The human minor histocompatibility antigen HA-1 as target for stem cell based immunotherapy of cancer : pre-clinical and clinical studies

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Chapter 1.

General Introduction

Contents

1.1. Prologue

Clinical results of immunotherapy of cancer are still largely poor – with one exception: allogeneic stem cell transplantation (SCT). The transfer of healthy hematopoietic stem cells (SC) and an allo immune system offers the possibility of applying marrow ablative doses of chemo- and radiotherapy and provides an immune-mediated anti-tumor effect referred to as graft-versus-tumor (GvT) effect. GvT effects after HLA matched allogeneic SCT are evident in patients with hematological malignancies (1) and in patients with solid tumors (2). Another illustration of successful immunotherapeutic effects is the use of infusions of donor lymphocytes (DLI) for the treatment of relapsed chronic myeloid leukemia after allogeneic SCT or for metastatic breast cancer (3,4). The GvT effects are positively correlated with the development of graft-versus-host disease (GvHD). Both GvT effects and GvHD are largely mediated by donor alloreactive T cells recognizing minor histocompatibility antigens (mHags) (5).

1.2. Molecular reasons for the immunogenicity of minor histocompatibility antigens

MHags are highly immunogenic T-cell epitopes that are presented in the context of HLA class I and II molecules on the cell surface of donor and recipient cells. These immunogenic T-cell epitopes are peptides that are derived from polymorphic and mostly intracellular proteins (6). mHags are encoded independently from human leukocyte antigen (HLA) by genes that are distributed over the entire genome. Some mHags (e.g. HA-1, HA-2 or HA-8) are encoded autosomally while others are encoded by genes on the Y-chromosome (eg. DBY, RPS4Y) (7). Differences between the amino acid sequences of donor and recipient mHags are in general due to a single nucleotide polymorphism (SNP) in the mHag genes. Mostly, only one of two alleles forms an immunogenic T-cell epitope (8). HA-1 is the best studied mHag and serves here as an example. The two mHag HA-1 alleles differ only by one amino acids (Histidine (H) <-> Arginine (R)) (8,9) in the HA-1 protein. Only the HA-1^{H} allele forms highly immunogenic T-cell epitopes (in HLA-A2 and –B60) (10). Thus, T-cells of an HA-1^{RR} donor show a strong immune response against HA-1 expressing cells of an HA-1^{H} patient after HLA-matched SCT. The most common reason for the missing immunogenicity of one of two mHag alleles is that it is not presented in HLA on the cell surface. For HA-1, there are clear differences in the dissociation rates of the HA-1^{H} and the HA-1^{R} peptide from HLA-A2 (11,12) leading to the formation of a stable complex of only HA-1^{H} with HLA-A2 on the cell surface (11,12). The missing presentation of one of two mHag alleles can also be caused by a frame-shift (13) or alternative splicing (14) of the non-immunogenic allele. Additionally, the mHag alleles can be differentially processed on the level of proteasomal cleavage (15) and TAP translocation (5,16).

1.3. Minor histocompatibility antigens as targets of the Graft-versus-Tumor effect

The in vitro recognition of leukemic cells by CTLs specific for the mHags HA-1 and HA-2 (HA-1 and HA-2 CTLs) isolated from patients after allogeneic SCT was instrumental for the assumption that the latter T-cells contributed to the GvT effect (17). Comparable in vitro lysis of leukemic cells has been found for CTLs specific for the mHags HB-1 (18) and BCL2A1 (19). The postulated GvT effect of HA-1 and HA-2 CTLs in vivo was underlined by the presence of the latter CTLs coinciding remission of chronic myeloid leukemia and multiple myeloma after DLI (20,21). Furthermore, chronic myeloid leukemia (CML) patients with GvHD have a reduced relapse risk and increased overall survival when

transplanted with an HA-1 mismatched compared to an HA-1 matched graft (22). Also the GvT effect after allogeneic SCT for solid tumors is at least partially mediated by mHag CTLs. The first indication for the relevance of the hematopoiesis restricted mHag HA-1 as target of the GvT effect against solid tumors was the finding of aberrant HA-1 mRNA expression in primary solid tumor cells and in vitro HA-1 CTL lysis of solid tumor cell lines (23). Further evidence for that hypothesis comes from a recent study in which HA-1, HA-3 and HA-8 CTLs lysing carcinoma cells were isolated from renal cell cancer patients with clinical responses after allogeneic SCT (24). This study indicates that both mHags with a broad (like HA-3 and HA-8) and restricted tissue distribution (like HA-1) might be involved in GvT effects.

