MOLECULAR MECHANISM OF GRAFT-VERSUS-HOST-DISEASE AND ITS CLINICAL CONSEQUENCES

MOLEKULARNE PODSTAWY CHOROBY PRZESZCZEP PRZECIWKO GOSPODARZOWI I JEGO KLINICZNE KONSEKWENCJE

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Summary: Graft-versus-host disease (GvHD) is a severe immunologic complication following allogeneic haematopoetic stem cell transplantation. Encountering foreign antigens by donor lymphocytes, specific sequence of molecular mechanisms, including cytokines, chemokines and other mediators of cellular cytotoxicity, is initiated. To develop GvHD, transplant recipient must be immune compromised and histoincompatible with immune-competent graft. Clinically, GvHD is characterized by the damage to the skin, gastrointestinal tract's mucosa, liver and other organs.
The project's aim was to introduce recent molecular summary of GvHD pathogenesis including miRNA and cytokines impact on the disorder.

Keywords: Graft-vs-Host-Disease, Molecular bases, Haematopoetic stem cell transplantation

Streszczenie: Choroba przeszczep przeciw gospodarzowi (GvHD) jest ciężkim powikłaniem immunologicznym po allogenicznym przeszczepie komórek macierzystych. Limfocyty dawcy napotykają obce antygeny, inicjując ciąg mechanizmów molekularnych, w których pośredniczą cytokiny, chemokiny i inne mediatory cytotoksyczności komórkowej. GvHD pojawia się w momencie osłabienia odporności biorcy po przeszczepie, przy towarzyszącej niezgodności histologicznej i zachowanej funkcji odpornościowej komórek przeszczepu. Klinicznie, GvHD manifestuje się uszkodzeniem skóry, błony śluzowej przewodu pokarmowego, wątroby i innych narządów.
Celem pracy było przedstawienie aktualnej wiedzy dotyczącej moleuklarnego aspektu patogenezy GvHD z uwzględnieniem wpływu miRNA i cytokin na chorobę.

Słowa kluczowe: Choroba przeszczep przeciwko gospodarzowi, podstawy molekularne, Przeszczep komórek macierzystch

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered as a curative option for childhood hematological and non-hematological disorders [46]. Being now a standard of care, it was firstly conducted successfully in 1968 [14]. HSCT is utilized widely in leukemia, refractory lymphoma and non-malignant diseases like metabolic, autoimmune or hematopoietic disorders. One of the most severe complications of allo-HSCT is graft-versus-host-disease (GvHD), which is associated with increased mortality rates [20].

GvHD is a severe immunogenic complication which occurs in transplant recipient's organism in response to antigenically foreign lymphocytes introduction. T-lymphocytes received from donor invade host's tissues, leading to tissue destruction [49]. GvHD is divided into two forms- acute (aGvHD) and chronic (cGvHD).

Acute GvHD is contractually agreed within 100 days after allogeneic haematopoietic stem cells transplantation (allo-HSCT) to occur [39]. Its clinical manifestation is characterized by skin symptoms such as erythema [48], maculopapular rush, blisters or exfoliation and gastrointestinal tract symptoms- diarrhoea, pain, bowel obstruction or jaundice [4].

Chronic GvHD occurs after 100 days from alloHSCT. The disorder could be the continuation of an acute form or progress as the concequence of an abnormal lymphocytes renewal which have been developed from stem cells in recipient's organism and in this case symptoms resemble autoimmunological disorders [59]. Clinical manifestations of cGVHD include skin changes such as scleroderma or lichen planus-like lesions, abnormal pigmentation, appendages disorders; mucous membranes-mucositis, xerostomia; eyes-dry conjunctivitis and scleritis [13]. Apart from them there are also gastrointestinal tract disorders [2] such as malabsorption syndrome, cholestasis and symptoms from the other organs like obliterative bronchiolitis, fascitis or arthritis.

According to most recent criteria, acute GvHD may also occur after day 100 as a late onset aGvHD and an overlap syndrome including features of both aGvHD and cGvHD can also appear [15]. It is a contentious issue whether aGvHD and cGvHD are two entirely disparate disorders or sequential phases of the same mechanism [50].

