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Microvascular injury after lung transplantation

Mark R. Nicolls¹, Joe L. Hsu¹, and Xinguo Jiang¹

¹VA Palo Alto/Stanford University

Abstract

Purpose of review—Airway microvessel injury following transplantation has been implicated in the development of chronic rejection. This review focuses on the most recent developments in the field describing pre-clinical and clinical findings that further implicate the loss of microvascular integrity as an important pathological event in the evolution of irreversible fibrotic remodeling.

Recent findings—When lungs are transplanted, the airways appear vulnerable from the perspective of perfusion. Two vascular systems are lost, the bronchial artery and the lymphatic circulations, and the remaining vasculature in the airways expresses donor antigens susceptible to alloimmune-mediated injury via innate and adaptive immune mechanisms. Pre-clinical studies indicate the importance of HIF-1 α in mediating microvascular repair and that HIF-1 α can be upregulated to bolster endogenous repair.

Summary—Airway microvascular injury is a feature of lung transplantation that limits short-term and long-term organ health. While some problems are attributable to a missing bronchial artery circulation, another significant issue involves alloimmune-mediated injury to transplant airway microvessels. For a variety of reasons, bronchial artery revascularization surgery at the time of transplantation has not been widely adopted, and the current best hope for this era may be new medical approaches that offer protection against immune-mediated vascular injury or that promote microvascular repair.

Keywords

Lung transplantation; microvessel; microvasculature; lymphatics; HIF-1 α

Introduction

A concept that has emerged in the last decade is that alloimmune rejection of blood vessels at the level of the microvasculature can result in regional tissue hypoxia (decreased tissue pO₂) and ischemia (diminished perfusion) [1]. When blood flow to tissues is attenuated for a protracted period, irreversible fibrotic remodeling ensues. In addition to alloimmune injury,

Corresponding Author: Mark R Nicolls, MD, Department of Medicine, Stanford University School of Medicine, VA Palo Alto Health Care System, 3801 Miranda Ave., 111P, Palo Alto, CA 94304, mnicolls@stanford.edu, 650 493-5000 x69289.

Conflicts of Interest: A patent application has been submitted “Microparticle Delivery Systems for HIF-1 Modulators to Prevent Transplant Rejection” 14/653,245. This intellectual property deals with the development of a topical solution that can be used as a way of promoting airway microcirculation. This is briefly alluded to as a possible medical approach to the problem of a compromised airway microcirculation (Jiang et al., Biomaterials 2014).

lung transplants are anatomically compromised from the outset as the bronchial artery circulation is not restored, the lymphatics are severed and neural connections are interrupted. These derangements of organ 'architecture' are being increasingly considered in the quest to optimize transplant health.

The Papworth Hospital Autopsy Study strongly suggested that the dropout of airway microvasculature is an important antecedent event for the development of obliterative bronchiolitis [2, 3]. Our group subsequently demonstrated in a pre-clinical study that alloimmune rejection could cause the total cessation of microvascular blood flow to transplanted airway tissue lasting days [4]. Importantly, the loss of blood flow identified those transplants that could not be rescued by immunotherapy; once perfusion was compromised, transplant airways progressed, inexorably, towards fibrotic remodeling.

The phenomena of microvascular dropout as an important pathological factor for chronic rejection is likely involved in several forms of solid organ and skin transplantation [2, 3, 5-8*]. These findings make microvessel injury and repair an attractive field of study. How a transplant is injured by the immune response is not simply reflected by the infiltration of cells but by the creation of a profoundly altered physiological state. This review is intended to complement other recent reviews and perspectives [1, 9*] by incorporating recent publications in the field into general concepts of microvascular injury after lung transplantation. This paper will discuss a new clinical study of airway hypoxia in lung transplantation, pre-clinical work evaluating innate immunity in vascular injury, a putative role for lymphatic disruption in allograft dysfunction, and the proclivity for *Aspergillus* invasion with microvessel damage. We conclude with a review of new insights into microvascular repair via hypoxia-inducible factors (HIFs).

