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REVIEW / DERLEME

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Role of Macrophages in Organ Transplantation

Organ Naklinde Makrofajların Rolü

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Abstract

Organ transplantation is a life-saving treatment option for patients with end-stage organ failure. Graft rejection is a significant complication that can develop after an organ transplant, and its pathophysiology depends on many variables. Macrophages are one of the main cell types of the innate immune system. Clinical studies showed that macrophages recognize the antigens and play an important role in graft rejection. Infiltration of macrophages is associated with an increased incidence of graft rejection. Macrophage-targeted therapeutic studies are required to prevent long- and short-term graft rejection and increase graft survival. This review focused on the potential macrophage-targeted therapeutic strategies to improve graft survival. Also, we reviewed the literature regarding the role of macrophages in organ transplantation.

Keywords: Macrophages, transplantation, graft survival, rejection, ischemia-reperfusion injury

Öz

Organ nakli, son dönem organ yetmezliği olan hastalar için hayat kurtaran bir tedavi seçeneğidir. Greft reddi, organ naklinden sonra gelişebilecek ciddi bir komplikasyondur ve patofizyolojisi birçok değişkene bağlıdır. Makrofajlar, doğuştan gelen bağışıklık sisteminin temel hücre gruplarındandır. Klinik çalışmalar, makrofajların antijenleri tanıdığını ve greft reddinde önemli rol oynadığını göstermiştir. Makrofaj infiltrasyonu, artan greft reddi insidansı ile ilişkilidir. Uzun ve kısa süreli greft reddini engellemek ve greft sağkalımını artırmak için makrofaj hedefli terapötik çalışmalara ihtiyaç vardır. Bu derleme, greft sağkalımını artırmak için potansiyel makrofaj hedefli terapötik stratejilere odaklandı. Ayrıca, organ naklinde makrofajların rolü ile ilgili literatürü gözden geçirdik.

Anahtar Kelimeler: Makrofaj, transplantasyon, greft sağkalımı, rejeksiyon, iskemi reperfüzyon hasarı

Introduction

Organ transplantation is an ideal treatment option for patients with end-stage organ dysfunction. The success of organ transplants depends on suppressing the host immune response and the immune cells participating in the rejection process[1]. Graft survival has risen to nearly 90%, especially with developments in surgical procedures and immunosuppressive drugs[2]. Conversely, chronic graft rejection can reduce long-term graft survival. Chronic graft rejection is particularly relevant to macrophages, which play a vital role in the innate immune system. It has been recognized since the 1970s that macrophages play a role in graft rejection[3].

Macrophages play an essential role in host defense, inflammatory processes, ischemia-reperfusion injury, and tissue homeostasis[4]. In addition, they are involved in

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the phagocytosis of pathogens and can present antigens and initiate adaptive immune responses[5]. Therefore, the identification and characterization of macrophages with different phenotypes may provide new therapeutic targets to improve graft survival following transplantation.

This review focused on potential macrophage-targeted therapeutic strategies to improve graft survival. In addition, we reviewed the literature regarding the role of macrophages in organ transplantation. We used the PubMed interface (pubmed.gov) to generate a query using the combination of the following two keyword groups: The first group included the keywords "organ transplantation", "graft rejection", "graft survival", while the second group included "macrophages" and "macrophage polarization". Each keyword in the same group was combined using the Boolean operator "OR", while the two groups were combined using the Boolean operator "AND".

Macrophages

Macrophages are important innate immune system cells that function as the initial line of defense against pathogens[6]. They contain various receptors involved in cell activation, antigen presentation, phagocytosis, and microorganism recognition (Figure 1). These receptors enable macrophages to respond to various immunological and inflammatory agents. In addition, macrophages express major histocompatibility complex (MHC) class II molecules under homeostatic conditions[7]. The expression of such receptors and surface markers divides macrophages into subsets, particularly in terms of their activation state and functional activity (Figures 1 and 2)[8,9].

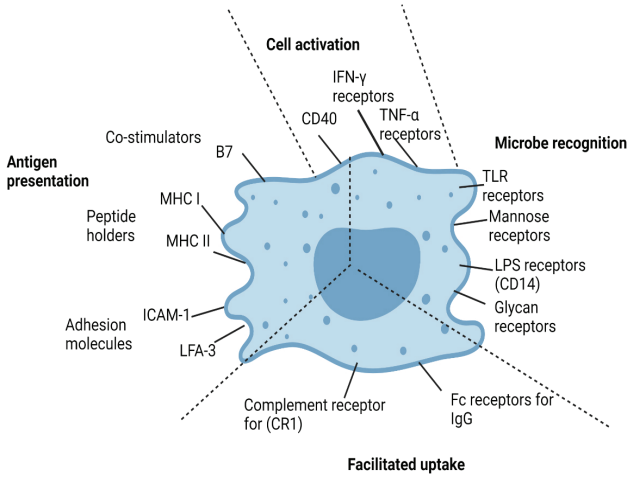

Figure 1. The function of macrophages is mediated by their surface features[8]. Figure were created with BioRender.com