Pathogenesis of aGvHD is currently described as initial tissue damage induced by the conditioning regimen followed by the denudation of auto- and alloantigens associated with massive inflammatory cytokine secretion, activating antigen presenting cells (APCs), auto- and alloantigen presentation mediated by APCs together with the costimulatory signaling prime donor's cytotoxic T-lymphocytes and their proliferation, followed by the migration of activated cellular effectors toward GVHD target tissues [28]. Immunopathophysiology of cGvHD

is more composite than in acute form. cGVHD includes multifarious interactions among allo-reactive and dysregulated T and B cells and innate immune populations entering macrophages, dendritic cells (DCs) and neutrophils that propagate pro-fibrotic pathways [7].

Pediatric population is at less risk for GvHD than adults, but endanger is still significant and increase with using alternative donor sources [24]. Due to the fact that data spanning over 25 years has shown a continued and constant increase in the annual numbers of HSCT and transplant rates for both allogeneic and autologous HSCT [43], there is a purposeful necessity to study its complications.

This review presents a complex summary of molecular bases of GvHD pathogenesis. Moreover, it describes the differences between GvHD in pediatric population and adults.

CELLULAR BASES OF GvHD PATHOGENESIS

The graft versus host reaction was firstly observed in a murine model after infusion of allogeneic stem and spleen cells. Tested mice survived irradiation and marrow aplasia, yet died of a 'secondary disease' consisting typical GvHD symptoms – rash, gastrointestinal distress, weight loss and liver damage [34]. Three requirements necessary for GvHD to occur were stated in 1966 by Billingham. These state as follows:

1. graft must contain immunologically competent cells, now identified as mature T lymphocytes;
2. recipient must be incapable of mounting an effective response to eliminate or reject the transplanted cells, i.e. due to chemotherapy-induced or radiotherapy-induced immunosuppression;
3. antigens of the recipient must be recognized as foreign by donor cells due to expression of tissue antigens that are not present in the transplant donor [5].

As presented above, GvHD occurs when donor T lymphocytes possess the response to the incompatible antigens on host cells [45]. Further research in this area led to the discovery of the human leukocyte antigens (HLA) which expression on cell surfaces is considered crucial in GvHD initiation via T cells activation [32]. HLAs (alternatively known as major histocompatibility complex – MHC) are present on the 6th chromosome [23]. Due to their immunological function, these exhibit high polymorphism [54]. MHC can be divided into two classes. Class I (HLA-A,-B and -C) molecules are expressed on almost all nucleated cell surfaces at varying densities. Class II (HLA-DR,-DQ and -DP) antigens are basically expressed on hematopoietic cells though their expression can be induced on different cells by inflammation or injury [45]. aGvHD occurence depends strongly on the HLA mismatch degree [12]. 60-80% patients receiving one-antigen mis-

matched grafts develop acute GvHD [12]. Nevertheless, HLA identity between recipient and donor does not guarantee uncomplicated post-transplant course. Around 40% of patients that receive HLA-matched grafts and optimal post-transplant immune suppression, can still develop aGvHD due to minor histocompatibility antigens (miHAs) disparity. Over 50 miHAs proteins have been identified so far [56]; some of them, such as HY or HA-3, are expressed on all body tissues, whereas other ones are tissue-specific and can even dictate the phenotype and target organ involvement of aGVHD. MiHAs are also associated with graft versus leukemia (GvL) phenomenon [9].

Several experimental models, including skin explant and murine systems, have been vital for understanding the immunobiology and pathophysiology of acute GvHD [53]. Similar progress in unravelling the mechanism of chronic GvHD has not been accomplished. Some mouse models mimic isolated features of cGvHD such as liver damage or skin fibrosis but none of them captures all of the interactions [53, 30]. This may be due to certain differences in cGvHD kinetics in human and experimental species.