Review

Airway Hypoxia After Lung Transplantation

In 2010, our group determined that the absence of a bronchial artery circulation following transplantation resulted in relative airway tissue hypoxia [10]. To further address the potential consequences of lower tissue oxygenation of airways, Duke University investigators recently evaluated patients following lung transplantation with endobronchial tissue oximetry and endobronchial biopsies [11]. Patients were evaluated 0, 3 and 30 days following transplantation for airway tissue oxygen saturation and expression of hypoxia-inducible genes. Patients were also monitored for 6 months for the development of large airway complications. Compared to native endobronchial tissues, donor tissue oxygenation was confirmed to be lower, paralleled by a significant up-regulation of hypoxic genes including *VEGFA*, *FLT1*, *VEGFC*, *HMOX1* and *TIE2* 30 days post-transplant. Increased *VEGFA*, *KDR* (*VEGFR2*), and *HMOX1* expression in hypoxic airways was correlated with extensive airway necrosis and central airway stenosis events. The authors of this study reasonably attribute the cause of airway hypoxia, and, by implication, airway pathology to the lack of a restored bronchial artery circulation.

The relative merits of bronchial artery revascularization continue to be discussed [12]. The surgery is feasible but generally requires an en bloc surgical approach wherein both lungs

are sewn in with a single tracheal anastomosis. Such an approach has been deemed cumbersome by some [13] and requires particular procurement techniques as well as special surgical training not readily available at most academic centers. In 2016, it appears unlikely that bronchial artery revascularization will be widely adopted in the near future. By contrast, non-surgical methods for 1.) reducing microvascular injury induced by alloimmune injury and 2.) promoting microvessel repair by recruiting endogenous cell populations are both pragmatic approaches that could be enacted in the next five years.

New Insights About Microvascular Injury After Lung Transplantation

Innate Alloimmune Immunity—In an orthotopic tracheal transplantation pre-clinical model, currently considered ideal for dissecting airway microvascular biology, our group determined that CD4 T cells and antibody-dependent complement activity were independently sufficient to cause microvascular injury [14]. While calcineurin inhibitors and steroids presumably address CD4-mediated injury in transplant recipients, complement-induced injury could be an important cause of vascular pathology and chronic rejection not currently addressed by standard therapy [15]. With this in mind, complement inhibitors will be an increasingly considered therapeutic strategy in transplantation, and randomized trials are already in process [16]. Although complement component 3 (C3) inhibition is known to be vasculoprotective, our group noted a paradoxical finding in C3-deficient mice which exhibited enhanced early microvascular injury during rejection [14]. In the genetic absence of C3, thrombin-mediated complement component 5 (C5) convertase activity leads to the generation of C5a, also known as anaphylatoxin, a substance that increases vascular permeability and vasodilation [17]. We recently demonstrated that microvessel thrombin deposition is significantly increased in C3 deficient recipients during acute rejection [18]. Thrombin colocalization within airway allograft microvessels was closely associated with significantly increased plasma levels of C5a, vasodilation and vascular permeability. NOX-D19, a so-called Spiegelmer (a protein-binding RNA oligonucleotide), is a C5a inhibitor that significantly improved tissue oxygenation, limited microvascular leakiness and prevented airway ischemia in C3-deficient transplant recipients. Thus, as complement inhibitors enter lung transplant clinics, the simultaneous targeting of C3 and C5a may be particularly effective for preventing microvascular injury.

As a central player in the innate immune response, neutrophils have long been known to be associated with lung transplant injury. Their accumulation in airway walls in bronchoalveolar fluid is associated with the development of obliterative bronchiolitis [19-21]. Our group recently noted that cyclosporine monotherapy does not protect microvessels against injury during acute rejection and airway allograft experience sustained ischemia [22**]. To target neutrophil action as a potential cause of microvascular injury, we examined the effects of the neutrophil elastase inhibitor, elafin, in mice undergoing orthotopic tracheal transplantation. While elafin monotherapy was similarly ineffective in preserving microvascular integrity, elafin combined with cyclosporine synergized to maintain graft perfusion during acute rejection. Elafin reduced both macrophage and neutrophil infiltration, and diminished allograft C3 and membrane attack complex (C5b-9) deposition. This study builds on the concept that the coordinated targeting of adaptive and innate immunity can preserve microvascular function.