1.4. Minor histocompatibility antigens expressed by malignancies

Most known autosomally encoded mHags like HA-1, HA-2, HA-3, HA-8, HB-1 and BCL2A1 are most probably derived from genes which are involved in tumorigenesis, while others, like the HY antigens, are most likely not (25). This hypothesis is based on the following reasons: First, exclusive, aberrant and over-expression of several mHags has been found in several malignancies. MRNA expression of the hematopoiesis restricted mHag HA-1 has been detected in microdissected carcinoma tissues from patients with various epithelial tumors as well as solid tumor cell lines (23,26). Like HA-1, the mHag BCL2A1 is restricted to the hematopoietic cell lineage and is also aberrantly expressed in various solid tumors. MRNA levels of both HA-1 and BCL2A1 are high in hematological malignancies (27,19). The mHag HB-1 shows only significant expression in acute lymphoblastic leukemia B cells and not in mature non-malignant B cells (18). The second indication for the possible involvement of several mHags in oncogenesis is based on the analysis of their structure and potential (patho-)physiological functions as exemplified by BCL2A1, HA-3 or HA-8. BCL2A1 is an anti-apoptotic protein that suppresses p53-induced apoptosis (25). HA-3 is encoded by the lymphoid blast crisis (Lbc) oncoprotein (15). Also for the mHag HA-8 is an association to malignancies likely since the HA-8 protein contains six Pumilio-family RNA binding (PUF) domains and deletion of PUF-8 leads in Caenorhabitis elegans to rapidly growing tumors (25).

1.5. Specific characteristics of the minor histocompatibility antigen presentation

The power of mHags in the GvT response is their ‘allo-ness’. MHags are HLA-restricted polymorphic peptides that are present in the SC recipient but not in the SC donor (6). Thus in contrast to autologous tumor associated antigens (TAAs), mHags are allo-antigens for the donor immune system. The mature T-cells in the SC graft or in the DLI are not „educated“ by the thymus of the patient and will therefore induce immune-responses that are not regulated by self tolerance (28). Another reason for strong immune responses against (known) mHags after allogeneic SCT is their mode of presentation by professional APCs. Basically, T-cells can be directly primed by tumor cells. An alternative pathway is cross-presentation of TAAs and mHags by professional APCs (29). So far, the relevance for these two pathways in vivo is at least for mHags unknown. Thirdly, professional APCs can directly present antigens to T-cells. This mode of antigen presentation is most likely used by the known mHags. In contrast to TAAs, all known mHags expressed by tumor cells are also endogenously expressed, processed and presented by hematopoietic cells including host APCs. Thus, as long as host APCs are still present in the patient, mHags efficiently induce CTL responses independently from cross-presentation

(Figure 1). CD4 T helper cells directed to MHC class II restricted mHag epitopes like the class II H-Y epitope (30) might play an important role in maturing mHag presenting APCs via CD40-CD40L interactions. The powerful induction of mHag CTLs by host APCs paves the way to mHag peptide vaccination after allogeneic SCT by boosting already primed donor derived mHag CTLs (see below).