MOLECULAR BASES OF GvHD PROGRESSION

The progression of aGvHD contains three phases (Fig. 1): activation of antigen presenting cells, activation of effector cells and in the end damage of target organs [15]. In the first one, host antigen presenting cells (APC) are activated by the presence of antigens. Due to primary disease, chemotherapy or total body irradiation introduced in the conditioning regimen, recipient's tissues are being profoundly damaged. This results in release of pro-inflammatory cytokines such as interleukin-1 (IL-1) or tumor necrosis factor α (TNF-α) that attract host APCs eventually activating donor T cells [62]. Several other danger signals including uric acid and metabolites of adenosine triphosphate (ATP) pathway are also released and are said to be involved in GvHD activation process as well [3]. As a result of tissue damage especially the GI tract mucosa becomes more permeable for extracorporeal molecules and inflammatory stimuli, for instance microbial products like lipopolysaccharide (LPS) [21]. Microbiota derived signals, toll-like receptors (TLRs) and NOD-like receptors (NLRs) have been shown to trigger the inflammation in epithelial tissues [44].

Secondary lymphoid tissue of the GI tract is said to be the primary site where the interaction between host APCs and donor T cells occurs [37]. The afferent phase where donor T lymphocytes are activated by recipient's APCs and respond to HLA or miHAs disparity in host cells is the core of the acute GvH reaction. CD4+ T lymphocytes induce acute GvHD to MHC class II molecules variations and CD8+ T cells

respond to variations within MHC class I [12]. The cytokines and danger signals released in first phase also indirectly costimulate this activation [11]. This results in rapid biochemical cascades inducing activated donor T cells to release large amounts of cytokines such as TNF-α, interleukin-2 (IL-2) and interferon gamma (IFN-γ).

Stimulated T-cells exhibit various activities, which can be divided in two groups. In the first group could be assigned all pathways, which result in IL-17 and TNF-α secretion, in the second, pathways, which result in antibodies production. Specific types of immune cells could be assigned to each group of observed disorders. Skin damage occurs in the presence of IL-17 and absence of IL-4 or IFN-gamma, which promotes differentiation of naive Th cells into Th17 lymphocytes [29]. Intestines and liver disorders are both mediated by Th1 lymphocytes, which are formed by IFN-gamma stimulation pathway. Curiously, IFN-gamma is being produced with IL-2, in the presence of IL-12 [29], which impact should be considered as well. T cell activation and IL-2 production are the focus points of current clinical prophylaxis and treatment approaches such as cyclosporine, mycophenolate, mToR inhibitors, other calcineurin inhibitors and monoclonal antibodies against IL-2 and its receptor [38].

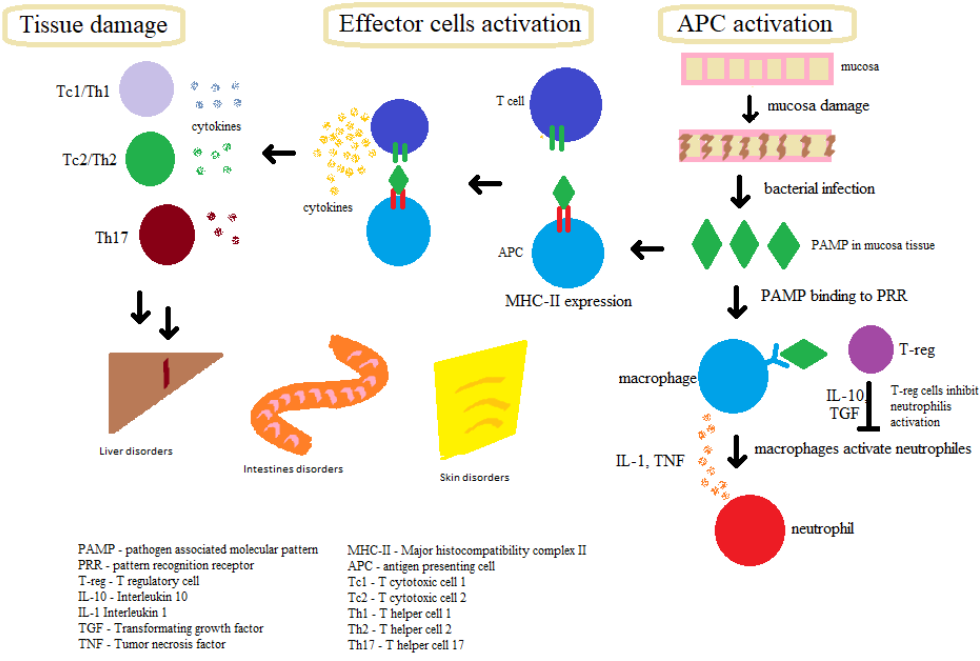

FIGURE 1. Molecular mechanism summary of GvHD
RYCINA 1. Molekularny mechanism GvHD