Activated platelets are a less-considered innate immune factor causing microvascular injury observed in transplanted organs. Ensminger and colleagues recently reported that platelet inhibition by clopidogrel improved the histology of murine orthotopic tracheal transplants [23] with less luminal fibrosis and inflammation with T cells and macrophages. Platelet inhibition resulted in significantly less IL-12, IL-4, IL-6, TNF- α , TGF- β , PDGF β , MCP1, P-/E-selectin, ICAM1 and CD40L. In keeping with the theme of synergy between simultaneous targeting of innate and adaptive immunity discussed above, clopidogrel synergized with both everolimus (target of rapamycin (TOR) inhibitor) and tacrolimus (calcineurin inhibitor) to produce better effects than monotherapy with either of these agents. Whether the efficacy of clopidogrel was linked to preserving microvascular flow, as it does in arteriosclerosis, was not tested in this study but remains an intriguing possibility. In summary, platelets, neutrophils and complement are three emerging innate immunity components amenable to therapy that appear to play roles in microvascular injury after lung transplantation. As with all aspects of immune modulation, safely moving forward with combination therapies requires a careful risk/benefit assessment. Over-immunosuppression carries grave risks, but if targeted innate immune therapies are limited to the periods of highest risk, such as during acute rejection episodes, it is possible that microvascular injury could be better controlled and chronic rejection avoided with medical therapy.

Lymphatics—In the fall of 2015, the NIH convened an international meeting in Bethesda entitled “The Third Circulation: Lymphatics as Regulators in Health and Disease Symposium.” The gathering reflected an emerging interest in this understudied microvascular system. One topic was the role of the lymphatics in lung transplantation; the severed lymphatic circulation is not restored at the time of organ implantation due to technical challenges. It is clear from basic science studies that the absence of normal lymphatic circulation can favor transplant acceptance [24], but the resulting ‘immunological ignorance’ of the transplant as a primary mechanism of graft acceptance is likely to be much less robust than dominant transplantation tolerance (because ignorance would be hard to be maintained indefinitely). The prevailing view has been that the lymphatic circulation is primarily harmful to allografts [25, 26]. By distinction, a recent study from El-Chemaly et al. [27**] highlights a potentially positive role for improved lymphatic flow in lung transplantation. In rejecting mouse orthotopic lung transplants, the Harvard team showed a marked decline in lymphatic vessel density in association with increased low-molecular weight hyaluronan, a pro-inflammatory molecule normally cleared by the lymphatics and associated with chronic rejection [28*]. Stimulating lymphangiogenesis with a VEGF-C analogue alleviated established rejection responses and improved hyaluronan clearance. In clinical specimens of resolving acute rejection in human lung transplant tissue, a similar reduction in hyaluronan was observed. Taken together, these results suggested that lymphatic vessel formation after lung transplantation mediates hyaluronan drainage and suggests that treatments which promote lymphangiogenesis have promise for improving graft outcomes. Clearly, the lymphatic microcirculation may have both damaging and salutary effects depending on the clinical context; promotion of lymphangiogenesis with simultaneous reduction of immunologic ‘danger’ signals [29] may ultimately promote a transplant organ's long-term health.

Aspergillus—One, perhaps unsurprising, consequence of having regional airway tissue ischemia is that host defenses are weakened against pathogens in those compromised areas. *Aspergillus* is a particularly serious airway complication focused on the anatomically-deranged anastomosis site. Our group postulated that regional tissue ischemia was directly related to the capacity for this fungal organism to invade tissue. To this end, we utilized a novel orthotopic tracheal transplant model of *Aspergillus* infection in which it was possible to determine the effects of tissue hypoxia and ischemia on airway infectivity. There was high efficacy for producing a localized fungal tracheal infection which was especially pronounced at the anastomotic site. Importantly, *Aspergillus* invasiveness directly correlated with the degree of regional graft hypoxia and ischemia (again, being most observed at the anastomosis site). On a historical side note, it should be noted that anastomotic ischemia and dehiscence plagued the early clinical lung transplant experience in the 1980s, complications attributed to the sacrifice of the bronchial artery circulation. Early attempts to mitigate this included a number of techniques including wrapping the anastomoses in omentum [30] which did not improve outcomes; however the introduction of the a variety of strategies including better preservation, improved distribution of flush solution, optimization of donor bronchial length (further enhanced by a telescoping anastomosis) and other modifications obviated the immediate need for other surgical approaches to improve airway perfusion [31]. Notwithstanding these improvements, the airway anastomosis remains vulnerable to ischemic injury. As will be discussed in the next section, non-surgical approaches which improve microvascular integrity at the anastomosis and throughout the transplant airways are promising avenues for future clinical interventions that may not only limit airway complications post-operatively but also prevent chronic rejection.