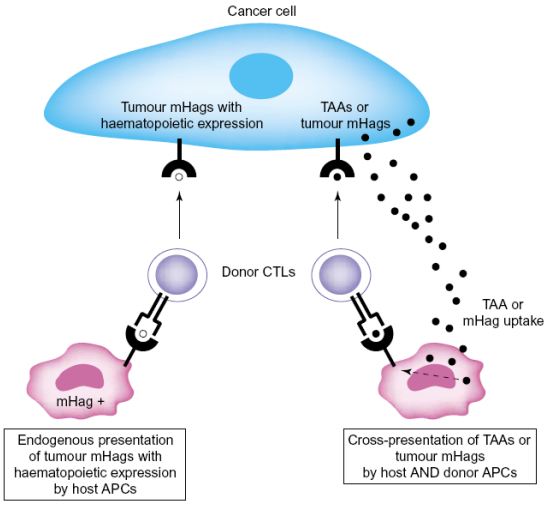

Figure 1. Modes of tumor antigen presentation by professional antigen presenting cells to donor cytotoxic T lymphocytes. TAAs or tumor/hematopoiesis restricted mHags ("tumor mHags") can be presented by professional APCs to donor CTLs after antigen uptake and subsequent cross-presentation in MHC class I molecules. In addition, those tumor mHags that are not only expressed by malignant cells but also constitutively expressed by normal hematopoietic cells (including APCs) can directly prime donor CTLs as long as mHag-positive host APCs are not completely replaced by mHag-negative donor APCs after allogeneic SCT.

1.6. Tissue distribution of minor histocompatibility antigens dissects GvHD and GvT effect

The simultaneous observation of clinical GvHD and GvT effects suggests that the mHags involved in both branches of the GvH response are overlapping (5). However, this would mean that enhancement of the GvT effect automatically increases the GvHD risk as indicated by the results of donor lymphocyte infusions (DLI**)** (31)**.**The observation that the GvT effect can be separated from GvHD on the basis of the tissue distribution of mHags was instrumental for the development of mHag-based strategies of safe stem-cell-based cancer immunotherapy (as discussed below). The first indication that GvHD and GvT effects can be separated was provided by in-vitro studies showing differential modes of recognition of various cell types by mHag-specific CTLs (32)**.** These studies concluded that some mHags are broadly expressed, while others are only detectable on hematopoietic cells. The broadly expressed mHags are expressed on cell types present within organs affected by GvHD, such as fibroblasts, melanocytes, and keratinocytes. This observation indicated that CTLs directed to broadly expressed mHags are particularly relevant for the development of GvHD. In fact, high numbers of H-Y specific CTLs could be detected in the skin of male patients suffering from severe GvHD and previously transplanted with stem cell grafts of HLA-matched female donors (33). An in-situ readout was performed to analyze the postulated differential effects of mHags in vivo (34). In a skin explant assay, skin sections of male HA-1^H healthy skin donors were incubated with CTLs specific for the broadly expressed mHag H-Y, or for the hematopoietic system–restricted mHags HA-1 and HA-2. CTLs specific for the H-Y mHag induced severe GvH reactions of grades III–IV, while CTLs specific for HA-1 and HA-2 induced no or weak GvH reactions. Thus, T cells directed to hematopoiesis-restricted mHags do not induce GvHD because they do not recognize non-hematopoietic skin components. The skin explant assay as executed in this

study, however, might not have provided the whole picture of GvHD, because APCs migrate out of the skin samples during in-vitro processing. Therefore, it is remarkable that it was also impossible to induce severe GvHD by addition of HA-1 expressing APCs (as a model for persisting recipient APCs) and HA-1 CTLs (35). Consequently, hematopoiesis- and solid tumor-restricted mHags are ideal targets to induce a GvT effect with low risk of GvHD after HLA-matched allogeneic SCT (5,17).

1.7. Selection and identification of minor histocompatibility antigens for immunotherapeutic application

The clinical decision for the selection of target antigens for mHag specific immunotherapy will be based on two criteria: high or exclusive expression of the target mHags on the malignancy to induce maximal GvT effects and no or low broad expression to avoid GvHD. Thus, for the selection of mHags as immunotherapeutic targets it is helpful to subdivide the mHags that are involved in the CTL mediated GvT effect into "tumor mHags" and broadly expressed mHags (e.g. HA-3, HA-8 and H-Y antigens). Tumor mHags are mHags that show a *functional* expression (i.e. recognized by CTLs) restricted to the malignancy or additionally to hematopoietic cells (including APCs).