The third phase in aGvHD mechanism, contains both innate and adaptive immune cells response, by the release of inflammatory mediators that exacerbate the T cell induced tissue injury, promote further inflammation process and possible target organs destruction. The effectors are mostly cytotoxic T cells (CTLs) and natural killer (NK) cells [12]. CTLs tend to use the Fas/FasL pathway and predominate in liver form or aGvHD while NK cells prefer the perforine/granzyme pathway and appear in GI tract and skin damage [58]. Chemokines attract T lymphocytes from lymphoid tissue to target organs where they eventually cause damage. In addition, microbial products such as lipopolysaccharide, leak through execissively permeable mucosa of GI tract and stimulate mononuclear cells (macrophages and monocytes) to release macrophage inflammatory protein 1 α (MIP) and large amount of other chemokines i.e. CCL2-CCL5, CXCL9, CXCL10 and CXCL11 [61]. This results in occurence of the cytokine storm, which is characteristic for aGvHD. The process is mostly present in the gastrointestinal tract which has the major role in its propagation and amplification. Moreover, the expression of integrins and its ligand MADCAM1 (mucosal vascular addressin cell adhesion molecule 1) are crucial for homing T cells to Peyer's patches during intestinal GvHD [37].

The pathophysiology of cGvHD is still poorly understood due to lack of satisfactory experimental models. Although cGvHD may occur *de novo,* aGvHD is the main risk factor of its development [55]. Therefore strategies aiming at T cell depletion are the main focus point to prevent cGvHD. As lymphoid tissue and immune organs such as thymus, spleen or bone marrow are the primary targets of aGvHD, arising thymic dysfunction seems to be the major risk factor of auto- and alloimmunity in cGvHD process [51]. The disturbed B cells development due to bone marrow niche damage reflects in elevated B-cell activating factor (BAFF) levels as a reliable predictor of probable cGvHD occurrence [52].

CYTOKINES ROLE IN GvHD

Cytokines, which are crucial for GvHD development could be divided in two groups, depending on the type of GvHD, which they promote – aGvHD or cGvHD. Due to the characteristics of both types, cytokines differ in the ability of promoting long term proinflammatory response connected with tissue fibrosis or rapid cells receptor-mediated apoptosis.

After recognition of microbial PAMP (pathogen associated molecular patterns) by PRR (pattern recognition receptors) or TCR (T-cell receptor), various

cytokines are produced. IL-1, IL-4, IL-6, IL-12, IFN-gamma and TNF- α are especially important in the proinflammatory response. Molecular pathways, promoted by these molecules could be further classified in three groups [19].

The first class leads to macrophages and monocytes differentiation and secretion of extra amounts of IL-1, IL-6 and TNF- α, which results in increased apoptosis. Also TGF-beta is secreted, but in comparison to the previously mentioned, it promotes tissue fibrosis, that results in cGvHD.

The second-class pathway is connected with NK cells, NKT cells and ILC activation, which results in tissue damage. By the activation of perforin (Prf1), granzyme (GzmB), CD95-CD178 and ADCC signalling pathways, the NK cells promote target cells apoptosis [63].

The third pathway consists of activated T cells, which produce cytokines, that would promote aGvHD as well as cGvHD. Tc1 and Th1 lymphocytes secrete IFN-gamma, TNF- α and IL-2, which results in cytolysis mediated by perforins and granzymes in aGvHD. Tc2 and Th2 cells synthesise IL-4, IL-5 and IL-13 and Tc17 and Th17 cells synthesise IL-17, IL-21 and IL-22. Cytokines from both groups promote fibrosis and trigger cGvHD [19]. There is also a correlation between cGvHD and CXCL9 elevated levels [26].

miRNA IMPACT ON GvHD

Several studies have revealed a significant role of miRNA in regulation of autoimmunity as well as synthesis of proinflammatory cytokines. Koenecke and Krueger [27] have described the process of formation of different types of Th cells in response to miRNA. The research have revealed that increased level of certain type of miRNA results in formation of specific type of T lymphocytes and NKT cells. miRNA impact on immune cells consists of maturation regulation and inhibition of essential proteins expression.

