolerant kidney transplantation patients	120
2007	A2/HA-1	HA-1 mismatch associated with chronic allograft nephropathy	115
2007	HA-1, HA-2, HA-3, HA-8, HB-1, ACC-1, ACC-2, HwA9, UGT2B17 and HY	Possibility to reduce immunosuppression despite minor H antigen mismatches	121
2008	HY	Acute and chronic rejection associated with male grafts in female recipients	111
2008	HY	De novo HY-antibody formation associated with acute rejection	112
2008	HA-1, HA-2, HA-3, HA-8, HB-1, ACC-1 and UGT2B17	Minor H antigen mismatches had no significant effect on death-censored 5-year graft survival	116
2009	HY	Acute, but not chronic rejection is associated with male grafts in female recipients	113
2012	HY	Less rejection of male donor kidneys in male recipients	114
2013	HA-1, HA-2, HA-3, HA-8, HB-1, ACC-1, ACC-2, HwA9, HwA10, HwA11, UGT2B17, LRH-1, LB-ECGF-1, CTSH, LB-ADIR, CD31 and HY	No effect of any minor in HLA-identical sibling transplantation	122

2.3 Minor H antigens in pregnancy

Pregnancy is considered to be the best experiment of nature to study transplantation. Although the fetus is haplo-identical to the mother, in general pregnancy goes without major (immunological) complications. This is mainly the result of the separate circulation of the mother and the fetus. Nevertheless this barrier between mother and child is not 100% secure. Still cells flow from mother to child and vice versa. This cell flow in mutual direction can lead to both cytotoxic and tolerogenic minor H antigen specific responses, which can be found for decades after pregnancy[123-128]. On the

one hand tolerogenic responses might play a role in the normal maintenance of pregnancy since in and around the uterus a tolerogenic environment is created[129-132]. On the other hand, minor H antigen HY specific cytotoxic responses might play a role in secondary miscarriages after a first born boy[133]. The clinical consequences of the presence of these responses further in life are difficult to predict. Probably they are of non-importance to women themselves. Nevertheless these immune responses become interesting when these women become HSCT donors[134].

3. Chimerism

Chimerism is retrieved from the Greek mythological figure Chimaera; a monster consisting partly of a lion, a goat and a dragon or a snake. Today chimerism is defined as the long term persistence of genetically different material within one individual[135]. Transplantation of a solid organ or the hematopoietic system leads to macrochimerism. Smaller quantities of chimeric cells are referred to as microchimerism. This can be detected after blood transfusion[136, 137] or after the physiological exchange of cells between mother and fetus during pregnancy[135, 138-140].

3.1 Microchimerism after pregnancy

By now it is generally accepted that fetal cells travel to the mother during pregnancy[135, 141]. Some of these cells have a stem cell like phenotype, which can remain in women for many years after full term pregnancy, resulting in fetal microchimerism (FMc)[138, 139]. Cells do not only travel from child to mother, but from mother to child as well[142]. These cells can reside in the offspring for decades and is referred to as maternal microchimerism (MMc)[135]. There is evidence that MMc might be replaced by FMc when girls grow up and become pregnant themselves[140]. FMc is frequently studied by the detection of (fragments of) the Y-chromosome, resulting from pregnancies of a boy. Strikingly, male microchimerism can be found in nulliparous women as well. This has been shown in peripheral blood and tissue analyses[143-145]. Therefore not only maternal cells but microchimeric cells of other sources present in the mother can travel to the child as well[135]. These cells can be derived from either previous male pregnancies of the nulliparous women's mother or from microchimeric cells already present in the mother from other sources. This phenomenon is referred to as transmaternal cell trafficking. With transmaternal cell trafficking male microchimerism in women with older brothers can be explained. Possible sources of male microchimerism in nulliparous women without older brothers are vanished male twins[146] or (un)known miscarriages of male fetuses[147-149]. Even male leukocytes present in semen may enter the female's circulation[150, 151].

