Evidence has accumulated to support the notion that injury-induced activation of the donor’s and the recipient’s innate immune system largely determines the outcome of organ transplantation. Future potential therapeutic strategies to suppress events of both innate immune systems, as well as approaches to mitigate allograft injury, are discussed with regard to inhibiting both complement activation and dendritic cell maturation, and to blocking innate effector functions. Applications of pharmacological drug therapy as well as gene-specific manipulations are theoretical tools to reach these goals. A variety of encouraging experimental data in this research field are already available and promise further discoveries that ultimately will lead to the design of appropriate clinical trials.

Key words: Immunosuppression, Innate immunity, Organ transplantation

Innate Immunity and Organ Transplantation

In contrast with the specificity of the adaptive immune response, innate immunity is characterized by extreme selectivity and protects an organism against jeopardizing injuries by being able to differentiate between innocuous “self” and potentially noxious substances ranging from “microbial nonself” (which are pathogen-associated molecular patterns [PAMPs]) to “damaged self” (which are damage-associated molecular patterns [DAMPs]). A whole family of cells is involved in the system, including dendritic cells (DCs), natural killer cells, and vascular cells. Via special receptors, such as Toll-like receptors (TLRs), these cells are able to recognize PAMPs in terms of exogenous ligands as well as DAMPs in terms of endogenous ligands [1-4]. After recognizing PAMPs, TLRs initiate intracellular signal transduction pathways that result—via activation of transcription factors such as NFκB, AP-1, and IRF3—in the expression of genes involved in inflammation, antiviral responses, and maturation of DCs [2, 5-9]. Besides innate cells, the mannose-binding lectin (MBL)-dependent complement activation pathway has been identified as a key instrument of innate immunity [10].

As reviewed, innate immune events play a critical role in organ transplantation [1]. Accumulating evidence suggests that not only allograft reperfusion injury but any condition of the donor and the recipient involved with non–antigen-dependent inflammatory pathways may activate the TLR-bearing cells of the innate immune response. Allograft injury leads to TLR-mediated maturation of donor-derived and recipient-derived DCs, which are associated with up-regulation of costimulatory molecules. Together with secretion of proinflammatory mediator substances, these events lead to the development of antigen-specific adaptive alloimmunity. In addition, experimental evidence suggests that TLRs, in particular TLR4, following interaction with DAMPs such as HSP70, appear to trigger the same intracellular signaling pathways as initiated by TLRs following recognition of PAMPs (Figure 1). Notably, postischemic reperfusion injury not only initiates an innate immune response by activating DCs but also through the MBL-dependent activation pathway as well. Additionally, a clonally specific natural IgM activates the classic pathway of the complement system. These events may subsequently contribute to additional tissue injury [11-13] (Figure 2).

Time Periods and Potential Targets for Suppressing Donors’ and Recipients’ Innate Immune Systems

As described elsewhere [3], donor brain death as well as allograft reperfusion injury represent a significant
oxidative injury that leads to DC maturation and up-regulation of a variety of inflammatory mediators [14-16]. Logically, involving the innate immune response of the donor and the recipient implies that any strategy to prevent acute allograft rejection by suppressing innate immune events must include modulation of both systems. The main goal of such treatment is to inhibit the injury-induced, TLR-mediated, and primarily NFκB-controlled maturation process of DCs. This approach is based on the paradigm of tolerogenic/immature, versus inflammatory/mature DCs (which has dominated the recent literature regarding the role of these antigen-presenting cells in mediating immune homeostasis). In fact, immature dendritic cells (iDCs) are prone to induce regulatory T cells and hence, promote tolerance, probably by secreting suppressive cytokines such as IL-10 [1, 17-19]. Notably, modalities in the deceased donor to prevent DC maturation include systemic and/or local intraorgan administration of potential agents, as well as ex vivo/in vitro manipulations, to generate iDCs from the spleen and/or peripheral blood monocytes, followed by transfer to the recipient [20].