Table 1. Currently known Tumor mHags. Tumor mHags comprise mHags which are suitable both for the treatment of hematological malignancies and solid tumors and mHags, which are only suitable for the treatment of hematological malignant diseases.

mHags suitable both for the treatment of hematological malignancies and solid tumors				mHags only suitable for the treatment of hematological malignancies			
mHag	**Peptide**	**HLA**	**Ref.**	**mHag**	**Peptide**	**HLA**	**Ref.**
HA-1	VLHDDLLEA KECVLHDDL	A2 B60	(10) (9)	HA-2	YIGEVLVSV	A2	(36)
BCL2A1	DYLQYVLQI KEFEDDIINW	A24 B44	(19)	HB-1	EEKRGSLHVW EEKRGSLYVW	B44	(18)
ECGF-1	RPHAIRRPLAL	B7	(37)	PANE1	RVWDLPGVLK	A*03	(38)
ADIR	SVAPALALFPA	A*02	(39)	LRH-1	TPNQRQNVC	B*07	(13)
				HMSD	MEIFIEVFSHF	B*44	(14)
				SP110	SLPRGTSTPK	A*03	(40)
				B8/HY	LPHNHTDL	B*08	(41)
				B52/HY	TIRYPDPVI	B*52	(42)
				CD19	PEIWEGEPPCLPPRD	DQA1*05/B1*02	(43)

Table 1 provides an overview of the currently known tumor mHags suitable for the treatment of both hematological malignancies and solid tumors and those tumor mHags only suitable for the treatment of hematological malignancies (5). With six tumor mHags HA-1, HA-2, HB-1, BCL2A1, SP110 and PANE1 alone, there are sufficient immunologically relevant mHag mismatches present in 21% (sibling donor) or 33% (matched unrelated donor) of the HLA-matched donor / patient couples allowing mHag specific immunotherapy (7). Evidently, further enlargement of the spectrum of tumor mHags is crucial for their broad clinical application. Despite the fact that also homozygous gene deletion in donor cells can generate mHags (44) most human mHags described so far are derived from genes that have non-synonymous single nucleotide polymorphisms (SNPs) in the coding sequence. This finding and the therapeutic prerequisite of functional tumor (and hematopoiesis) restricted mHag expression are the rationale to focus the search for new tumor mHags on onco-related proteins containing genetic

polymorphisms. The observed preferential generation of mHag CTLs against polymorphic peptides derived from onco-related proteins in clinical situations (25) supports the potential success of that "reverse immunology" approach. Important tools in this strategy are computer analysis predicting proteasomal cleavage (PAPROC, Netchop) and epitope reconstitution (BIMAS, SYFPEITHI) (Table 2) (45).

Table 2. Algorithms that predict proteasomal cleavage and epitope reconstruction.

Algorithm	URL
PAProc	http://www.paproc.de/
NetChop	http://www.cbs.dtu.dk/services/NetChop-3.0/
BIMAS	http://bimas.dcrt.nih.gov/molbio/hla_bind/
SYFPEITHI	http://www.syfpeithi.de/

Known autologous TAAs (46,47) might be good candidates for the search for mHag epitopes. Considering the crucial role of professional host APCs in priming mHag CTLs after allogeneic SCT those proteins that are constitutively expressed also by hematopoietic cells appear to have an advantage over tumor restricted TAAs like the cancer/testis antigens (e.g. MAGE-A1,2,3,4,6,10,12 or NY-ESO-1), differentiation antigens (e.g. Melan-A, MART-1 or gp100) or unique tumor antigens (e.g. HSP70-2M or MART-2).

