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Macrophages as Effectors of Acute and Chronic Allograft Injury

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Abstract

Organ transplants give a second chance of life to patients with end-stage organ failure. However, the immuno-logical barriers prove to be very challenging to overcome and graft rejection remains a major hurdle to long-term transplant survival. For decades, adaptive immunity has been the focus of studies, primarily based on the belief that T cells are necessary and sufficient for rejection. With better-developed immunosuppressive drugs and protocols that effectively control adaptive cells, innate immune cells have emerged as key effector cells in triggering graft injury and have therefore attracted much recent attention. In this review, we discuss current understanding of macrophages and their role in transplant rejection, their dynamics, distinct phenotypes, locations, and functions. We also discuss novel therapeutic approaches under development to target macrophages in transplant recipients.

Keywords

Transplantation; Rejection; Chronic rejection; Innate immunity; Macrophages; Inflammation

Introduction

Allograft Rejection—A Brief Overview

Allograft rejection occurs when the immune system in transplant recipients recognizes the donor' tissues as foreign entities [1]. Since 1958, T lymphocytes have been recognized as the main cell type infiltrating and damaging the allografts [2]. These observations have argued for the dominant role of adaptive immune cells in allograft rejection. However, recent studies have demonstrated that, besides adaptive immune cells, innate immune cells also play an important role in transplant rejection. In many aspects, organ transplantation provides an ideal setting for activation of innate immunity. Innate immune cells can be

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activated by ischemia-reperfusion injury that releases damage-associated molecular pattern molecules (DAMPs) that serve as danger signals, when subsequently recognized by pattern recognition receptors (PRRs), which are highly expressed by innate immune cells [3]. In this context, dendritic cells (DC) activated by danger molecules mature into potent antigen-presenting cell (APC); such DCs also secrete pro-inflammatory cytokines and up-regulate costimulatory molecules for efficient T-cell priming for rejection [4]. In addition, mature APCs migrate to secondary lymphoid organs where they are the most efficient cells in the activation of naïve T cells to trigger rejection [3]. Activated T cells also recruit a large number of innate cells including macrophages and granulocytes into the allograft where they either directly or indirectly mediate graft failure. Following transplantation, macrophages can also differentiate into many functionally different subsets, mediating phagocytosis of necrotic cells, secretion of pro-inflammatory cytokines, production of reactive oxygen species, as well as mediating tissue repair, regeneration, and immunoregulation [5]. Other innate cells involved in allograft rejection include natural killer (NK) cells. It has been shown that NK cells act as mediators of solid organ rejection by amplifying early graft inflammation [6]. Indeed, Maier et al. showed that in fully mismatched heart transplantation, CD28 knockout recipients experienced prolonged graft survival when NK cells were also depleted in the recipient mice [7]. In certain models, NK cells also act as immunoregulatory cells facilitating transplant survival. We demonstrated that NK cells promote transplant survival by killing donor APCs that migrate out of the graft, so that priming for host alloreactive T cells is inhibited [8]. It should be mentioned that innate immune cells also express diverse receptors for cytokines, antibodies, complement products, necrotic cells, and cell debris [9–11], thus any responses resulting in complement activation, antibody production, and cellular demise will dramatically affect the activation and effector functions of innate immune cells [12]. All these data support the proposition that the innate immune system exerts significant influence on transplant outcomes.

Limitation of Current Anti-rejection Therapies

From a clinical standpoint, current immunosuppression therapies are very effective in promoting short-term graft survival, but do little in promoting long-term transplant outcomes. For example, the introduction of calcineurin inhibitors in the 1980s has dramatically improved rates of early engraftment and the current immunosuppressive therapies have significantly lowered the incidence of acute rejection. Paradoxically, those therapies do not prevent chronic rejection. This is clearly demonstrated in renal allograft survival in the clinic where long-term graft survival remains unchanged, despite a dramatic reduction in rejection rates [13]. Data from kidney biopsies showed that several months before the histological signs of chronic damage, there is already up-regulation of adaptive (T, B cells) and innate (dendritic cell and NK cells) transcripts, illustrating the complex interplay between innate and adaptive immune cells in chronic allograft rejection [14].