To obtain a specific type of Th cell, first CD4+ T-lymphocytes have to be differentiated [36] by interaction with miR-17-92 [60] and miR-142 [35]. However, central role in the process is assigned to miR-155, that controls responsiveness to IL-2, therefore regulates Th1 and Th17 lymphocytes formation [40]. Other miRNAs types, that are believed to play role in Th17 cells differentiation are miR181a (promote also NKT formation) [16] and miR-29 (acts as a repressor of IFN-gamma). Furthermore, miR-29 downregulates Th1 cells transcription factors – T-bet and Eomes [31], essential in genetical maturation of the cells. T-reg cells are formed by molecular interaction with the miR-155 [40] and miR-146a [57].

NKT cells are formed by the miR-181a mediated pathway [16]. Interestingly, targeting the expression of essential for NK cells function proteins, like Prf1 and GzmB with miR-27a* regulates their cytotoxicity properties [25].

BIOMARKERS OF GvHD

General set of biomarkers of aGvHD obtained by Paczesny et al. include IL-2Rα, TNFR1, IL-8 and HGF [42]. On the other hand, markers especially useful in cGvHD differentiation consist of: ST2 (IL-1 receptor), CXCL9 (chemokine with CXC motif 9), matrix metalloproteinase 3, and osteopontin [64]. However useful, there is still a need to develop a tissue and grade specific markers of GvHD.

McDonald et al. have established that TIM3 (plays a key role in inhibiting Th1 response [8]), IL-6 and sTNFR1 (Soluble tumour necrosis factor receptor-1) levels had utility in the peak grade of most severe grades of aGvHD (3 and 4) predictions [33]. Advances have also been done in field of mortality prediction. High levels of ST2 and sTNFR1 have corresponded with the mortality in first year after transplantation as well as with the severity of GvHD [33].

Tissue specific biomarkers identified by means of the skin explant model include BAFF, IL-33, CXCL9, CXCL10, CXCL11 [54] and Elafin [41]. Not only their occurance seems promising in GvHD detection, but also the fact, that their levels correspond with the grade of GvHD [1].

Current research have revealed the utility of REG3α as a lower gastrointestinal tract and liver disorders biomarker. Previously proposed markers – HGF and cytokeratin fragment 18, have not discerned GvHD from non-GvHD diarrhea, which is a serious drawback over REG3α [17].

The information about genetic predispositions (like mutations in cytokines and interleukin genes [18]) could be used as a biomarker of GvHD as well. With the use of NGS (next generation sequencing), mutations in genes involved in the disease could be easily detected and potentially used as a marker of GvHD.

CONCLUSIONS

Better understanding of molecular bases of GvHD has led to a significant improvement in treatment. In the early 1990, blockade of nonspecific proinflammatory cytokines (IL-1) by monoclonal antibodies have been widely studied [10]. Nowadays, comprehension of the molecular mechanism has resulted in more specific targets discovery. Cytokines and hormones role in the pathogenesis has enabled pharmacological prevention of the disorder [6]. Methotrexate (folic acid

antagonist), Cyclosporine (calcineurine inhibitor), Tacrolimus (inhibitory for T cells activation), Corticosteroids (antiinflammatory hormones), Mycophenolate mofetil (MMF) (inhibits the proliferation of T and B cells), Antithymocyte globulin (supress thymocytes maturation), Sirolimus (prevention of organ rejection) and Alemtuzumab (anti CD52 monoclonal antibody) are now widely used as a prevention drugs, supressing the occurrence of GvHD [47].

Future development of GvHD treatment methods will mainly focus on specific targeting of immune cells in order to supress inflammatory response. B and T cells function suppression in collaboration with T regulatory cells stimulation, seems to be a promising strategy for treatment on the cellular level. Inhibiton of cytokines expression by highly specific monoclonal antibodies or miRNA is a potentially good strategy as well [22]. For the wide clinical application, there is still a need for further invesigations.

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REFERENCES

[1] Ahmed Ss, Wang Xn, Norden J, Pearce K, El-Gezawy E, et al. Identification and validation of biomarkers associated with acute and chronic graft versus host disease. *Bone Marrow Transplant.* 2015; **50**(12):1563-71.