In this sense, future immunosuppressive strategies should begin in the donor and continue during organ preservation (eg, via manipulations during ex vivo warm organ perfusion [21]), and end in the recipient perioperatively and postoperatively. Consequently, this kind of therapeutic modality represents a time-limited approach! With regard to designing clinical trials—for example, with the aim of inhibiting NFκB—the transient nature of this treatment is immensely advantageous for the recipient because long-term inhibition of transcription factors is not

**Figure 1.** Oversimplified schematic illustration of intracellular TLR-triggered/mediated signaling pathways leading to DC maturation. Via signal transduction (eg, via involvement of adaptor molecules such as MyD88, TIRAP/Mal, TRIF, and TRAM), the 3 key transcription factors NFκB, AP-1, and IRF3 are activated. Inhibition of DC maturation may be (potentially) achieved by agents such as TLR-blockers and TLR antagonists (monoclonal anti-TLR antibodies, TAK-242, E-5564), inhibitors of signal transduction molecules (eg, TRIF by resveratrol), inhibitors of transcription factors (NFκB by LF15-0195, PDTC, decoy ODNs, and inhibition of AP-1 by MAPK inhibitors). Only those agents mentioned in the text are listed.

AP-1: activator protein-1; DAMPs, damage-associated molecular patterns; DC, dendritic cell; ERK, extracellular signal-regulated protein kinase; IRF3, interferon regulatory factor 3; IKK, IκB kinase; IRAK, Interleukin-1-receptor-associated kinase; JNK, c-Jun-N-terminal protein kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; moAbs, monoclonal antibodies; MyD88, myeloid differentiation marker 88; NFκB, nuclear factor-kappa B; PAMPs, pathogen-associated molecular patterns; PDTC, pyrrolidine dithiocarbamate; TAK1, transforming growth factor-beta (TGFβ)-activated kinase 1; TBA, TAK1-binding protein; TBK1, TANK-binding kinase 1; TLR, Toll-like receptor; TRAF6, TNF-receptor-associated factor 6; TRAM, TRIF-related adaptor molecule; TRIF, TRIF-domain containing adaptor inducing IFN-β.
compatible with life [22].

In the following, “innate” targets of potentially interfering agents are described by distinguishing a) mitigation of ROS-mediated donor organ injury, b) inhibition of complement activation, c) prevention of maturation of donor-derived and recipient-derived DCs, and d) blockade of innate effector functions including cytokine and chemokine secretion and adhesion molecule expression.

Mitigation of ROS-Mediated Allograft Injury
Interventions that reduce the generation or the effects of reactive oxygen species (ROS) are known to exert beneficial effects in a variety of models of shock, inflammation, and postischemic reperfusion injury. Additionally, amelioration of allograft reperfusion injury by the free-radical scavenger superoxide dismutase (SOD) exerts a beneficial effect on both acute and chronic rejection events [23]. As already mentioned (Figure 1), innate immune pathways are characterized by great complexity and probable redundancy. Therefore, with the aim of suppressing them, attempts should focus mainly on bypassing this complexity and redundancy by trying to address the early “upstream” initiating event (namely the allograft injury) rather than the subsequent “downstream” cascading events. This implies, however, that primarily, clinicians keep the oxidative injuries to the donor organ as low as possible. In fact, during the past years, a large list of antioxidative agents has been published. These agents have been proven experimentally and clinically to be effective and safe. Some agents have gained increasing attention, among them edaravone, SOD-mimetics, and cobalt protoporphyrin-induced hemeoxygenase-1 (HO-1).

Edaravone, a synthetic free-radical scavenger, was developed as a neuroprotective agent. The drug is approved in Japan for treatment of acute cerebral infarction. In canine renal autotransplantation, the drug effectively reduces postischemic reperfusion injury, and in mice, it has been shown to significantly prolong the survival time of cardiac allografts [24, 25].

Figure 2. Schematic illustration of the MBL-dependent pathway (“innate lectin pathway”) of complement activation (blue color) as compared with the classic and alternative pathways. The MBL-dependent pathway is activated by pathogens and by reactive oxygen species-mediated reperfusion injury. Injury-induced natural IgM antibodies may also activate complement via the classic pathway (not shown in this schematic illustration). Inhibition of complement activation may be achieved by TP-10 (soluble complement receptor antagonist) and the monoclonal antibody against C5 (pexelizumab). Only those agents mentioned in the text are listed.