At present, the goals of immunosuppressive therapies have shifted from the prevention of acute rejection toward the prevention of chronic rejection and induction of immune tolerance. Existing therapies such as cyclosporine, tacrolimus, mycophenolate, and mTOR inhibitors most effectively target the T-cell-mediated pathway, while therapies against innate immune cells are not readily available. While treatments targeting T cells alone often

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improve graft survival, they do not achieve long-term graft survival or true tolerance [15]. Various types of innate immune cells such as NK cells [16], DCs [17], macrophages [18], and mast cells [19] exhibit a variety of effector and regulatory functions in the allograft response. Therefore, therapies that are rationally designed and strategically deployed in targeting key pathways of both the innate and adaptive arms of the allograft response may have the best chance to promote long-lasting graft survival in transplant recipients.

The Diversity of Macrophages

Phenotypes

Because of the tremendous overlap in surface markers expressed by diverse subtypes of macrophages, it has been extremely difficult to identify the exact subtype of macrophages in vivo. Macrophages are also very dynamic, and a variety of environmental signals can influence the phenotype and polarization status of macrophages, suggesting that macrophages exhibit tremendous plasticity (Fig. 1).

M1 macrophages, also referred to as “classically activated macrophages,” differentiate in response to cytokines from Th1 cells, such as interferon- γ (IFN-γ), tumor necrosis factor-α (TNF-α), and engagement of Toll-like receptors by microbial products or DAMPs [20, 21]. M1 macrophages have the unique ability to produce high levels of inducible nitric oxide synthase 2 (iNOS2) that can function in eradicating bacterial, fungal, and viral infections. In addition, M1 macrophages display a pro-inflammatory phenotype via secretion of IL-1, IL-6, TNF-α, and IL-23, which sustain potent inflammatory responses [22•]. Although M1 macrophages are advantageous during acute infections, their prolonged presence, especially under sterile inflammation conditions, results in tissue damage.

M2 macrophages are referred to as “alternatively activated macrophages” implicating a distinct phenotype to “classically activated macrophages” M1 cells. M2 are anti-inflammatory macrophages involved in tissue repair, phagocytosis, and angiogenic and pro-fibrotic functions [23–25]. Because of the phenotypic heterogeneity of M2 macrophages, they have been divided into M2a, M2b, M2c, and M2d [22•]. M2a macrophages differentiate in response to combination of IL-4 and IL-13 [26, 27]. They express high levels of arginase-1 (Arg-1), mannose receptor (CD206), and transforming growth factor β (TGF-β). The arginase expression, which is a default mode in tissue macrophages, can be boosted by IL-4/13 or TGF-β signaling, and accelerate wound healing and tissue repair [28]. The M2b macrophage phenotype is triggered by immune complexes and bacterial lipopolysaccharide (LPS) [29], and M2c by IL-10 and glucocorticoids. The M2d macrophages are the major inflammatory component of tumor microenvironments. They differentiate in response to IL-6 and adenosines, and have an immunosuppressive role that promotes tumor metastasis and progression [30, 31].

Anatomic Locations and Functions

Macrophage heterogeneity is also associated with their diverse locations throughout the body. Because of their fundamental role in maintaining homeostasis and resolution of inflammation, tissue resident macrophages are considered to be “M2-like” [32].

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Macrophages present in the skeletal bones are referred to as osteoclasts; Kupffer cells, in the liver; and microglia, in the brain. However, the majority of tissues have several types of resident macrophages with distinct functions (Table 1). For example, in the brain, microglia remove dead neurons and promote neuronal survival [33, 34], while meningeal macrophages play a role in immune surveillance [35].

Mature macrophages constantly survey their surrounding microenvironment for signs of tissue damage or foreign organisms. When detecting dead cells or toxic materials, macrophages function as phagocytes to remove these detrimental factors. For example, Kupffer cells in the liver facilitate the removal of pathogens and toxins from the circulation. Macrophages are equipped with numerous cell surface pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), scavenger receptors, C-type lectin receptors, and NOD-like receptors, which can recognize pathogens, foreign substance, and dead or dying cells [36]. The signaling associated with PRRs subsequently activates transcriptional mechanisms, which lead to phagocytosis, cellular activation, and release of cytokines and growth factors [37, 38]. Overall, various surface receptors and secreted cytokines interact with each other to monitor the changes in organ/tissue microenvironment and homeostasis.