[2] Akpek G, Chinratanalab W, Lee LA, Torbenson M, Hallick JP, et al. Gastrointestinal involvement in chronic graft-versus-host disease: A clinicopathologic study. *Biol. Blood Marrow Transplant.* 2003; **9**(1): 46-51

[3] Apostolova P, Zeiser R. The role of danger signals and ectonucleotidases in acute graft-versus-host disease. *Hum. Immunol.* 2016; **77**(11):1037-47.

[4] Ball LM, Egeler RM. Acute GvHD: pathogenesis and classification. *Bone Marrow Transplant.* 2008; **41**(S2): S58-64.

[5] Billingham RE. The biology of graft-versus-host reactions. *Harvey Lec*. 1966; **62**: 21-78.

[6] Carpenter Pa, Sanders JE. Steroid-refractory graft-vs.-host disease: past, present and future. *Pediatr. Transplant.* 2003; **7**: 19-31.

[7] Cooke KR, Luznik L, Sarantopoulos S, Hakim FT, Jagasia M, et al. The Biology of Chronic Graft-versus-Host Disease: A Task Force Report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. *Biol. Blood Marrow Transplant.* 2017; **23**(2): 211-34.

[8] Das M, Zhu C, Kuchroo VK. Tim-3 and its role in regulating anti-tumor immunity. *Immunol. Rev.* 2017; **276**(1): 97-111.

[9] De Bueger M, Bakker A, Van Rood J, Van Der Woude F, Goulmy E. Tissue distribution of human minor histocompatibility antigens. Ubiquitous versus restricted tissue distribution indicates heteroge-

neity among human cytotoxic T lymphocyte-defined non-MHC antigens. *J. Immunol.* 1992 *(Baltimore, Md 1950).*

[10] Dinarello CA, Thompson RC. 1991. Blocking IL-1: interleukin 1 receptor antagonist in vivo and in vitro. *Immunol. Today*. **12**(11):404-10.

[11] Dustin ML. Role of adhesion molecules in activation signaling in T lymphocytes. *J. Clin. Immunol.* 2001; **21**(4): 258-63.

[12] Ferrara J, Levine J, Reddy P, Holler E. Graft-verus-Host Disease. *Lancet*. 2009; **373**(9674): 1550-61.

[13] Filipovich AH. Diagnosis and manifestations of chronic graft-versus-host disease. *Best Pract. Res. Clin. Haematol.* 2008; **21**(2): 251-57.

[14] Gatti R, Meuwissen H, Allen H, Hong R, Good R. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet*. 1968; **292**(7583): 1366-69.

[15] Ghimire S, Weber D, Mavin E, Wang XN, Dickinson AM, Holler E. Pathophysiology of GvHD and other HSCT-related major complications. *Front. Immunol.* 2017; **8**: 79.

[16] Ghorbani S, Talebi F, Chan WF, Masoumi F, Vojgani M, et al. MicroRNA-181 Variants Regulate T Cell Phenotype in the Context of Autoimmune Neuroinflammation. *Front. Immunol.* 2017; **8**: 758.

[17] Harris AC, Ferrara JLM, Braun TM, Holler E, Teshima T, et al. Plasma biomarkers of lower gastrointestinal and liver acute GVHD. *Blood*. 2012; **119**(12): 2960-63.

[18] Harris AC, Ferrara JLM, Levine JE. Advances in predicting acute GVHD. *Br. J. Haematol.* 2013; **160**(3): 288-302.

[19] Henden AS, Hill GR. Cytokines in Graft-versus-Host Disease. *J. Immunol.* 2015; **194**(10): 4604-12.

[20] Hierlmeier S, Eyrich M, Wölfl M, Schlegel PG, Wiegering V. Early and late complications following hematopoietic stem cell transplantation in pediatric patients – A retrospective analysis over 11 years. *PLoS One.* 2018; **13**(10): e0204914.

[21] Hill GR, Ferrara JL. The primacy of the gastrointestinal tract as a target organ of acute graft-versus-host disease: rationale for the use of cytokine shields in allogeneic bone marrow transplantation. *Blood.* 2000; **95**(9).

[22] Hippen KL, Loschi M, Nicholls J, Macdonald KPA, Blazar BR. Effects of MicroRNA on Regulatory T Cells and Implications for Adoptive Cellular Therapy to Ameliorate Graft-versus-Host Disease. *Front. Immunol.* 2018; **9**: 57.