3.2 Clinical consequences of microchimerism and subsequent immunization

The influence of FMc has merely been studied in the context of auto-immune diseases[141, 152-155] and cancer[156-158]. Conflicting results have been published regarding this subject, describing either no association or a positive association between the presence of microchimerism and the incidence of auto-immune diseases or cancer. It is unknown which role microchimeric cells play in the pathogenesis of these diseases. Microchimeric cells are often found in autoreactive tissue. It remains questionable whether the presence of these cells are the cause or the consequence of auto-immunity. It is unknown whether microchimeric cells react against host tissue resulting in tissue damage or that the host reacts against the microchimeric cells, leading to inflammation and auto-immune reactivity[159]. Furthermore there is evidence that FMc might play a role in regeneration of damaged tissue[160].

Immune responses after transplantation are possibly associated with chimerism. A beneficial effect of microchimerism has been described with established microchimerism and alloreactive Treg in the setting of solid organ transplantation[161-163]. Until now the influence of the presence of microchimerism in a HSCT donor or recipient on outcome of the transplant is unknown.

4. The human T cell repertoire

It is generally accepted that the T cell repertoire is almost naïve at birth and is educated throughout life. Education of T cells starts in the thymus by rearrangement of the T cell receptor (TCR) and by positive and negative selection[164-166]. The specificity of the TCR is determined by the alpha and beta chain. During thymic selection 55 different alfa chains can be combined with 73 different beta chains. Together with the junction area (N-region) this combination leads to a variety of TCRs. To prevent auto-immunity only TCRs with intermediate affinity to self-peptide presented in host MHC will survive, referred to as positive selection[167]. The thymocytes will further develop to become either $CD4^{pos}$ or $CD8^{pos}$ T cells. When matured, the T cells leave the thymus naive. Although they have a specific TCR, which can only recognize a limited number of antigens, these T cells are not antigen specific yet. Only upon antigen recognition in combination with specific co-stimulation they will become mature antigen specific T cells. The many different TCRs enable T cells to make adequate immune responses against many different antigens. This results in a broad T cell repertoire. In combination with different co-stimulatory molecules $CD4^{pos}$ and $CD8^{pos}$ T cells have distinct functions. $CD8^{pos}$ cytotoxic or killer T cells recognize the antigen in the context of HLA class I molecules on the surface of antigen presenting cells (APC) like dendritic cells (DC), monocytes and B cells. With or without the help of $CD4^{pos}$ T cells they

play an important role in antigen specific immune responses. A subclass of T cells, namely regulatory T cells (Treg), keep the immune system in balance and minimize auto-immunity[168]. Natural Treg are merely $CD4^{pos}CD25^{high}Foxp3^{pos}$. In general these T cells do not act in an antigen specific manner and maintain tolerance against auto-antigens[169]. $CD8^{pos}$ Treg seem to regulate in a more antigen specific manner[170, 171]. Until now the identification of specific regulatory markers on $CD8^{pos}$ Treg has been difficult. The few human studies describing $CD8^{pos}$ antigen specific Treg describe different markers, like Foxp3, CTLA-4, CD40L, LAG-3, CD127, TGF-beta[120, 171-173].

4.1 Minor H antigen specific T cell repertoire

As described in paragraph 2, minor H antigens are presented in MHC class I or MHC class II molecules. In general $CD4^{pos}$ T helper cells recognize antigens presented in class II molecule and $CD8^{pos}$ cytotoxic T cells, recognize antigens presented in the HLA class I molecule. Accordingly different CD4 and CD8 mediated minor H antigen specific responses have been described[49, 94, 174, 175]. Most of the studied minor H antigen specific responses in transplantation are $CD8^{pos}$ T cell mediated responses. This has several reasons. Firstly, the first described minor H antigens were $CD8^{pos}$ and played an important role in antigen specific responses after transplantation. HLA-A2 restricted HY specific responses are important in GvHD[44, 47] and HLA-A2 restricted HA-1 specific responses play an important role in GvL[176]. Secondly, it is technically easier to study $CD8^{pos}$ T cells; tetramer availability is merely HLA class I restricted and in vitro culturing and functional read-out systems have been further developed for CD8 mediated responses.

Apart from cytotoxic responses, tolerogenic responses against minor H antigens have been studied. Years after BMT[177] and renal transplantation[120] minor H antigen specific regulation has been described. Also after normal pregnancy[127] these responses are present in many women. It seems that minor H antigen specific $CD8^{pos}$ Treg express CTLA-4 and TGF-beta and may regulate in an IL-10 dependent manner[120, 127].