In many infections and tissue stress situations, when homeostasis is disrupted, the resident mononuclear phagocyte populations of a certain organ are insufficient to mediate microbial control and subsequent tissue repair. In this case, monocytes are recruited from bloodstream to peripheral tissue through chemotactic cues such as CCL2, CX3CL1, and CCL5 [39–41]. Monocytes quickly differentiate into macrophages at the site if M-CSF is present. These newly recruited cells exhibit pro-inflammatory “M1-like” phenotype and secrete mediators such as TNF-α, nitric oxide (NO), and IL-1, which are the main components of host defense. In *Listeria monocytogenes*–infected mice, deficiency of TNF and NO leads to difficulty in clearing the primary bacterial infection [42]. Unfortunately, reactive oxygen and nitrogen intermediates produced by activated macrophages also damage neighboring tissue, and, if left unchecked, they will cause unresolved inflammation [43]. In a model of chronic venous leg ulcer, the presence of unrestrained pro-inflammatory M1 macrophages led to impaired wound healing [44].

In contrast to pro-inflammatory M1 macrophages, M2 macrophages exhibit an anti-inflammatory and wound-healing phenotype. As one of the first signals released during tissue injury, IL-4 produced by basophils and mast cells rapidly converts resident macrophages into M2-like cells programmed to promote wound healing [6]. When adaptive immune responses come into effect, they also lead to the production of IL-4, which is thought to be the primary pathway for maintenance of wound healing macrophages in vivo [45]. To achieve this function, M2 macrophages produce growth factors such as TGF-β and platelet-derived growth factor (PDGF), which are key mediators of fibrosis [46]. Studies showed that subcutaneous injection of TGF-β to newborn mice induces angiogenesis and activates fibroblasts [47–49]. Arg-1, a prototypic M2 marker in the mouse, is also a primary wound healing protein transcriptionally induced by the TGF-β family of proteins. Its products include ornithine, a substrate for synthesis of polyamines, and collagen, which helps to promote fibrosis and tissue healing [28]. Additionally, the consumption of L-

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arginine by Arg-1 suppresses T-cell proliferation, which suggests that Arg-1 expressing M2 macrophages indirectly dampen the $CD4^+$ T-cell effector response [50–52].

Macrophage Activation, Polarization, and Memory

It is commonly agreed that macrophage polarization is a tightly controlled process comprising a set of signaling pathways, and transcriptional and posttranscriptional regulation. In response to various environmental cues, macrophages acquire distinct phenotypes and adopt a plethora of polarization states. Therefore, understanding the mechanisms associated with the dynamic changes of macrophage polarization is of great importance.

At the transcriptional level, IRF/STAT signaling plays a central role in modulation of macrophage polarization [53]. When macrophages are stimulated by IFN-γ, JAK-mediated tyrosine phosphorylation is triggered leading to subsequent STAT1 phosphorylation. The phosphorylated STAT1 then moves to the nucleus, binds specific DNA elements, and directs transcription of iNOS, major histocompatibility complex (MHC) II, and IL-12 [54], which are characteristic for M1 macrophage polarization. Studies have revealed that STAT1-deficient mice have severe defects in eradicating intracellular bacterial and viral pathogens. LPS is also a potent stimulant of M1 polarization. It binds to TLRs, especially TLR4, and triggers two subsequent mediators MyD88 and TRIF, thus leading to the activation of nuclear factor kappa B (NF-κB). As a vital transcription factor of M1 activation, NF-κB modulates expression of a great number of inflammatory effectors, such as TNF-α, IL-1β, IL-6, and cyclooxygenase 2 (COX2) [55, 56]. In addition, IRF3 and IRF5 have also been proven to be important mediators of M1 polarization. High expression of IRF5 directly activates transcription of genes encoding the IL-12 subunit p40 (IL-12p40), IL-12p35, and IL-23p19, and represses the gene encoding IL-10 [57••, 58].