HIF-1 α and Endogenous Mechanisms of Microvascular Repair

A pre-clinical study written by our group in 2007 [4] demonstrated that the loss of a functional airway microcirculation due to acute rejection identified allografts that could no longer be rescued with immunotherapy. These airways were destined to undergo fibrotic remodeling exhibiting profound airway tissue hypoxia (8mm Hg pO₂) observed in conjunction with absent regional blood flow for days. Given these studies, a follow up 2011 study investigated HIF-1 α , the so-called master-regulator of hypoxic responses, to determine what role this gene played in the normal repair of injured airway microvessels [32]. In this orthotopic tracheal transplant study, HIF-1 α was demonstrated to be a key mediator airway microvascular repair. Grafts with a conditional knockout of *Hif1a* revealed diminished recruitment of recipient-derived Tie2⁺ angiogenic cells to the allograft, poor repair of damaged microvasculature, hastened loss of microvascular perfusion, and accelerated denudation of epithelial cells. By contrast, increasing graft HIF-1 α expression extended airway microvascular perfusion, preserved epithelial integrity, extended the time window for the graft to be rescued from chronic rejection, and limited chronic rejection. HIF-1 α overexpression induced proangiogenic factors such as Vegf, Sdf1, and Plgf, and promoted the recruitment of Tie2⁺ cells which became incorporated into injured blood vessels. These studies set the stage to further investigate the role of HIFs as an important focus for microvascular repair.

We next explored the role of the von Hippel–Lindau protein (VHL) which controls protein levels of hypoxia-inducible factors (HIFs) to see how it affects vascular repair and tissue perfusion in transplant airways [33]. This study specifically evaluated VHL haploinsufficiency in Tie2 lineage cells in order to evaluate genetically-upregulated HIF in vascular endothelial cells; lower VHL production in cells leads to higher HIF-1 and HIF-2 levels. Recipient with endothelial VHL haploinsufficiency appeared to promote donor airway microvascular perfusion in association with increased angiogenic factors, SDF-1 and angiopoietin 1. *In vitro*, VHL-haploinsufficient pulmonary endothelial cells were more angiogenic and resistant to serum deprivation-induced cell death. In recipients with HIF-1 α deficiency in Tie2 lineage cells, the process of microvascular repair was impaired and suggested a strong role for recipient-derived HIF-1 α in the repair of injured donor tissues. As described above, *Aspergillus fumigatus* has a proclivity for invading ischemic airway tissue, and we determined that the genetic upregulation of HIFs limited the invasiveness of this pathogen. By promoting microvascular integrity and also mitigating the virulence of *Aspergillus*, the genetic enhancement of HIF-1 α was suggesting that medical approaches enhancing this pathway might be clinically helpful in lung transplant patients.

As genetic manipulation of HIFs is not yet a feasible approach, we sought a safer approach for upregulating this pathway *in vivo*. To this end, we next utilized deferoxamine mesylate (DFO) is an FDA-approved iron chelator which has been shown to upregulate cellular HIF-1 α [34*]. We developed a nanoparticle formulation of DFO that was topically applied to airway transplants at the time of surgery and showed that the DFO solution promoted airway microvessel repair following transplantation; augmentation of vascular function was associated with the production of SDF-1 and placental growth factor (PLGF). DFO-treated airways featured endothelial cells with higher levels of p-eNOS and Ki67, decreased apoptosis, and attenuated perivascular reactive oxygen species. DFO nanoparticles were also able to effectively penetrate the pig and human airways. This study showed the feasibility of using a topically-applied solution at the time of surgery to promote airway anastomotic microvascular repair perhaps by enhancing the fusion of donor and recipient microcirculations at the anastomosis site. This approach also indicates a potential role for disseminated or inhaled delivery of selected iron chelators during acute rejection episodes (outside of the peri-transplant period) to repair alloimmune-injured microvasculature.

Conclusion

In 2016, five year lung transplant survival rates are still below 60%, and more needs to be done to limit currently-unaddressed destructive pathways; vascular health of lung transplant airways is a compelling target for a new therapy. Recent studies show that current surgical approaches lead to relatively hypoxic airways that remain susceptible to complications. Promotion of lymphatic and microvascular health may be feasible approaches to promote lung transplant health in the immediate post-operative period as well as for the extended life of the patient.

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* of special interest

** of outstanding interest

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Key Points

- Microvascular injury may be an important cause of chronic rejection in lung transplantation.
- Lung transplants function without surgically-restored bronchial artery and lymphatic circulations; two anatomic derangements which could have an influence on the long-term health of the organ.
- Medical approaches to compromised microcirculations may enhance long-term transplant health.