MBL, mannose-binding lectin; MASP-1, MBL-associated serine protease 1; MASP-2, MBL-associated serine protease 2; SP-A, surfactant protein A.; IgM-ab, immunoglobulin M antibody.
Another promising antioxidant is M-40403. The drug is a synthetic manganese containing an SOD-mimetic that selectively removes superoxide anions. In experiments in rats, treatment with M-40403 exerts a protective effect against postischemic reperfusion injury [26]. Although first clinical trials with this SOD mimetic so far have failed, the substance remains interesting for treating allograft reperfusion injury.

Cobalt protoporphyrin-induced HO-1 expression can be used therapeutically to ameliorate consequences of ischemia reperfusion injury and has been shown to improve allograft survival. Experiments in rats demonstrate that HO-1 promotes graft protection by reducing graft immunogenicity [27]. Donor treatment with protoporphyrin even may be avoided by adding the substance to a preservation solution as demonstrated by successful induction of HO-1 in canine kidneys during ex vivo warm perfusion [15]. Experiments in mice have revealed that hepatic reperfusion injury represents a case for innate immunity in which HO-1 modulates proinflammatory responses that are triggered via TLR4 signaling, a putative HO-1 repressor [28]. Of special interest is a report that demonstrates the capacity of intracellularly expressed HO-1 to block maturation of DCs, and to inhibit proinflammatory and allogeneic immune responses while preserving IL-10 production [29].

Moreover, following therapy with natural antioxidants (ie, the bioflavonoids quercetin and curcumin), HO-1 induction appears to contribute to improved early outcomes in clinical renal transplantation [30].

Inhibition of the MBL-Dependent Complement Cascade

As mentioned, there is evidence suggesting that reperfusion injury activates the complement system by initiating the lectin pathway as well as the classic pathway using a clonally specific natural IgM. Thus, potential strategies for suppressing innate immune events include attempts to interfere with the classic and lectin-mediated complement activation pathway. Endogenous soluble-complement inhibitors, antibod-
ies, or low-molecular-weight antagonists, which either block key proteins of the cascade reaction or neutralize the action of the complement-derived anaphylatoxins, have been tested in recent years, successfully, in various animal models. Promising results consequently have led to the first clinical trials [31]. Recently, pexelizumab, a novel anti-C5 complement monoclonal antibody fragment that prevents complement-mediated myocardial damage from myocardial ischemia and reperfusion, has been developed. Two large clinical trials, which have shown some clinical benefit, currently are underway in coronary artery bypass surgery and acute myocardial infarction patients undergoing primary percutaneous revascularization [32,33]. In addition, TP-10, a soluble complement–receptor-1 inhibitor, which inhibits the activation of the complement system by inactivating C3a and C5a convertases, has been investigated for its use in reducing ischemia-reperfusion injury in lung transplantation. Data from 1 multicenter control trial of 4 lung transplant programs look promising and show that short-term complement inhibition with TP-10 leads to a significant decrease in the duration of mechanical ventilation [34].

Preventing Maturation of DCs
With regard to donor brain death and various surgical procedures associated with donor organ removal, preservation devices, and implanting the allograft in the recipient, complete prevention of allograft injury as the key event of DC maturation appears illusory. Therefore, other potential modalities to inhibit DC maturation in the course of the “down-stream cascade” must be considered. In principle, methods for manipulating biological systems include applying pharmacological drugs (e.g., monoclonal antibodies or fusion proteins), or decoy-oligodeoxynucleotides, antisense oligodeoxynucleotides, ribozymes, and interfering RNAs. These manipulative applications may be performed either in the donor (including ex vivo/in vitro generation of iDCs), in the donor organ (during ex vivo warm perfusion [21]), or in the recipient. Taking these principles into account, preventing DC maturation may be achieved by interventions directed at membrane receptors and intracellular molecular levels, respectively. They include blockade of Toll-like receptors and inhibition of pathways at the levels of a) signal transduction, b) transcription, and c) translation (Figures 1 and 3).

