Review

Thymic Peptides in Immune Reconstitution and Clinical Outcome after Allogeneic Hematopoietic Cell Transplantation

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Posted Date: 29 August 2024

doi: 10.20944/preprints202408.2128.v1

Keywords: hematopoietic cell transplantation, thymic peptides, immune reconstitution

Review

Thymic Peptides in Immune Reconstitution and Clinical Outcome after Allogeneic Hematopoietic Cell Transplantation

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Abstract: Patients with hematologic malignancies or non-malignant diseases may undergo allogeneic hematopoietic cell transplantation (HCT), which represents a potential curative treatment. However, they are still at risk of life-threatening complications, such as relapse, acute graft-versus-host disease (GvHD), and opportunistic infections. These complications are more likely if T cell reconstitution is delayed during the initial 3-4 months after HCT. Therefore, it is of clinical importance to advance early peripheral T cell expansion. The thymus is the cradle of T cell production, but it is extremely sensitive to conditioning drugs used in HCT. As a result, egress of T cells from the thymus is abrogated during the first 3-6 months after HCT. Instead, early T cell reconstitution depends on peripheral expansion of engrafted donor T cells. However, besides its established function to produce T cells, the thymus also produces thymic peptides with hormone-like activity. These molecules play an essential part in the development and nature of immune responses, and may have a role in modulating T cell expansion and function after HCT. In this review, we investigate the role of thymic peptides in shaping the dynamics of immune reconstitution early after HCT. Furthermore, we summarize current reports on clinical application of thymic peptides post-HCT and discuss their potential use in improving patient outcomes.

Keywords: hematopoietic cell transplantation; thymic peptides; immune reconstitution

Key points

- Human thymus produces thymic peptides that are important in normal T cell homeostasis - T cell production, maturation and activation *(134)*
- Thymic peptides with hormone-like activity have been tested in a variety of clinical conditions and are safe for administration

Introduction

Patients with various hematologic malignancies or non-malignant diseases may undergo allogeneic hematopoietic cell transplantation (HCT), which represents a potential curative treatment. The success of this therapy is affected by the high risk of life-threatening complications post-HCT, such as transplantation-related mortality, (opportunistic) infections, acute graft-versus-host disease

 doi:10.20944/preprints202408.2128.v1

(GvHD), and malignant relapse. These complications have been highly associated with a delayed immune reconstitution (IR)[1]. In particular delayed CD4 T cell reconstitution in the first 3 months post-HCT predicts survival of patients with GvHD, viral reactivation, or relapse (in case of acute myeloid leukemia)[1]. Therefore, advancing early peripheral T cell expansion should be of high interest, as it could improve HCT success.

Although, the exact mechanism remains undisclosed, T cell reconstitution in the first months post-HCT depends on peripheral expansion (PE) of infused T cells [2]. Only after thymic regeneration, T cell reconstitution is supported further by naïve T cell formation through thymopoiesis [3]. Thymopoiesis generally takes months to even years to occur [4], and is important for replenishing T cell receptor (TCR) diversity [5]. However, the human thymus is not only pivotal for T cell development, it also produces thymic peptides with hormone-like activity that are important in normal T cell homeostasis. Previous observations also pointed out that graft T cell survival post-infusion depends on TCR binding [6], and that the T cell proliferation may be stimulated by cytokines and hormones, such as interleukin (IL)-7 or thymosins [3], [4].

Thymosins or thymic peptides, such as thymosin alpha-1 (Ta1) and its pro-peptide prothymosin alpha (PTMA) are mainly produced by thymic epithelial cells (TEC) and they can stimulate expansion and regulation of T cells in blood and tissues [7]. Thymic peptides are molecules that are highly abundant in cellular nuclei and they have rudimental intracellular functions [8]. Moreover, they stimulate pathways that are shared by cytokines [9], suggesting a potential synergy in their effects. Due to such rudimental roles, especially in normal T cell homeostasis and expansion, they might stimulate and regulate PE early post-HCT.