ICAM-1: Intercellular adhesion molecule-1, IFN-γ: Interferon-γ, Ig: Immunoglobulin, LFA-3: Leukocyte function-associated antigen-3, LPS: Lipopolysaccharide, MHC: Major histocompatibility antigen I or II, TNF-α: Tumor necrosis factor-α

Macrophages originate from myeloid precursors in the bone marrow, differentiate from monocytes, and take on distinct features depending on the tissues in which they are found[7,10]. For example, macrophages are osteoclasts in bone, Kupffer cells in the liver, and microglia in the brain (Figure 3). These tissue-specific macrophage subpopulations can modify their phenotype and function in response to environmental signals[6].

Macrophages have two well-defined phenotypes: Classically activated macrophages (M1) induced by lipopolysaccharide (LPS) or interferon-gamma (IFN-γ), and alternatively

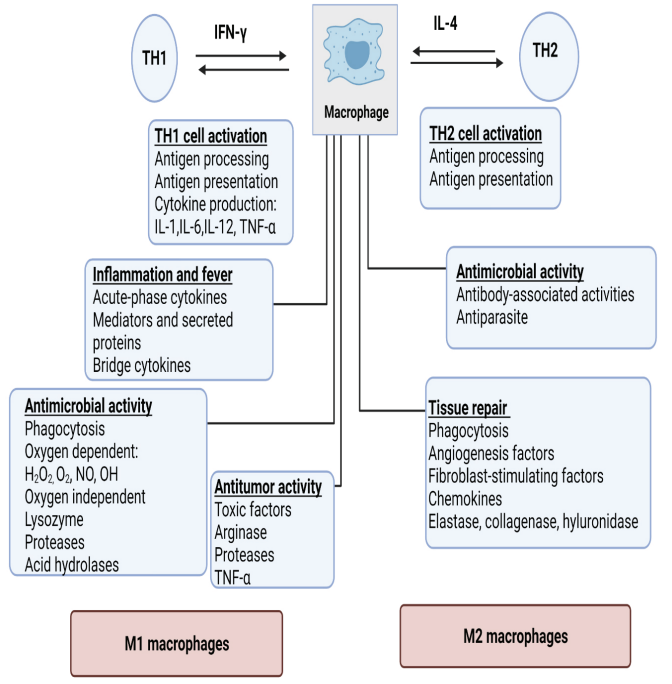

Figure 2. The many functions of the macrophage family[9]. M2 macrophages facilitate wound healing and promote angiogenesis and tissue repair. M1 macrophages promote antimicrobial activity and inflammation. Figure were created with BioRender.com

H_2O_2: Hydrogen peroxide, NO: Nitric oxide, O_2: Oxygen radical, OH: Hydroxyl radical, TH: T helper (cell), TNF-α: Tumor necrosis factor-α, IFN-γ: Interferon-γ; IL: Interleukin

activated macrophages (M2) induced by interleukin (IL)-4 or IL-10 (Figure 2)[10]. M1 macrophages are potent pro-inflammatory cells that secrete cytokines such as nitric oxide (NO) and reactive oxygen species (ROS). They express high levels of MHC class II, CD80, CD86, CD215, CCR7, CCL8/15/20, and CXCL9/10/11/13 on the cell surface[7]. In contrast, M2 macrophages have anti-inflammatory features and are associated with wound healing and fibrosis[10]. They are induced in the presence of IL-4 and IL-13; they differ in terms of the expression of CD163, CD169, CD206 (mannose receptor), and CD209 (DC-SIGN). M2 macrophages are classified into M2a-b-c-d subgroups based on the differences in the cytokine environment in which they are activated[11].

In addition, regulatory macrophages (Mreg) have anti-inflammatory features and play a protective role in graft recipients[6].

Macrophages in Ischemia– Reperfusion Injury (IRI)

IRI involves both innate and adaptive immune cells. Clinical studies have shown that macrophages play a role in short- and long-term IRI. Furuichi et al.[12] reported that monocyte chemoattractant protein-1 (MCP-1) plays a crucial role in the pathogenesis of renal IRI by activating macrophages and stimulating macrophage infiltration. Zhang et al.[13] showed that targeting T-cell immunoglobulin mucin-1 (TIM-1) on $CD4^+$ T-cells in a liver graft reduced T-cell-mediated activation of macrophages and the severity of IRI.