As described above antigen specificity of the T cell is determined by its TCR. But within one individual and within the population the same antigen can be recognized by different TCRs leading to similar immune responses. Nevertheless some antigens are recognized by a limited number of TCRs. This has been described in relation to bacterial or viral antigens and in autoimmunity[178-180]. Strikingly, it seems that recognition of the minor H antigen HA-1 is restricted to a single TCR Vbeta chain[181, 182]. HA-1 antigen specific T cells have been isolated by tetramer selection or clonal expansion from unrelated individuals. All the retrieved T cell clones expressed the TCR Vbeta TRBV7-9. Since HA-1 is a favorite target for antigen specific immunotherapy this finding has led to adoptive immunotherapy protocols in which the TCR is transferred[101-105].

Although good pre-clinical results have been made with TCR adoptive transfer studies it is not known whether HA-1 specific Treg also share this TRBV7-9. If so, infusion of HA-1 specific T cells might lead to adverse effects, meaning increasing the chance to relapse, instead of reducing this chance.

5. Aim of this thesis

In this thesis minor H antigen specific cytotoxic and regulatory immune responses are studied in health and disease. In the first three chapters several aspects of cell exchange and transmaternal cell trafficking between mother and child during pregnancy are investigated. It is questioned whether these responses influence transplantation outcome.

In chapter 2 the presence of minor H antigen specific cytotoxic T cells against non-maternal antigens in cord blood is described. It is generally believed that the immune system and therefore also cord blood is naïve and antigen inexperienced at birth. Before it has been described that already in cord blood minor H antigen specific T cells against non-inherited maternal antigens are present[126]. In this chapter we investigated whether transmaternal cell trafficking leads to microchimerism in cord blood. Furthermore we questioned if these few non-maternal cells traveling to a new fetus can result in minor H antigen specific responses.

In chapter 3 possible consequences of this transmaternal cell trafficking in HSCT is explored. Taking birth order into account in HLA-identical sibling transplantation leads to better transplantation outcome when the donor is transplanted with its younger sibling[183, 184]. Due to transmaternal cell trafficking the younger sibling might have come into contact with non-shared antigens of his older sibling in a tolerogenic environment during pregnancy[185]. We questioned whether it is possible to relate this birth order effect to minor H antigen mismatches. This was investigated in an unique international collaborative study, in which we analyzed a group of 311 HLA-identical sibling transplantations.

As described above, after pregnancy microchimerism and minor H antigen specific cytotoxic and regulatory responses can be present. In chapter 4 we studied whether there is a correlation between the detectable presence of microchimerism in peripheral blood and minor H antigen specific regulatory responses. To address this question a cohort of women from whom detailed obstetric and family history could be collected, was studied. As a proof of principal the minor H antigen HY was used. In all these women male microchimerism in different leukocyte subsets was determined. Both class I and class II HY specific regulation was subsequently tested.

These first chapters study minor H antigens in relation to or in the context of HSCT.

In chapter 5 minor H antigen responses are studied in HLA-identical sibling renal transplantation. With a large international multicenter study we studied the effect of 15 autosomally encoded minor H antigens and the HY antigen on rejection after renal transplantation.
In the last chapter we studied the T cell receptor of HA-1 specific T cells in more detail. HA-1 specific TCR-transferred T cells are currently under study for clinical application. Therefore we questioned whether the formerly described restricted TCR Vbeta usage of HA-1 specific CTL[181, 182] is also applicable for HA-1 specific Treg which is crucial information for the clinical application of HA-1 TCR transferred T cells.

In conclusion, this thesis emphasizes the presence of minor H antigen specific immune responses directly after birth, which will be present throughout life. The presence of minor H antigen mismatched microchimeric cells obtained through pregnancy from a mother or a child play a crucial role in this. Subsequent immunization against minor H antigens can lead to both cytotoxic and tolerogenic responses. Furthermore HA-1 specific T cells can share the same TCR Vbeta, yet being functionally different. The here performed studies enhances our understanding of immune reactions after HSCT and if applicable after renal transplantation, especially regarding the birth order effect and the assumed less favorable role of women as transplant donors.

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