1.8. Balancing GvT effect and GvHD in the SC based immunotherapy of cancer

Despite selective immunotherapeutic targeting of tumor mHags, an efficient GvT may not be feasible without manageable GvHD. In this GvT/GvHD balance, host APCs that survive the SCT procedure play an important role by maintaining the expression of host mHags. The fact that host-derived APCs expressing host mHags are responsible for the initiation of GvHD has been shown in a MHC-matched, mHag-mismatched murine model (48). Therefore, depletion of host APCs might be helpful to prevent GvHD (49). However, GvT effects after DLI are far more powerful in mixed chimeras, i.e when host APCs are still present, compared to fully allogeneic chimeras (50). This bidirectional effect of host APCs might on the one hand explain why the association between HA-1 mismatch and GVHD is still controversial (51-53). On the other hand, it implies that in the host APC mediated balance between GvHD and GvT effect, timing of the immunotherapeutic intervention is important. Finally, despite the aim to prevent GvHD it has to be considered that GvHD might also be a driving force of the GvT effect (54) e.g. by generation of a proinflammatory environment. GvHD associated soluble factors like interferon-γ and tumor-necrosis-factor-α (55) can induce maturation of mHag expressing APCs (56) and up-regulation of target molecules on malignant cells (57). These mechanisms are supportive for mHag specific CTL responses. Broad mHag specific CD4 T helper cells further contribute to these processes by the production of proinflammatory cytokines and maturation of APCs (30). Noteworthy, proinflammatory cytokines can suppress tumor growth by direct interaction with cancer cells at least in vitro (58) and even more important via inhibition of neoangiogenesis (59). Ambiguously enough, the selective targeting of tumor mHags may well have its optimal immunotherapeutic effect during GvHD (Figure 2).

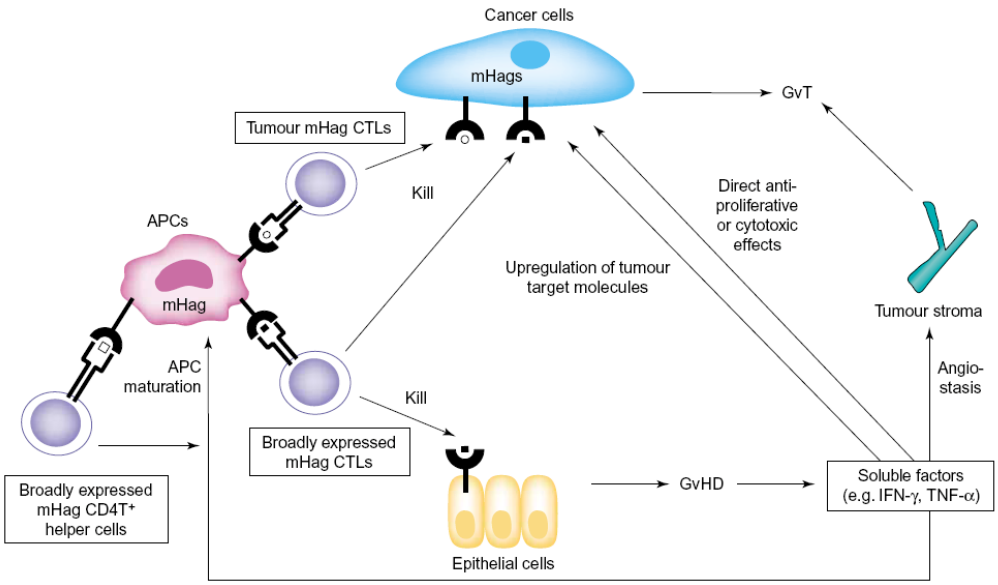

Figure 2. The supportive influence of GvHD on the GvT effect in the effector phase of mHag CTLs. CTLs specific for tumor mHags can electively eliminate tumour cells, whereas CTLs specific for broadly expressed mHags destroy not only tumor but also normal epithelial cells, resulting in GvHD. GvHD-associated soluble factors can contribute to the GvT effect by non-tumor specific inhibition of neoangiogenesis or via direct anti-proliferative or cytotoxic effects on tumor cells. Soluble factors can also support tumor-specific effects of CTLs by enhancing antigen presentation on tumor cells and by induction of APC maturation. CD4+ T helper cells specific for broadly expressed mHags can also induce the maturation of mHag-expressing APCs via CD40–CD40L interactions.