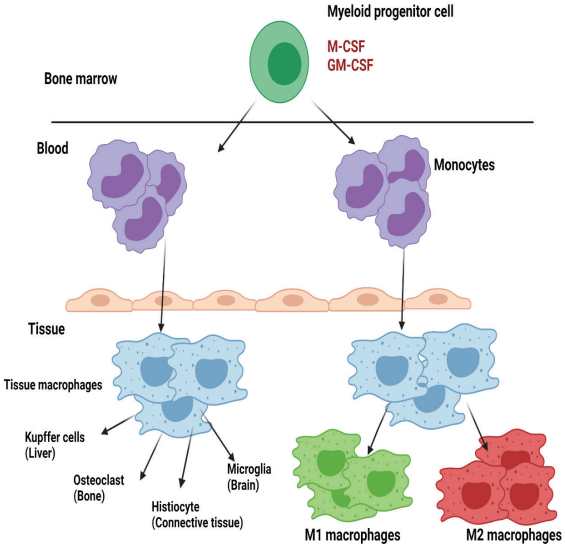

Figure 3. Origin and types of macrophages. Figure were created with BioRender.com

According to Busuttil et al.[14], selectin antagonists (rPSGL-1) reduce hepatic IRI and the severity of macrophage infiltration.

M1 macrophages cause damage during IRI, whereas M2 macrophages promote damage repair. In addition, it was stated that M1 macrophages may mediate the inflammatory process during the initiation of IRI, whereas M2 macrophages play a role in the pathophysiology of IRI.

Macrophages in Acute Rejection

In acute rejection, macrophages constitute 38-60% of graft-infiltrating cells in human graft biopsies and contribute to graft injury through various mechanisms[7]. Macrophage depletion has been proven to alleviate graft injury and reduce inflammation in multiple experimental animal models[15]. When macrophages infiltrate the graft, they exhibit a pro-inflammatory phenotype by secreting inflammatory cytokines and directly causing tissue damage. Pro-inflammatory macrophages are the primary source of reactive oxygen and nitrogen species that can directly damage the graft and increase the risk of acute rejection[7]. Pro-inflammatory cytokines secreted by macrophages, such as IL-1, IL-6, IL-12, IL-18, tumor necrosis factor-alpha (TNF-α), and IFN-γ, play a role in various processes, including the activation of endothelial cells and cytotoxic T-cells[16]. Oliveira et al.[17] reported that IL-18 expression increased during acute graft rejection.

The presence of $CD68^+$ macrophages was also associated with acute rejection[3]. van den Bosch et al.[18] reported that high $CD68^+$ and $CD163^+$ M2 macrophage counts were related to severe fibrosis in post-transplant 1-year graft biopsies. Toki et al.[19] showed that infiltrating macrophages in renal grafts had the $CD68^+CD206^+$M2 phenotype one year after transplantation.

It was also reported that the levels of monocyte colony-stimulating factor (M-CSF) were high in the grafts after acute rejection, and this finding was consistent with the increased macrophage/monocyte infiltration[20]. Monocytes can be detected in the circulation before the clinical symptoms of acute rejection occur. Ordikhani et al.[2] denoted that $CD16^+$ monocytes could inhibit T regulatory (Treg) cells, and this inhibition might be responsible for acute graft rejection.

Macrophages in Chronic Rejection

Chronic rejection is the leading cause of long-term graft loss that occurs months or years after organ transplantation. It is characterized by progressive neointima formation,

tissue fibrosis that leads to vascular blockage, and graft vasculopathy[21]. There is strong evidence that macrophages contribute to chronic rejection. Macrophages accumulate in significant amounts around graft vessels in chronically rejected grafts. In biopsies of human cardiac grafts, the number of macrophages is greater than that of T-cells in grafts[22].

The endothelial cells of the graft blood vessels produce considerable amounts of the chemokine fractalkine (CX3CL1). Monocytes/macrophages expressing the fractalkine receptor (CX3CR1) are recruited from the circulation to the vicinity of blood vessels by CX3CL1. The macrophages cause the vascular smooth muscle cells to overproliferate, producing large numbers of fibrogenic factors such as fibroblasts and collagen. These factors cause graft tissue fibrosis and vascular lumen occlusion, resulting in chronic transplant rejection. Actin is required for macrophage receptor expression and recycling, and the RhoA pathway regulates it. Interfering with the RhoA pathway causes dysfunction of actin filaments and actin-dependent activities, including receptor production and recycling. Decreased CX3CR1 receptor expression makes macrophages less responsive or non-responsive to fractalkine, preventing their infiltration into the graft and chronic rejection (Figure 4) [1].