Because of their importance in T cell homeostasis and immune modulation, some thymic peptides have recently gained renewed clinical interest. In this review, we discuss their biological effects and examine their current applications as therapies (Table 1). Specifically, we focus on the application of thymic peptides to improve T cell reconstitution and outcome post-HCT.

Thymic peptides and their clinical applications

Thymosin alpha (Ta1)

One of the thymic peptides that is gaining quite an interest in the context of HCT is thymosin alpha 1 (Ta1). Ta1 is derived from prothymosin α (PTMA) and consists of only 28 amino acids with an acetylated N-terminal [7]. Originally it was identified in the TEC in the subcortical capsule [10], but more sensitive radio-immunoassays also localized it in the TEC-like cells in the thymic medulla [11]. Additionally, Ta1 was measured in the serum of healthy individuals within the range of 0.1-1.0 ng/ml [10], [12]. According to some reports, Ta1 levels are somewhat lower in women, aged patients [10], and in patients with dysregulated immune responses [10], [13]. Additionally, Covid-19 research, reported Ta1 levels to be correlated with longevity of humoral responses [14]. Therefore, physiological Ta1 levels might be a key to normal functioning of immune system [13].

Indeed, Ta1 was reported to have a broad range of biological activities ranging from immune-enhancing and immune-restorative to immune-attenuative effects [7], [15], [16]. Through interactions with Toll-like receptors (TLR) 9 and 2, Ta1 promotes expansion of natural killer (NK), T helper (Th) 1, dendritic (DC) and cytotoxic T cells. It enhances expression of proinflammatory IL-2 and interferon (IFN)-α, and stimulates macrophage phagocytic abilities and T cell-dependent antibody production [7], [15], [17]. Furthermore, Ta1 enhances stem cell expansion and differentiation in immunosuppressed mice [7]. Additionally, Ta1 enhances the recognition of virally-infected or tumor cells by directly upregulating the expression of major histocompatibility complex (MHC) class I and II, and beta-2 microglobulin [15]. On the other hand, Ta1 dampens the immune response and induces immune tolerance, averting a pro-inflammatory cytokine storm by positively affecting regulatory T cells (Treg) and IL-10 production through activation of indoleamine-2,3-dioxygenase in plasmacytoid DCs [15], [16]. Because of these various immunomodulating properties, Ta1 is under extensive evaluation for therapeutic use in immune-related diseases ranging from autoimmunity to cancer.

 doi:10.20944/preprints202408.2128.v1

The synthetic form of Ta1, called thymalfasin, has already been evaluated in a variety of clinical conditions, such as infectious diseases, immunodeficiencies, aging, and cancer [7]. In the last three decades, thymalfasin has proven its worth in the treatment of viral infectious diseases such as chronic hepatitis B and C, AIDS, sepsis, and more recently Covid-19 [18], [19], [20], [21]. When used as an adjuvant to influenza vaccines in immunocompromised and elderly patients, it successfully enhanced T cell-mediated antibody responses [22], [23]. In patients with primary immunodeficiencies, thymalfasin displayed an IL-2-mediated immune restorative effect [24]. Similarly, encouraging results are also expected in the treatment of psoriatic arthritis [13]. Recently, thymalfasin administration increased T cell numbers and thymic output (increased TREC) in lymphodepleted SARS-CoV-2 and Human immunodeficiency virus-1 (HIV) infected patients [19], [25]. Furthermore, thymalfasin was effective in metastatic melanoma, lung cancer, breast cancer and hepatocellular carcinoma treatments [26]. The latest comprehensive review, including more than 30 trials and over 11 000 patients, reports that thymalfasin is a well-tolerated and effective immune modulator [27].