1.9. Considerations for the individual design of SC based immunotherapy

The rationale to apply mHag specific immunotherapy in a particular patient is based on two diagnostic procedures. First, a genomic typing of the allelic variants of the targeted mHag needs to be performed for the patient and the potential donor (60,61). A second analysis should determine the expression – and best: the functional recognition - of the target mHag on the malignancy of the patient. Despite generally high mRNA expression levels for HA-1 on leukemic cells and many solid tumor cells (27,23) the expression in the individual case might be impaired antigen processing and presentation (62). Finally, the chance for generation of a mHag specific response after allogeneic SCT might depend on the immunization status and gender of the SC donor. GvHD is more likely in recipients of female donors and especially those with a history of pregnancy compared to nulliparous donors or male donors (63). Verdijk et al. found that mHag CTLs directed to the infant's paternal antigens can be present in the blood of healthy multiparous women up to 22 years after last delivery (64). Similarly, recent murine studies demonstrated that multiparity induces priming to H-Y antigens (65). Donor immunization may also play an important role in cord blood transplantations since Mommaas et al could isolate HA-1 CTLs with anti-leukemic efficacy from cord blood of neonates with HA-1 allelic disparity with their mothers (66). However, the impact of mHag specific immunizations of the SC donors on the success of mHag specific immunotherapy is still unknown. Besides donor related properties, the success of mHag specific

immunotherapy will be dependent on the condition of the patient. Experiences from allogeneic SCT for leukemia (1) indicate that mHag specific immunotherapy is best performed after maximal reduction of the tumor load in a status of minimal residual disease. This is not only due to the unfavorable ratio between mHag CTLs and tumor cells in patients with established tumors but also because of a cancer-induced immunosuppressive environment (67), neovascularization-supported tumor growth (68) and the still unknown tumor-infiltrative capacity of mHag CTLs. Non-myeloablative conditioning appears sufficient to enable hematopoietic engraftment and to evoke GvT response with limited toxic site effects (2).

1.10. Cellular adoptive immunotherapy

To date, there are two options to exploit mHag differences between donor and recipient in adoptive immunotherapy of hematological malignancies and solid tumors after allogeneic SCT and DLI. One option is the adoptive transfer of in vitro generated SC donor derived mHag CTLs. This is possible since mHag CTLs can be generated using donor derived dendritic cells in large numbers in vitro (69,70). However, the repetitive stimulation of antigen-specific T-cells with antigen-loaded dendritic cells is associated with a progressive loss of proliferative activity of the T-cells (71). Additionally, the number of available dendritic cells is often limited and can hamper the generation of large numbers of mHag CTLs. Artificial APCs coated with HLA-A2/mHag complexes, CD80, and CD54 might help to selectively enrich mHag CTLs for adoptive immunotherapy (72). An alternative to the laborious and expensive generation of mHag CTLs on donor derived DCs is the transfer of mHag specific T cell receptor (TCR) genes into donor peripheral blood mononuclear cells which has been shown to be successful for the mHags HA-2 (73) and for HA-1 (74). However, the relatively low avidity of the transferred TCRs is associated with low lysis capacity. Also autoreactivities due to TCR rearrangements cannot be excluded which might hamper broad clinical application. Interestingly, it is possible to generate epitope specific CTLs in an HLA-mismatched setting from HLA-A2 negative individuals as initially shown for self antigens like HLA-A2/cyclin-D1 (75) and later also for the mHag HLA-A2/HA-1 (76). Undesired alloreactivity is a major problem of this approach and so far there do not exist protocols with which non-self HLA, mHag CTLs can reliably be generated at clinical grade.