Macrophages are driven to the M2 state by IL-4 and IL-13 stimulation. IL-4 and IL-13 bind to the IL-4 receptor α (IL-4Rα) and transduce signals through a JAK-STAT6 pathway [59, 60]. Importantly, STAT6 regulates transcription of many M2 macrophage genes, including genes encoding Arg-1, CD206, resistin-like α (Fizz1), and chitinase 3-like 3 (Chi3l3) [26, 61]. The transcription of M2 macrophages is also regulated by several other transcription factors such as peroxisome proliferator-activated receptor γ (PPARγ) [62, 63] and Kruppel-like factor 4 (KLF-4) [64]. PPARγ is a master regulator of lipid metabolism and directs adipose tissue macrophages to acquire an anti-inflammatory M2-like phenotype. Atherosclerotic lesion studies showed a positive correlation between the expression of M2 markers and PPARγ [63]. In contrast, the PPARγ-deficient macrophages are resistant to M2 polarization and likely to develop insulin resistance.

Epigenetic regulation via chromatin modifications has recently attracted more and more attention in macrophage polarization and led to the hypothesis that epigenetic enzymes serve as a link between the environment, cellular metabolism, and macrophage phenotype [65]. The Jumonji domain-containing-3 (Jmjd3), a histone 3 Lys27 (H3K27) demethylase, promotes M2 polarization and immune responses against helminth infection through IRF4 [66]. In addition, Jmjd3 is essential for M1 responses to LPS stimulation [67, 68]. Histone deacetylase 3 (HDAC3) stimulates M1 activation and at the same time hinders M2

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polarization [69]. Macrophages lacking HDAC3 display a hyper-M2 phenotype and limit *Schistosoma mansoni* egg-induced inflammation [70]. Another interesting finding of epigenetic programming involves ATF7, which mediates LPS-induced epigenetic changes in macrophages. LPS stimulation induces phosphorylation of ATF7, which results in enhanced protection against pathogens. Importantly, the change of ATF7 can be maintained for 3 weeks after priming with LPS, suggesting a memory-like behavior of macrophages [71•]. This finding led to the idea of "trained immunity" in which, due to epigenetic modifications, the initial infection boosts the responsiveness of macrophages to secondary infection [72].

Macrophage in Acute and Chronic Rejection

In solid organ transplantation, the graft infiltrating macrophages originate from two sources: donor resident macrophages transferred to the recipient at the time of surgery and recipient monocytes recruited into the transplanted organ [4]. Initial macrophage accumulation resulting from ischemiareperfusion injury has been detected as early as the first hour post-kidney transplantation [73]. The calprotectin antigen (L1) is present in circulating monocytes and can be used to identify newly recruited macrophages. In an acute kidney rejection model, the percentage of L1 expressing macrophages is dramatically elevated, indicating that recipient-derived monocytes are a crucial source of infiltrating macrophages [74]. Monocytes in the bloodstream are recruited to the transplanted kidney through binding to chemoattractants such as monocyte chemoattractant protein-1 (MCP-1, CCL2) [75], CX3CL1 [76], and macrophage inflammatory protein-1α (MIP-1α) [77]. Subsequently, they infiltrate the graft parenchyma with the help of the platelet endothelial cell adhesion molecule-1 (PECAM-1) and CD99 [78]. These newly infiltrated macrophages propagate through local proliferation, thus amplifying the rejection response [79]. For quite a long time, recipient-derived macrophages have been considered to be more important in organ rejection than donor-derived macrophages. In fact, certain types of resident macrophages are able to persist for a long time and affect the long-term outcome of allograft survival [80]. Resident macrophage persistence depends on their half-life, which varies according to their origin and locations. Fate mapping studies revealed that cardiac macrophages are derived from both the yolk-sac and fetal monocyte progenitors. A disruption of local homeostasis causes influx of monocytes from the blood as well as local expansion of cardiac resident macrophages, indicating that both local proliferation and recruitment contribute to macrophage repopulation in the transplanted organ [81••, 82].