Some time ago, thymalfasin was investigated as a potential therapeutic agent for quicker IR following HCT. In eight HCT patients who developed an infection post-HCT, subcutaneous administration of 1.6 mg/day Ta1 for four weeks, resulted in an increase of IFN-γ, IL-2, IL-10 and IL-12 levels, with no difference in T cell numbers in comparison to the control group [28]. Another clinical trial with 30 adult recipients of human leukocyte antigen-matched sibling T cell-depleted HCT, conditioned with TBI or chemotherapy, concluded that subcutaneous administration of 1.6 mg/day Ta1 for 16 weeks from the day of the transplant, improved polymorphonuclear and DC functions, accelerated the rate at which pathogen-specific CD4+ T cells appeared, and lowered non-relapse mortality [29]. In acute myeloid leukemia patients, thymalfasin in combination with epigenetic regulators decitabine and chidamide, resulted in higher survival, lower relapse rate, an increase in effector T cells counts (Th1 and CD3+CD4-CD8+ T cells) and no apparent GvHD [30]. Overall, there were no adverse events or episodes of GvHD registered. Ta1 was rendered to be safe in clinical use [29], and may have a favorable effect on IR.

Possibly, Ta1 could be implemented in the HCT treatment as a prevention tactic for life-threatening complications, such as GvHD, viral reactivations and relapse. Due to such a potential, Ta1 deserves to be investigated into more detail. The field could benefit from more Ta1 clinical trials and interventions, but also *in vitro* studies that would confirm its exact mechanism. Additionally, by measuring endogenous Ta1 levels post-HCT, we could assess recovery of thymic function of each patient, which could further allow us in-time reaction and improve overall HCT success rate.

Thymomodulin (TMD)

Partial acid lysis of calf thymus produces thymic derivate called thymomodulin (TMD) [31]. TMD, therefore, consists of multiple thymic peptides, which have a molecular weight range of 1-10 kD. This thymic peptide derivate has a great biological activity with apparent effects on T, B, NK and bone marrow stem cells [31].

Similarly to other thymic factors, it affects maturation and function of T cells [31], [32], [33]. *In vitro* TMD treatments stimulated T cells and increased the release of tumor necrosis factor (TNF) and granulocyte-macrophage colony stimulating factor (GM-CSF) in macrophage-lymphocyte cultures [31], [34], [35]. TMD treatment also positively impacted production of bone marrow CSF by T cells and/or monocytes, and indirectly affected bone marrow colony growth [31], [34], [35], [36]. Besides stimulating CSF production, TMD enhanced the NK activity of human cord blood lymphocytes, increased macrophage HLA-DR expression and mitogen-induced T cell proliferation in peripheral blood lymphocytes [34], [35]. Furthermore, TMD induced appearance of surface B markers, and myelopoiesis in human bone marrow granulocyte/macrophage precursors [31]. In another *in vitro* study with spleen cells of aged mice, TMD significantly increased IFN-γ production [33]. Additionally, in *Mycobacterium* infected mice, treatment with TMD in combination with IL-2 reversed T cell unresponsiveness [33].

 doi:10.20944/preprints202408.2128.v1

TMD was also successfully tested in clinical setting, in atopic dermatitis, chronic bronchitis, viral hepatitis, HIV, recurrent respiratory infections (RRI) and rheumatoid arthritis patients. In that clinical trial, oral 3-month TMD treatment (2-3 mg/kg body/day) normalized patients' low or high CD4/CD8 ratio [31]. Similarly, in HIV infected patients, oral TMD treatment (60 mg/day, 50 days) increased their CD4 T cell levels and improved their symptoms [37]. TMD treatment also reduced RRI symptoms, improved neutrophil functions and increased CD3 and CD4 T cell counts and IgA levels in saliva [31], [38], [39]. Additionally, TMD (administration of 120-180 mg/day, for 2-3 months) prevented RRI relapse by enhancing phagocytic response of alveolar macrophages and serum Ig-s levels [31]. Overall, TMD showed positive effects in acute hepatitis B, anergy, atopic dermatitis, bronchial asthma, chronic liver disease, perennial allergic rhinitis and in ageing [31], [35], [39]. Such potential might be due to TMD's direct modulating impact on T and B function, but also stimulative effect on other phagocytic cells, such as macrophages [35].