Blockade of Toll-like receptors: As shown experimentally, a monoclonal antibody against TLR2 and/or the lipid-A–like TLR4-antagonist, E5531, can block TLR-mediated DC maturation [35]. A variety of monoclonal antibodies against TLRs are commercially available for diagnostic purposes including anti-TLR2-, anti-TLR3-, anti-TLR4-, and anti-TLR9-antibodies. In principle, their therapeutic use is feasible. In fact, with the aim of intervening in TLR2-driven toxemia associated with bacterial infection, treatment of mice with a monoclonal antibody against TLR2 inhibits the release of inflammatory mediators such as TNFα and prevents a lethal shocklike syndrome [36]. Clinical use of monoclonal anti-TLR-antibodies may be problematic since TLRs are expressed not only on DCs but also on vascular cells. Therapeutic application of such antibodies, therefore, may be associated with endothelial cell damage leading to thromboembolic complications. However, such a complication may be avoided by using TLR-blocking proteins, or TLR-antagonists. In fact, a novel small molecule, TAK-242, has been shown in in-vitro experiments to suppress production of multiple cytokines by selectively inhibiting TLR4 intracellular signaling [37]. Interestingly, this TLR4 antagonist is currently undergoing clinical trials for the treatment of sepsis [38, 39]. A similar compound, E-5564, a synthetic antagonist of bacterial endotoxin, is also being developed to treat and/or prevent clinical sepsis [40, 41].

Inhibition of signal transduction: Adaptor molecules such as myeloid differentiation marker 88 (MyD88) and TIR-domain containing adaptor inducing IFN-β (TRIF) play a crucial role in signaling transduction cascades leading to the activation of key transcription factors [42]. Recently, resveratrol, a phytoalexin with anti-inflammatory effects, has been shown to inhibit NFκB activation induced by TRIF, but not by MyD88, indicating that this substance specifically inhibits TRIF signaling in the TLR3 and TLR4 pathways [43]. The results raise the possibility that certain dietary phytochemicals may modulate TLR-derived signaling and inflammatory target genes as those that are involved in postischemic reperfusion injury.

Inhibition of transcription: Decoy-oligodeoxynucleotides (ODNs) bearing the consensus binding sequence of a specific transcription factor have been explored as tools for manipulating gene expression in living cells. This strategy involves the intracellular delivery of decoy ODNs, which are then recognized and bound by the target factor.

The methodology has been applied to block forms of NF-κB activity by using a single NF-κB decoy ODN sequence that is identical to the consensus sequence.
of the NF-κB binding site. Experimental studies have shown that LPS-induced DC maturation can be prevented by administering NFκB ODN decoys, and that the maturation of DCs induced by allogeneic T cells is inhibited. The study findings also demonstrate the potential of NFκB ODNs (in addition with transgenic costimulation-blocking molecules) to render DCs capable of promoting long-term organ transplant survival [44]. Suppression of NFκB also has been reported in rat hearts by administering decoy ODNs to the organ in the perfusion solution [45]. The key limiting factor of this methodology for clinical use lies in the subcellular localization of those ODNs, a problem that must be addressed before meaningful data interpretation can be made [46].

In another in vitro study, treatment of iDCs with the antioxidant and NFκB inhibitor pyrrolidine dithiocarbamate (PDTC) led to an arrest in their maturation as reflected by down-regulated major histocompatibility complex antigens and costimulatory molecules, suppressed immunostimulatory cytokines, and an impaired capability to support allogeneic T-cell activation [47].

A recent in vitro study with the 15-deoxyspergualine analogue LF15-0195 showed that DCs treated with this substance before activation failed to express maturation markers. Further data from that study indicated that LF15-0195-induced blockade of NFκB signaling at the level of IkB kinase (IKK) promoted generation of “tolerogenic” DCs that inhibited Th1 polarization and increased Th2 polarization in vitro and in vivo [48]. A recent report extends these results by demonstrating that a short-course treatment with LF15-0195 induces donor-specific tolerance of cardiac allografts in rats and expansion of splenic CD4CD25 regulatory T cells [49].