Macrophages in Acute Rejection

Macrophages account for 38–60 % of infiltrating leukocytes in human transplant biopsies and have been implicated in acute rejection of the allografts [2, 83, 84]. Macrophage depletion is proven to mitigate graft injury and decrease inflammation in multiple animal experimental models [84, 85]. Once macrophages infiltrate the allograft, they display a pro-inflammatory phenotype by secreting inflammatory cytokines and directly damage graft tissue. For example, IL-1β, IL-12, IL-18, TNF-α, and IFN-γ produced by macrophages exert a variety of functions including activation of endothelial cells, promotion of cytotoxic T-cell generation, and induction of colony stimulating factor-1 (CSF-1 also M-CSF) and MCP-1 production [86]. On the other hand, infiltrated macrophages are also the primary source of reactive oxygen (ROS) and reactive nitrogen species (RNS). ROS and RNS

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directly damage allograft tissue and subsequently aggravate acute rejection [87–89]. Though the above pro-inflammatory profile fits M1 macrophages, recent studies suggest that M1 may not be the only macrophage subtype acting in acute rejection. In kidney allografts with acute tubular necrosis, increases in M2 macrophage transcripts, including Arg1, Mrc1, Mmp12, and Ear1, parallel deterioration of the transplanted organ [90]. Some studies suggest that these BM2-like^ macrophages derive from M1 macrophages in situ in the grafts [91].

Macrophages in Chronic Rejection

Chronic rejection is a leading cause of allograft failure in clinical transplants. Though the mechanisms of chronic rejection are not fully understood, the main symptoms of chronic rejection are tissue fibrosis and graft vascular disease (GVD, also referred to as vasculopathy) [92]. GVD is manifested by neointima formation and progressive vessel narrowing, which eventually lead to ischemia of the graft [92]. In chronically rejecting allografts, macrophages and $CD4^+$ T cells accumulate around the graft vessels [93]. In human cardiac allograft biopsies, the macrophages outnumber T cells [94, 95]. Post-transplantation treatment with carrageenan depletes 30–80 % of macrophages, leaving the T, B, and NK cell functions intact, and dramatically (by 70 %) reduces GVD, indicating that macrophages play a major role in the development of GVD [96]. Studies from our laboratory showed that tampering with the RhoA pathway affects macrophage actin cytoskeleton, prevents them from entering a transplanted heart, and inhibits chronic rejection of cardiac allografts in a rodent model [97].

It is intriguing regarding what are the subpopulations of infiltrating macrophages in chronically rejecting grafts. In acute rejection, the infiltrating macrophages contribute to tissue injury and amplify T-cell-mediated rejection. In contrast, chronically activated macrophages exert their pro-fibrotic function and promote interstitial fibrosis [98]. The study of macrophage subtypes present in renal allografts showed that 1 year after transplantation, 92 % of infiltrating macrophages exhibited a $CD68^+CD206^+$ M2-like phenotype. In addition, the total number of infiltrating macrophages positively correlated with the degree of fibrosis [99]. Similarly, Ikezumi et al. [91] showed that $CD163^+$ macrophages are the major macrophage population localized in areas of interstitial fibrosis in chronic kidney allograft injury [100]. Another study showed that 6 weeks after cardiac transplantation, the mRNA levels of five M2 markers (Ym1, Fizz1, VEGF, TGF-β, and CD206) were elevated in the interstitium when compared to those markers 2 weeks after transplantation [101].

Though the main function of M2-like macrophages include wound healing, tissue repair, and angiogenesis, which are regarded as beneficial [102], their sustained activity may cause long-term side effects, such as fibrosis and neointima formation in chronic rejection. Blocking the P2×7 receptor (P2×7R), which is preferentially expressed by M2 macrophages, inhibits M2 induction in vitro. Combined usage of P2×7R and CTLA-4Ig after heart transplantation prevents GVD and improves allograft survival, indicating the dominant role of M2-like macrophages in aggravation of chronic rejection [103].