Despite such clinical potential, up to this date there is no published data on TMD clinical trials in the context of HCT. Nevertheless, other studies pointed towards TMD properties that could be advantageous in HCT. For instance, few studies found that TMD has protective benefits for radiation and chemotherapy. In mice, TMD increased leukocyte levels and exhibited radioprotective effect in cyclophosphamide treated and TBI mice respectively [31]. TMD treatment increased the uptake of ^{59}Fe isotope by erythrocytes and enhanced the DNA synthesis in the thymus and bone marrow cells, which further lead to increase in survival rate of chemotherapy and TBI mouse models [31]. Additionally, TMD (5 mg/mouse) restored levels of thymic hormone activity in thymectomized mice [31], which could be relevant for the conditioning-induced hypothymism in HCT patients [32]. In a study with patients undergoing radiotherapy, TMD treatment (20 mg/day) statistically reduced incidence of low leukocyte counts [35]. In irradiated mice and cancer patients treated with chemotherapy, TMD stimulated myelopoiesis [36]. Overall, TMD boosts the host's immune cells important for proper function, adequate defense, and general survival of the organism. It is generally regarded as clinically safe, due to its low toxicity exhibited in multiple studies [36]. TMD also has a longer serum half-life in comparison to most cytokines [36] which is yet another reason why it could be regarded as a great alternative for treatment of immunosuppressed patients undergoing HCT treatment. However, to further examine mechanism of action and efficacy of TMD, prospective studies are needed.

Thymulin (TM)

Another thymic peptide exclusively produced by the thymus is thymulin (TM). TM activity was measured only in a few patient cohorts and it was correlated with age and serum concentration of thyroid hormones T_3 and T_4 [40]. Lower levels of circulating TM were found in mal- or undernourished, nutrient-deficient, HIV and *Trypanosoma cruzi* infected patients and murine models [41], [42], [43]. Additionally, lower TM serum levels were measured in zinc (Zn) deficient patients [44]. Zn is relevant in many thymic reactions, including regeneration of TEC and T cell reconstitution [45], and it is an essential component of TM peptide. TM has anti-inflammatory properties and can directly or indirectly modulate immune responses [46], [47], [48], [49], [50]. It inhibits pro-inflammatory cytokines TNF-a, IL-5, IL-17 and IFN-y, suppresses p38 [49] and inhibits the NF-kappaB and c-Jun N-terminal kinase (JNK) signaling pathways [46], [48].

TM has been beneficial in multiple animal disease models [46], [48],[49]. In diabetic and CFA mice, TM respectively reduced physiological impairments and thermal hyperalgesia and paw edema [48],[49]. In athymic mice, neonatal TM gene therapy restored the serum TM levels, increased corticotrope cell density, volume density and cell surface [51], [52]. TM gene therapy was proposed for prevention of some endocrine and metabolic alterations [47], [50], which can also be seen in thymus-deficient *in vivo* models [47], [50]. Overall, TM might play a role in signaling between the immune, endocrine and the nervous system [53], [54], [55], and it could be a central physiological mediator of thymus-pituitary gland communication [51], [52]. Due to its anti-inflammatory properties and successful implementation in athymic mice, TM gene therapy could be beneficial in HCT treatment.

 doi:10.20944/preprints202408.2128.v1

Thymopoietin (TMPO)

The 49 amino acid long thymic peptide thymopoietin (TMPO) can be found in plasma in range of 0.25 ng/ml to 1 ng/ml [56]. TMPO (-α) genes regulate cell cycle [57], and have an effect on neuromuscular transmission [58]. TMPO might also mediate immune responses, and have an impact on peripheral T cells [59], [60]. According to multiple reports, TMPO is upregulated in several types of cancer, including lung, breast, colorectal, gastric, ovarian, esophageal, Wilms, cervical, bladder, prostate and thymus cancer, as well as retinoblastoma, hepatocellular carcinoma and osteosarcoma [61], [62]. However, its antisense RNA competes with endogenous RNA and prevents it from inhibition of downstream oncogenes expression [61]. Therefore, TMPO could be a cancer therapy target and reliable biomarker for different cancer types, such as breast cancer [61], [62].