Besides NFκB, AP-1 (activated by the 3-tiered mitogen-activated protein kinase (MAPK) - cascade) plays a crucial role in establishing effector functions of innate cells [50]. MAPK inhibitors can prevent activation of this transcription factor. Many MAPK inhibitors (p38α, MEK1, and MEK2) have been discovered and experimentally developed; some of them have advanced to clinical trials in patients with autoimmune diseases and malignancies. In particular, discovery of p38alpha and a pyridinylimidazole-based p38alpha inhibitor initiated a huge effort by many companies to develop p38alpha inhibitors (eg, AMG-548, BIRB-796, SCIO-469, and SCIO-323, and VX-702) as potential treatments for inflammatory diseases [51-54]. An orally bioavailable and highly selective inhibitor of p38, RO3201195, has been tested successfully in transplant models and has been selected recently for advancement into phase-I clinical trials [55, 56]. Besides the p38-inhibitors, MEK1- and MEK2- inhibitors as well as the JNK/SAPK- and Raf-1 inhibitors have been developed as inhibitors of AP-1, predominantly in terms of anti-tumor agents. Prominent members of these drug categories are PD98059, PD184352, U0126, RoO92210, L783277, and LLZ16402 as well as SP600125, CEP1347, and Bay43-9006 [57-60].

Inhibition of translation: Besides the strategy of transcriptional gene silencing, which acts to prevent mRNA synthesis, posttranscriptional gene silencing is another approach to gene inactivation that acts to degrade existing mRNA. Ribozymes, antisense oligodeoxynucleotides (antisense ODNs), and RNA interference have been discovered to induce gene silencing by this approach [61] (Figure 3).

Ribozymes are RNA molecules that can catalyze the cleavage and formation of covalent bonds in RNA strands at specific sites. Gene-tailored ribozymes have been designed, produced, and administered to cells to induce specific gene silencing. At present, this technology has advanced so much that many “hammerhead” ribozymes are being used in clinical trials of antiviral therapy [62]. In regard to a strategy to prevent maturation of innate DCs, one interesting study shows that the transcription factor IRF3, involved in innate pathways during reperfusion injury [1], can be down-regulated by a ribozyme targeted to IRF3 mRNA [63].

Antisense technology is the sequence-specific binding of an antisense ODN to a target mRNA, resulting in prevention of gene translation. Use of antisense ODNs as therapeutic agents has generated considerable enthusiasm in the medical community. The last few years have seen a rapid increase in the number of antisense molecules progressing past phase-I, phase-II, and phase-III clinical trials [64,65]. A study showed that antisense ODNs, effectively incorporated by DCs and targeting CD80 or CD86 mRNA, specifically suppressed expression of CD80 or CD86 in DCs and inhibited their capacity to elicit proliferative responses. Injection of these “tolerogenic” DCs significantly prolonged the survival of heart allografts [66]. Similar results have been obtained from a similar experiment showing that antisense ODNs, down-regulating costimulatory molecules, confer diabetes-preventive properties to nonobese diabetic mouse dendritic cells [67].
RNA interference (RNAi) is an endogenous gene-silencing mechanism that involves double-stranded RNA-mediated sequence-specific mRNA degradation. The discovery of this pathway, together with elucidation of the structure and function of short interfering RNA (siRNA) and microRNA (miRNAs)—the effector molecules of RNA interference—has had an enormous impact on experimental biology. siRNA and miRNA are incorporated into an RNA-induced silencing complex and serve as guides for silencing their corresponding target mRNAs based on complementary base-pairing. Since virtually every gene in the human genome contributing to a disease becomes amenable to regulation, there is currently an intense research effort aimed at developing siRNA for therapeutic purposes. Whereas locally administered siRNAs have already entered the first clinical trials, strategies for successful systemic delivery of siRNA are still in a preclinical stage of development. Besides unsolved problems in delivery, another major obstacle for their clinical use as inhibitors of gene expression is the potential induction of inflammatory cytokines and interferon responses. Therefore, the key challenges for further clinical development of siRNAs are largely dependent on development of improved, suitable delivery strategies (eg, targeted nonviral delivery systems) that combine high specificity and efficiency with a low immunostimulatory and tumorigenic potential [68-70]. There is no doubt that RNA interference technology is of high interest to transplant medicine, the goal being to improve allograft function and survival [71]. In my opinion, siRNA strategies will play a dominant role in future trials to suppress innate immune events in organ transplantation. With the aim of inhibiting DC maturation, the master transcription factors NFκB, AP-1, and IRF3, other upstream and/or downstream signaling molecules must be included when selecting targets of siRNA gene silencing (multigene silencing). The feasibility of siRNA gene silencing of NFκB subunits as well as those of TAK1, IKKα, and IKKβ, using siRNAs, already has been demonstrated to result in the generation of Th2-promoting DCs as well as in defining the distinct in vivo roles of TAK1, IKKα, and IKKβ in cytokine-induced activation of the NFκB pathway [72, 73].