M2 macrophages constitute the most common type of macrophages in chronic renal graft injury, and it has been suggested that they are associated with the severity of fibrosis and graft rejection[23]. Kaul et al.[24] reported that mRNA levels of M2 macrophage markers (Ym1, Fizz1, VEGF, TGF-β, and CD206) increased after heart transplantation. Despite the critical role of M2 macrophages in chronic rejection, M1 macrophages contribute to the production of proteases, ROS, and NO and play a significant role in graft damage[25].

Liu et al.[26] investigated the role of macrophage depletion in preventing chronic rejection after heart transplantation. This study showed that macrophage depletion after heart transplantation could reduce chronic rejection by altering M2 polarization and expression levels of IFN-γ, TNF-α, MCP-1, and IL-10. Manipulation of M1/M2 macrophage polarization was also used to prevent graft rejection. Zhao et al.[27] showed that M1/M2 macrophage polarization depended on tumor necrosis factor receptor-associated factor 6 (TRAF6) and the mammalian target of rapamycin (mTOR).

Wu et al.[28] investigated the differences between M1 and M2 macrophages and identified the adenosine triphosphate (ATP) gated ion channel (P2x7r) as a hallmark of M2 cells. Interestingly, blocking P2x7r using oxidized ATP (oATP) prevented M2 polarization *in vitro* and graft infiltration *in vivo*, leading to long-term graft survival (Figure 5). This study showed that targeting graft-infiltrating M2 macrophages could reduce the risk of chronic rejection and increase graft survival[28].

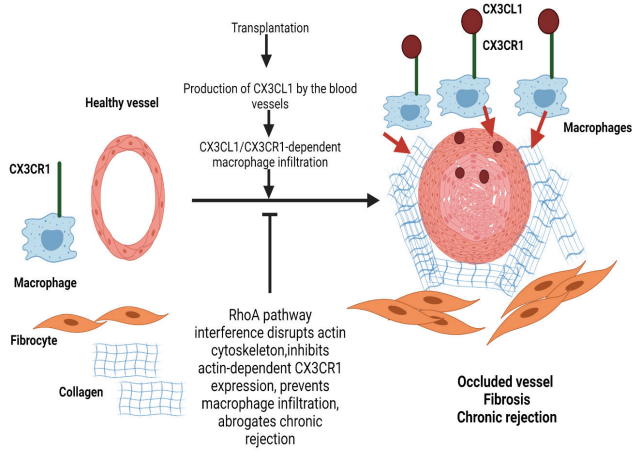

Figure 4. Role of macrophages in chronic rejection(1). Figure were created with BioRender.com

CX3CL1: Chemokine fractalkine, CX3CR1: Chemokine fractalkine receptor

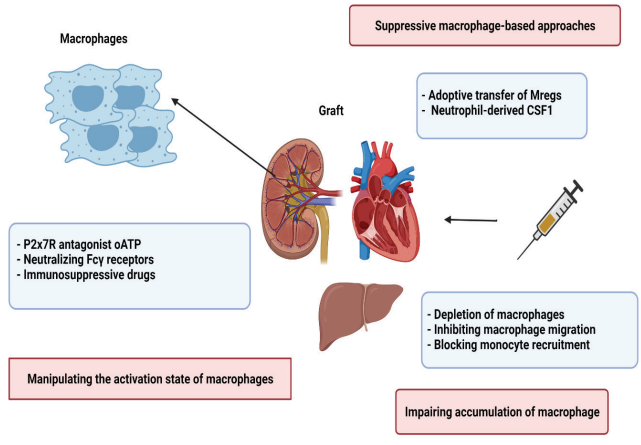

Figure 5. Macrophage-targeted treatment for graft tolerance[30]. Macrophage-targeted therapy strategies include immunosuppressive drug, macrophage proliferation inhibitors, chemokine antagonists, macrophage activation inhibitors, and macrophage depletion strategies. Figure were created with BioRender.com

CSF1: Colony stimulating factor 1, oATP: Oxidized adenosine triphosphate

Macrophage-targeted Therapies

Data regarding the critical role of macrophages in rejection processes form the basis for the development of macrophage-targeted therapies to improve graft survival. The main goals of these therapies are to induce graft tolerance and save patients from chronic rejection[21]. Macrophage-targeted therapy strategies include toll-like receptor (TLR) antagonists, macrophage proliferation inhibitors, chemokine antagonists, macrophage activation inhibitors, and macrophage depletion strategies[29].