In murine spleen or bone marrow cells, TMPO selectively induced maturation of T thymocytes, and was able to restore the balance regardless of initially enhanced or suppressed immune responsiveness [58]. In glioblastoma cells, lack of TMPO significantly inhibits cell proliferation, arrests cell cycle at G2/M phase and promotes apoptosis [63]. TMPO administration (1.5 ng/ml) enhanced proliferative response peripheral T cells from murine lymph nodes and spleen [64].

Its synthetic form, thymopentin (TP-5) was tested safe to use (absent toxicity) both in animal models (10 mg/kg for 4 weeks in rats and dogs), and human (1 mg/kg for 1 year, 100 patients) [58]. It was efficient immune modulator in a number of pathologies [58], where it simultaneously activated different T cell subtypes [65]. In atopic dermatitis patients, TP-5 (3x week, 50 mg, 6 weeks), TP-5 increased usually reduced cytotoxic T cell subsets and improved cytotoxic T cell function [66]. Additionally, TP-5 showed promising results in DiGeorge syndrome and primary T-cell defect diagnosed patients, suggesting it could be used for treatment of immunodeficient patients [67], such as patients undergoing HCT treatment. Even though TMPO or TP-5 were not tested in HCT, they possess some advantageous properties that could be exploited in the HCT setting. These advantageous properties include mediation of immune responses, and an increase of T cell counts and T cell variety in immunodeficient patients [67].

Thymic humoral factor (THF)

THF is an immunomodulatory octapeptide which endogenous levels in human serum have to date not been published. THF showed potential in treatment of immunodeficiencies, viral infections such as chronic hepatitis B, and cancer [68], [69], [70]. *In vitro,* THF impacted clonal expansion, differentiation and maturation of T cells observed upon THF treatment [71], [72], [73].

THF had a positive effect on T cell lectin response, antibody response to SRBC, and overall cytotoxic activity [71]. In autoimmune rat models, THF reduced IL-6 and an increased in IL-10 levels in serum but also had beneficial effect on liver damage and fibrosis [74]. In a murine model, THF increased cytomegalovirus-neutralizing antibodies and improved NK activity in early infection stages[75]. In tumor mouse models, daily subcutaneous applications of 200 ng of THF/mouse for a week, upregulated thymocytes and peripheral blood cell counts, and statistically reduced metastases and local tumor growth [76]. Furthermore, THF was able to reconstitute reduced erythrocyte rosette (E-rosette) forming cells in some of the sclerosing panencephalitis patients, which is why THF was suggested as an addition to immunotherapy in some individuals [77]. Similarly, in systemic lupus patients, THF treatment significantly increased E- rosette forming cells of peripheral blood lymphocytes [78].

THF has not been tested in the HCT setting, but other clinical studies showed beneficial properties that could be exploited for HCT patients. For instance, THF treatment increased the size of CD4 and CD8 cells that were initially decreased due to the infection [75]. It was proposed that this positive restoration of CD4 and CD8 cells, might be partially due to the restoration of IL-2 levels [71], [75], [79]. Besides increased IL-2 production, THF treatment in AIDS patients improved cellular immunocompetence [71], and normalized the Th and T suppressor/cytotoxic cells by modulating the T cell differentiation [71], [80]. In patients with different type of neoplasms or secondary immune deficiencies caused by chemotherapy and radiotherapy THF treatment was able to recover defective

 doi:10.20944/preprints202408.2128.v1

cell-mediated immunity [71]. Adding THF to anticancer chemotherapeutic regimens could potentiate the antitumor drug activity, and possibly even repair conditioning-induced damage to T cells in patients with immunogenic and non-immunogenic tumors [81]. In the same study, THF positively affected overall survival of immunogenic tumor bearing mice, and directly stimulated proliferation of myeloid stem cells [81]. To sum up, THF showed HCT-advantageous properties, such as a potential to restore CD4 and CD8 cell levels, improved cellular immunocompetence and post-conditioning immunity recovery, which would make it a great candidate to test in the clinical HCT setting.