Blockade of Innate Effector Functions

Strategies to suppress events at the efferent arm of innate immunity include the use of monoclonal antibodies or fusion proteins against cytokines, chemokines, adhesion molecules, and molecular methods. Pharmacological agents already have been developed to treat certain autoimmune diseases (eg, rheumatoid arthritis, Crohn’s disease) but unfortunately not organ transplantation. Currently, humanized/chimeric monoclonal antibodies and fusion proteins against TNFα (eg, infliximab, adalimumab, and etanercept) are registered and approved for the treatment of certain autoimmune diseases [74-76]. With the aim of suppressing innate immune events in organ transplantation, these agents could be useful to treat (“off-label”) the donor (IV systemically), the allograft during bench surgery (IA locally), and the recipient during allograft reperfusion (IV systemically).

Monoclonal antibodies against the adhesion molecules ICAM-1 (enlimomab) and LFA-1 (efalizumab) have been developed for treating transplant patients; however, they are designed primarily to prevent alloimmune-mediated acute rejection. Data about these antibodies from prospective multicenter trials show no convincing efficacy [77, 78]. Application of these antibodies in higher dosages during surgery—in the donor during organ removal and in the recipient during reperfusion—might lead to better results (as is the case with polyclonal antilymphocytic preparations—they contain antibodies against adhesion molecules) [79].

The first gene-silencing studies aimed at inhibiting innate effector functions have been performed successfully using either antisense ODNs or siRNAs, and this supports their use as potential therapeutics. According to those studies, modified antisense ODNs directed against the cytokine receptor, TNFRI, and the chemokine receptor, CXCR4, inhibit the function of these proinflammatory mediators [80, 81]. ICAM-1 antisense ODNs prevent reperfusion injury to renal isografts; and modified ICAM-1 antisense ODNs inhibit in vitro ICAM-1 mRNA expression and block in vivo postischemic reperfusion injury, allograft rejection, and CsA-induced nephrotoxicity in rats [82,83]. In 1 clinical trial, a beneficial effect of ICAM-1 antisense ODN (ISIS 2302) administered to kidney transplanted patients could be observed [84].

Initial experimental approaches of introducing siRNA to silence chemokine receptors (MIP-2 and CXCR4) [85, 86] as well as adhesion molecules (ICAM-1 and E-selectin) also have proven to be successful [87, 88].

Conclusions

Experimental and clinical evidence has accumulated...
in support of the hypothesis that injury-induced activation of donor and recipient cells belonging to the innate immune response leads to a subsequent adaptive alloimmune response in the recipient, which largely determines the outcome of organ transplantation. It therefore seems to be time to consider potential therapeutic strategies that will suppress events of innate immunity rather than adaptive alloimmunity. In contrast to the need for long-term suppression of alloimmune events (which are associated with long-term toxicity), such strategies apply to a short-term, time-limited therapeutic approach that includes treatment of the donor, the ex vivo preserved allograft, and the recipient. Major targets of such treatment include mitigation of allograft injury, inhibition of injury-induced activation of complement and maturation of DCs, and blockade of innate effector functions. Pharmacological drug therapy, as well as gene-specific treatment modalities applied to the donor and the recipient (eg, ex vivo treatment of DCs and the allograft after removal from the donor) would be the theoretical tools to reach these goals. A variety of promising experimental data in this research field are already available; however, the question remains, What agents will ultimately win the race to become effective and safe treatment modalities in clinical organ transplantation? The design and performance of clinical trials with antioxidative drugs could start tomorrow; siRNAs appear to be extremely attractive for use in clinical trials once the major obstacles (eg, inferior delivery, inflammatory responses) have been solved. In conclusion then, for members of the transplant community, there truly is a treasure of new ideas with which to start experimental and clinical research in the fascinating field of transplantology.

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