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Despite the fact that M2-like macrophages are persistently detected in chronically rejecting grafts, the development of GVD and induction of vascular damage through the production of eicosanoids, deleterious proteases, ROS, and nitric oxide [104] point to functions typical for M1 macrophages instead. In addition, IFN-γ is both required and sufficient to develop GVD in a cardiac transplant model. IFN-γ stimulation is followed by an elevation of expression of MHC II, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 [105]. The presence of IFN-γ in the allograft also points toward the activity of M1 macrophages.

While M1/M2 differentiation is intriguing, the exact phenotype found in chronically rejecting allograft remains unknown. Because of the heterogeneity of macrophages, it is extremely difficult to identify the phenotypes of macrophages present in allograft. It is also possible that a fraction of macrophages may be undergoing a phenotype switch or that, at a certain point in the development of chronic rejection, macrophages display dual characteristics [106, 107].

Recently, there is evidence that a subset of chronic rejection cases might be mediated by alloantibody [108]. HLA-specific antibody has been detected in blood of transplant patients. Among patients needing cardiac re-transplantation due to late terminal heart graft failure, 47.5 % were diagnosed with antibody-mediated rejection with severe coronary arteriosclerosis [109]. In a large multicenter trial, HLA-specific antibodies were detected in 21 % of renal allografts and 14–23 % of heart, liver, and lung transplants [108]. What is more, 60 % of the very late heart rejection patients had evidence of intravascular macrophage infiltration and the presence of donor-specific antibody (DSA) within the graft [110]. The exact correlation between DSA induction and macrophage infiltration remains unknown. On one hand, complement fixation during antibody-mediated rejection (AMR) can lead to the generation of complement split factors, C5a, a potent chemoattractant for monocyte recruitment, as well as macrophage activation [111]. On the other hand, a study following lung transplantation indicates that 94–100 % of the alveolar macrophages are donor derived, which respond well to anti-HLA framework antibody with secretion of inflammatory cytokines, thus playing an essential role in inducing obliterative disease post-transplantation [80].

Therapeutic Approaches: Challenges and Opportunities

With much attention on macrophages in organ transplantation and their roles in graft injury and chronic graft loss, there is a clear need in developing macrophage-targeted therapies in further improving allograft survival. Strategies for macrophage-centered therapies include macrophage deletion, inhibition of their activation and migration, modulation of macrophage subsets, and promotion of immune regulation in favor of tolerance induction.

One of the major goals in transplantation is the induction of graft tolerance, which would free patients of chronic rejection and of lifelong treatment with immunosuppressive drugs. Therapies that target macrophages should be a key component in such efforts. There is evidence that conditional monocyte and macrophage ablation effectively reduced graft infiltrating macrophages in renal transplants 7 days after transplantation in a murine model [85]. A more practical method to mitigate macrophage infiltration, which has been tested in a range of animal models and in patients, includes usage of antagonist of M-CSFR or M-

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CSF to selectively deplete macrophage and DC subsets [112]. An alternative strategy involves blocking monocyte recruitment by targeting CCR- and CXCR-mediated chemotaxis [113, 114]. Because of the diverse function of macrophages in acute and chronic rejection, manipulation of their activation status may also help to alleviate rejection. Indeed, glucocorticoids, commonly used as immunosuppressive drugs, have been shown to preferentially promote the survival of anti-inflammatory monocytes [115]. Ligation of macrophage Fcγ receptors (FcγR) may also help in redirection of pro-inflammatory macrophages to immunoregula-tory cells through up-regulation of IL-10 [116]. Furthermore, in a heart transplant model, TIM-4hiCD169^{+} tissue resident macrophages that share certain properties with M2 cells home to draining lymph nodes and favor preferential induction of antigen-stimulated Tregs, thus promoting tolerance of cardiac allografts [117]. Recent studies also indicate that tolerance might be achieved by adoptive transfer of regulatory macrophages (Mregs) [118]. Mregs are induced by combined stimulation of M-CSF and IFN-γ, and express markers distinct from M1 and M2 cells. Interestingly, a single dose of Mregs before transplantation significantly prolonged allograft survival in a murine cardiac model [119]. The Mreg-based therapy has been extended to clinical trials now. Two patients who received donor-derived Mregs within 24 weeks of renal transplantation have shown stable renal function 6 years post-transplantation [4, 120]. Those patients are free from acute rejection, signs of subclinical rejection as well as lack of anti-donor reactivity. The immunosuppressive function of Mregs is mainly established through a direct suppression of polyclonal T-cell proliferation and survival, possibly through iNOS-dependent pathway. Additionally, Mregs may secrete anti-inflammatory mediators and help to promote tissue repair. Clearly, these data highlight the promise of macrophage-directed therapies in transplantation.