Future perspectives and concluding remarks

Life-threatening complications post-HCT (relapse, GvHD, opportunistic infections) demand urgency in early T cell reconstitution. As *de-novo* T cell production and diverse TCR repertoire maintenance depend on the thymus, it should be of great interest to further explore its role in IR. To possibly optimize and expand treatment and intervention options in the HCT setting, we examined current knowledge on thymic peptides with hormone-like activity.

Overall, the described thymic peptides (Table 1) have been linked to peripheral expansion of T cells and have been used in multiple clinical trials to drive T cell production, maturation and activation [82]. So far, the only peptide that has been evaluated in the HCT setting is Ta1. However, other thymic peptides were rendered as safe for administration in various other patient cohorts [68], [69], [70], and their properties could be beneficial to HCT patients. Namely, these thymic peptides restored T cell counts [29], [49], [53], [56], [59], modulated function [74], [82], potentiated antitumor activity [76], [81], and enhanced overall thymic output [19], [25]. Besides, they increased cytomegalovirus-neutralizing antibodies [75], stimulated myeloid stem cell proliferation [81] and mediated thymus-pituitary gland communication [51], [52].

Not only could thymic peptides expedite early T cell reconstitution and improve overall IR, they also have a potential to suppress GvHD and relapse. Namely, they can enhance Treg expansion, and promote graft-versus-tumor effect (GvT) and graft-versus-leukemia effect (GvL). While Treg expansion can be enhanced by THF or Ta1 via immunostimulatory IL-2 and IL-10 [83], [84], Treg suppressive function can be improved by TMD via increased release of TNF [85]. Increased release of TNF can also promote GvT [85], that is mediated by NK cells [86], [87], which activity could be enhanced by Ta1, TMD, TM and THF. On the other hand, inhibition of TNF-a with TM could be used in the treatment of steroid-refractory GvHD [85], [88], [89]. Besides, GvL can be promoted by IFN-γ [90], [91] which is increased by Ta1 and TMD. Furthermore, thymic peptides could be beneficial for bone-marrow recovery and overall survival post-ionizing irradiation. TMD can stimulate GM-CSF, that was besides G-CSF shown to decrease the duration of neutropenia and shorten hospitalization in the AML patients in the HCT setting [92], [93], [94]. Overall, thymic peptides have many beneficial properties and are important for T cell homeostasis and immune modulation. Therefore, this immune modulating potential of thymic peptides should be investigated during IR after HCT.

Generally, IR mechanisms post-HCT have not been thoroughly investigated and sufficiently described. Similarly, there are still many unknowns about thymic function and -regeneration post-thymic injury, that is caused by conditioning regimens, prophylaxis, and other therapies applied in HCT treatment. Investigating the association between endogenous thymic peptides and T cell recovery and -function, as well as outcome, could provide further rationale for clinical application of these molecules in HCT. In addition, the endogenous levels of thymic peptides could be a quantitative representation of thymic damage and could even elucidate the mechanistic differences between pediatric and adult IR. This knowledge not only enables the identification of patients who might benefit from thymic hormonal interventions, but in combination with other thymic output measures, such as recent thymic emigrants (RTE) or T cell receptor excision circles (TREC), could allow us to understand how preserving thymic function might affect hormone levels.

By monitoring the thymic output, we could establish patterns determining successful early T cell recovery, and possibly recognize novel intervention opportunities to support this further. Possibly, thymic peptides could be beneficial in limiting thymic injury caused by conditioning regimens. These insights encourage more mechanistic studies and prospective trials that focus on the

 doi:10.20944/preprints202408.2128.v1

preservation of thymic function. Additionally, it would be highly beneficial to further explore how we could successfully adopt thymic peptide therapies in the HCT setting.

Funding: Hannah Kunstek is supported by funding from the HE/MSCA 2021 co-fund program, The Máxima Butterfly, project number 101081481. All authors contributed equally.

Authorship and Conflict-of-Interest Statements: None of the authors has a relevant conflict of interest.

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