1.11. Vaccination

Another, more practical and potentially efficient strategy is ‘vaccination’. In this concept mHag peptides are administered to the patient where donor derived APCs will boost a mHag specific immune response of T cells already primed by mHag expressing host APCs (77). HA-1 and HA-2 CTLs emerging after DLI after allogeneic SCT are highly effective to induce complete remissions of relapsed hematological malignancies (20,21). This indicates potent priming and expansion of mHag specific donor CTLs in vivo. MHag vaccination will boost mHag CTLs in patients with partial or full donor chimerism, i.e. when host APCs are progressively replaced by mHag negative donor APCs. Unclear is the optimal protocol to boost mHag CTLs by vaccination with regard to the extend of the immune response and the avoidance of tolerance. The variables include the choice of delivery system (naked DNA, recombinant vectors, short peptides, long peptides, recombinant protein, antigen loaded dendritic cells), dose, route of administration, frequency of vaccination and immunological adjuvants. An extensive discussion of these variables for the autologous setting has recently been performed by Scheibenbogen et al. (78), Jaeger et

al (79) and Figdor et al. (80) and is beyond the scope of this introduction. A vaccination trial in the latter context with WT-1 peptide provides important information also for the design of peptide vaccination studies in the allogeneic setting. This study indicated (at least for WT-1) that intradermal administration of vaccines containing a single nonamer peptide in incomplete Freund's adjuvant can basically induce clinical responses in leukemia, breast and lung cancer patients which correlate with immunological responses as determined with tetramer analyses (81). A potential danger for life-long anti-tumor reactivity is the development of peripheral or central tolerance in donor CTLs against tumor mHags. Allogeneic SCT however provides the unique option to partially overcome tolerance by repetitive deliveries of non-tolerant mature CTLs via DLI. First phase I/II mHag peptide vaccination studies have been started for hematological malignancies (Koen van Besien, personal communication) and renal cell carcinoma (Niederwieser, personal communication). Aim of these studies is to investigate after non-myeloablative SCT the potency of mHag HA-1 (and HA-2 for hematological malignancies) peptide vaccination to boost mHag CTL responses in combination with DLI.

1.12. Today's unsolved problems in mHag specific immunotherapy

This summary of the current status of mHag mediated GvT effects shows that mHag specific immunotherapy after allogeneic SCT may have the potential to treat and - potentially – to cure cancer. However, a series of questions and problems related to the selection of patients for immunotherapy, immunotherapeutic approaches and clinical guidance of immunotherapy remained at the moment of starting the experimental work described in this thesis:

1. The direct and formal proof of concept that the interaction of mHag CTLs with established leukemia and solid tumors can evoke strong anti-tumor effects was missing due to the absence of appropriate in vitro and in vivo cancer immunotherapy models.

2. The optimal clinical prerequisites for the success of mHag specific cancer immunotherapy were unknown.

3. It was unknown which specific immune escape mechanisms in leukemia and solid tumors need to be considered for the selection of patients for mHag specific immunotherapy.

4. In vitro generated mHags CTLs for adoptive cellular transfer progressively loose their expansion potential. Therefore, new protocols sustaining the expansion potential of mHag CTLs were required.

5. The optimal design of mHag peptide vaccines for boosting the mHag specific immune response after allogeneic SCT was unknown.

6. Clinical and immunological markers to evaluate the success of mHag specific immunotherapy had not been defined.

1.13. Aims of the thesis

The aims of the research presented in this thesis were:

1. To provide the first proof of concept in novel in vitro and in translational animal models that mHag specific immunotherapy of human leukemia (chapter 2) and solid tumors (chapter 3 and 4) can be effective.

2. To determine the optimal clinical prerequisites for mHag specific cancer immunotherapy (chapter 2-4).

3. To identify mechanisms allowing leukemia (chapter 5) and in solid tumors (chapters 6) to escape mHag specific immunotherapy.

4. To find novel approaches to generate therapeutic quantities of mHag CTLs in vitro for adoptive cellular immunotherapy (chapter 7).

5. To design optimal mHag peptide vaccines (chapter 8) and

6. To identify suitable parameters to determine the immunological and clinical response to mHag specific cancer immunotherapy (chapter 9)

The hematopoiesis-restricted mHags HA-1 and HA-2 served as examples for immunotherapeutically exploitable mHags in all chapters.

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