Neutralizing the Fc receptor or treating patients with immunosuppressive drugs such as glucocorticoids and rapamycin inhibitors suppress pro-inflammatory macrophages and promote graft survival (Figure 5)[30]. Glucocorticoids, which are commonly used immunosuppressive drugs, promote the survival of anti-inflammatory monocytes[31]. Rapamycin, a prototypical inhibitor of mTOR, is considered an immunosuppressive agent and is currently used to prevent kidney transplant rejection[32]. Rapamycin has a selective effect on M1/M2 survival and leads to changes in cytokine release depending on the type of polarization. Rapamycin therapy breaks the balance in favor of an M1-like inflammatory response *in vivo*. M1 is resistant to rapamycin-induced apoptosis; it inhibits M2 polarization and promotes suppressor macrophage generation[33]. The differences in the sensitivities of M1 and M2 to rapamycin suggest that different intracellular pathways regulate survival[32]. In addition, macrophages treated with rapamycin have impaired antigen-presenting abilities and reduced CD80 expression[3]. Rapamycin also inhibits the production of the inflammatory mediator iNOS in macrophage cell lines[34].

Bortezomib is a proteasome inhibitor. This agent downregulates the immunological response of T-cells and is increasingly being used for the treatment of antibody-mediated rejection. It was shown to reduce inflammatory cytokine production in LPS-stimulated macrophages *in vitro*[3]. In addition, bortezomib has potent suppressive effects on humoral immunity. It leads to an increase in the $CD4^+$ T-regulatory cell population and decreases the serum levels of several pro-inflammatory and angiogenesis-inducing cytokines and chemokines. Gastrointestinal events, hematological toxicity, and peripheral neuropathy are the most common side effects of bortezomib[35].

Calcineurin has multiple effects on macrophage functions. The calcineurin inhibitors cyclosporin A (CsA) and tacrolimus (FK506) regulate TLR-mediated pathways in myeloid cells and cause macrophage activation by inhibiting the calcineurin/NFAT pathway[3]. High non-therapeutic concentrations of FK506 affect the maturation and polarization of macrophages. Thus, macrophage polarization shifts to an M2-like phenotype in the presence of FK506[36]. Clinical studies showed that FK506 was more effective than CsA in inhibiting macrophages during chronic rejection. Compared with FK506, CsA is more likely to promote fibrosis in kidney allografts[37]. CsA enhances the allograft infiltration of macrophages. Kakuta et al.[38] reported that CsA promoted the infiltration of $CCR5^+$ and $CXCR3^+$ macrophage grafts in rat kidney allograft transplantation. Significant macrophage infiltration was also found in the kidneys of rats afflicted by CsA nephrotoxicity. CsA may enhance the production of macrophage-derived molecules involved in chronic allograft injury[33].

Butyric acid is used to treat autoimmune disorders; it inhibits IL-12 and induces IL-10 production in human monocytes. Thus, butyric acid is associated with the formation of anti-inflammatory macrophages[39].

Mycophenolic acid is a widely used immunosuppressive and antimetabolite drug. Several studies have reported the effects of mycophenolic acid on macrophage functions. Weimer et al.[40] showed that mycophenolic acid could suppress the production of IL-1β and IL-6 by activated monocytes, but the effects of mycophenolic acid on monocyte differentiation are unknown. Overexposure to mycophenolic acid has frequent mild-to-moderate adverse effects, which lead to increased patient non-adherence and affect patients' quality of life. Bunnapradist et al.[41] confirmed that gastrointestinal side effects are dose-dependent in patients treated with mycophenolic acid. Otherwise, underexposure to mycophenolic acid may be linked to the risk of graft rejection and long-term allograft survival after transplantation[42]. In summary, manipulating the activation of macrophages may help to weaken both acute and chronic rejection.

Conclusion

The use of macrophage-targeted therapies is becoming popular in transplantation immunology. Significant accumulation of macrophages in the grafts and the close association of this process with poor transplant outcomes have increased researchers' interest in studies regarding macrophage function and macrophage-targeted treatment regimes. Subsequently, the identification of *in vivo* signaling pathways that affect macrophage polarization and function

expanded the number of potential new macrophage-targeted treatments that enable graft survival. However, further research is needed to better understand macrophages' roles in graft survival. In addition, comprehensive research concerning different macrophage phenotypes is vital for developing new macrophage-targeted therapy strategies that support short- and long-term graft survival.

Ethics

Authorship Contributions

Concept: T.Ö., M.P., İ.P., Design: T.Ö., M.P., Data Collection or Processing: T.Ö., Literature Search: T.Ö., Writing: T.Ö., M.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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