Conclusion

Emerging data provide strong support that macrophages are key players in the allograft response. Significant macrophage infiltration in the grafts has been linked to poor prognosis. Macrophages are heterogeneous and are able to mold their functions in response to different stimuli in the local environment. M1, or classically activated macrophages, preferentially drive Th1 responses, while M2 or alternatively activated macrophages promote Th2 responses. The balance of M1/M2 cells and their interplay with various populations of innate lymphoid cells in transplantation rejection as well as in long-term graft survival remain poorly understood.

Although significant advances have been made in the past few years in our understanding of the contribution of macrophages to graft outcomes, the mechanisms used by macrophage to promote tissue inflammation, adaptive response, and tissue repair and remodeling, especially in chronic rejection, remain unclear. Further studies are required to better understand the different facets of macrophages and their functions in transplant settings, so that novel therapeutics can be designed to improve transplant outcomes.

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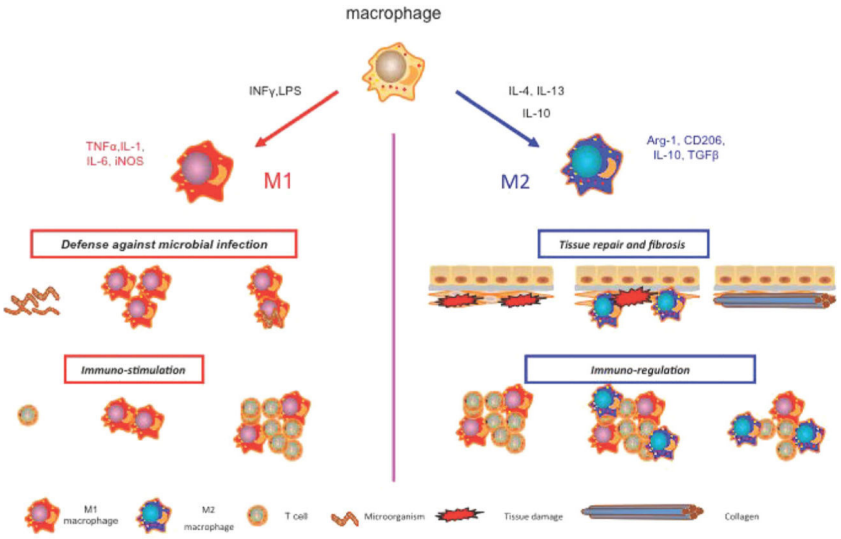

Fig. 1.

Macrophages can be polarized into different subsets with distinct functional attributes. M1 cells are induced by TLR ligands and Th1 cytokines, and exhibit potent pro-inflammatory features; M2 cells develop in the presence of IL-4 and IL-13 (Th2 cytokines), and express regenerative and pro-fibrotic activities. Some M2 cells can be immunosuppressive

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Table 1

Macrophages at different anatomic locations exhibit different phenotypes and functions

Tissue	Cell type	Main Function
Blood	Ly-6C^{lo} monocytes	Patrolling, early responses, tissue repair
Liver	Kupffer cells	Clearance of microorganisms and cell debris from the blood
	Motile liver macrophages	Immune surveillance
Lung	Alveolar macrophages	Immune surveillance of lung inhaled pathogens and clearance of surfactant
	Interstitial macrophages	Regulates DC maturation and activation
Heart	Cardiac macrophages	Pro-inflammation, wound repair, fibrosis
Skin	Langerhans cells	Interaction with T cells
	Dermal macrophages	Immune surveillance
Gut	Intestinal macrophages	Maintenance of intestinal homeostasis
Kidney	Kidney macrophages	Pro-inflammation, wound repair