[23] Horton R, Wilming L, Rand V, Lovering RC, Bruford EA, et al. Gene map of the extended human MHC. *Nat. Rev. Genet.* 2004; **5**(12): 889-99.

[24] Jacobsohn DA. Acute graft-versus-host disease in children. *Bone Marrow Transplant.* 2008; **41**(2): 215-21.

[25] Kim T-D, Lee SU, Yun S, Sun H-N, Lee SH, Et Al. Human microRNA-27a* targets Prf1 and GzmB expression to regulate NK-cell cytotoxicity. *Blood*. 2011; **118**(20): 5476-86.

[26] Kitko CL, Levine JE, Storer BE, Chai X, Fox DA et al. Plasma CXCL9 elevations correlate with chronic GVHD diagnosis. *Blood.* 2014; **123**(5): 786-93.

[27] Koenecke C, Krueger A. MicroRNA in T-Cell Development and T-Cell Mediated Acute Graft-Versus-Host Disease. *Front. Immunol.* 2018; **9**: 992.

[28] Kuba A, Raida L. Graft versus Host Disease: From Basic Pathogenic Principles to DNA Damage Response and Cellular Senescence. *Mediators Inflamm.* 2018; **2018**: 9451950

[29] Kumar S, Mohammadpour H, Cao X. Targeting Cytokines in GVHD Therapy. *J. Immunol. Res. Ther.* **2**(1): 90-99

[30] Lee SJ. New approaches for preventing and treating chronic graft-versus-host disease. *Blood*. 2005; **105**(11): 4200-4206.

[31] Ma F, Xu S, Liu X, Zhang Q, Xu X, et al. The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-γ. *Nat. Immunol.* 2011; **12**(9): 861-69.

[32] Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood.* 1990; **76**(8).

[33] Mcdonald GB, Tabellini L, Storer BE, Lawler RL, Martin PJ, Hansen JA. Plasma biomarkers of acute GVHD and nonrelapse mortality: predictive value of measurements before GVHD onset and treatment. *Blood*. 2015; **126**(1): 113-20.
[34] Micklem HS. Radiation chimaeras. *Int. J. Radiat. Biol.* 1968; **13**(5): 503-503.
[35] Mildner A, Chapnik E, Varol D, Aychek T, Lampl N, et al. MicroRNA-142 controls thymocyte proliferation. *Eur. J. Immunol.* 2017; **47**(7): 1142-52.
[36] Monticelli S. MicroRNAs in T helper cell differentiation and plasticity. *Semin. Immunol.* 2013; **25**(4): 291-98.
[37] Murai M, Yoneyama H, Ezaki T, Suematsu M, Terashima Y, et al. Peyer's patch is the essential site in initiating murine acute and lethal graft-versus-host reaction. *Nat. Immunol.* 2003; **4**(2): 154-60.
[38] Nash RA, Antin JH, Karanes C, Fay JW, Avalos BR, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Blood. Blood*. 2000; **80**(7): 1838-45.
[39] Nassereddine S, Rafei H, Elbahesh E, Tabbara I. Acute Graft Versus Host Disease: A Comprehensive Review. *Anticancer Res.* 2017; **37**(4): 1547-55.
[40] O'connell RM, Kahn D, Gibson WSJ, Round JL, Scholz RL, et al. MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. *Immunity*. 2010; **33**(4): 607-19.
[41] Paczesny S, Braun TM, Levine JE, Hogan J, Crawford J, et al. Elafin is a biomarker of graft-versus-host disease of the skin. *Sci. Transl. Med.* 2010; **2**(13): 13ra2.
[42] Paczesny S, Krijanovski OI, Braun TM, Choi SW, Clouthier SG, et al. A biomarker panel for acute graft-versus-host disease. *Blood*. 2009; **113**(2): 273-78.
[43] Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, et al. Use of haploidentical stem cell transplantation continues to increase: The 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant.* 2017; **52**(6): 811-17.
[44] Penack O, Holler E, Van Den Brink MRM. Graft-versus-host disease: Regulation by microbe-associated molecules and innate immune receptors. *Blood*. 2010; **115**(10):1865-72.
[45] Petersdorf EW MM. Genetics of risk factors for graft-versus-host disease. *Semin. Hematol.* 2006; **43**: 11-23.
[46] Presland RB. Biology of chronic graft- vs -host disease: Immune mechanisms and progress in biomarker discovery . *World J. Transplant.* 2016; **6**(4): 608.
[47] Ram R, Storb R. Pharmacologic prophylaxis regimens for acute graft-versus-host disease: past, present and future. *Leuk. Lymphoma*. 2013; **54**(8): 1591-1601.
[48] Reynaert H, De Coninck A, Neven AM, Van Camp B, Schots R. Chemotherapy-induced acral erythema and acute graft-versus-host disease after allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1992; **10**(2): 185-87.
[49] Rocha V, Wagner JE, Sobocinski KA, Klein JP, Zhang M-J, et al. Graft-Versus-Host Disease in Children Who Have Received a Cord-Blood or Bone Marrow Transplant from an HLA-Identical Sibling. *N. Engl. J. Med.* **342**(25): 1846-54.
[50] Santos E Sousa P, Bennett CL, Chakraverty R. Unraveling the mechanisms of cutaneous graft-versus-host disease. *Front. Immunol.* 2018; **9**: 963.
[51] Sarantopoulos S, Ritz J. Aberrant B-cell homeostasis in chronic GVHD. *Blood*. 2015; **125**(11): 1703-7.
[52] Sarantopoulos S, Stevenson KE, Kim HT, Bhuiya NS, Cutler CS, et al. High Levels of B-Cell Activating Factor in Patients with Active Chronic Graft-Versus-Host Disease. *Clin. Cancer Res.* 2007; **13**(20): 6107-14.
[53] Schroeder MA, Dipersio JF. Mouse models of graft-versus-host disease: advances and limitations. *Dis. Model. Mech.* 2011; **4**(3): 318-33.
[54] Sette A, Sidney J. HLA supertypes and supermotifs: a functional perspective on HLA polymorphism. *Curr. Opin. Immunol.* 1998; **10**(4): 478-82.
[55] Socié G, Ritz J. Current issues in chronic graft-versus-host disease. *Blood*. 2014; **124**(3): 374-84.

[56] Spierings E. Minor histocompatibility antigens: Past, present, and future. *Tissue Antigens*. 2014; **84**(4): 374-360.
[57] Stickel N, Prinz G, Pfeifer D, Hasselblatt P, Schmitt-Graeff A, et al. MiR-146a regulates the TRAF6/TNF-axis in donor T cells during GVHD. *Blood*. 2014; **124**(16): 2586-95.
[58] Van Den Brink MRM, Burakoff SJ. Cytolytic pathways in haematopoietic stem-cell transplantation. *Nat. Rev. Immunol.* 2002; **2**(4): 273-81.
[59] Vigorito AC, Campregher PV, Storer BE, Carpenter PA, Moravec CK, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. *Blood*. 2009; **114**(3): 702-8.
[60] Wu T, Wieland A, Lee J, Hale JS, Han J-H, et al. Cutting Edge: miR-17-92 Is Required for Both CD4 Th1 and T Follicular Helper Cell Responses during Viral Infection. *J. Immunol.* 2015; **195**(6): 2515-19.
[61] Wysocki CA, Panoskaltsis-Mortari A, Blazar BR, Serody JS. Leukocyte migration and graft-versus-host disease. *Blood*. 2005; **105**(11): 4191-99.
[62] Xun C, Thompson J, Jennings C, Brown S, Widmer M. Effect of total body irradiation, busulfan-cyclophosphamide, or cyclophosphamide conditioning on inflammatory cytokine release and development of acute and chronic graft-versus-host disease in H-2-incompatible transplanted SCID mice. *Blood.* 1994; **83**(8).
[63] Yoon SR, Kim T-D, Choi I. Understanding of molecular mechanisms in natural killer cell therapy. *Exp. Mol. Med.* 2015; **47**: 141.
[64] Yu J, Storer BE, Kushekhar K, Zaid MA, Zhang Q, et al. Biomarker Panel for Chronic Graft-Versus-Host Disease. *J. Clin. Oncol.* 2016; **34**(22): 2583.

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