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Environmental Exposures – The Missing Link in Immune Responses After Transplantation

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Abstract

In transplantation, immunosuppression has been directed at controlling acute responses, but treatment of chronic rejection has been ineffective. It is possible that factors that have previously been unaccounted for, such as exposure to inhaled pollution, ultraviolet light, or loss of the normal equilibrium between the gut immune system and the outside environment may be responsible for shifting immune responses to an effector/inflammatory phenotype, which leads to loss of self-tolerance and graft acceptance, and a shift towards autoimmunity and chronic rejection. Cells of the immune system are in a constant balance of effector response, regulation, and quiescence. Endogenous and exogenous signals can shift this balance through the aryl hydrocarbon receptor, which serves as a thermostat to modulate the response one way or the other, both at mucosal surfaces of interface organs to the outside environment, and in the internal milieu. Better understanding of this balance will identify a target for maintenance of self-tolerance and continued graft acceptance in patients who have achieved a “steady state” after transplantation.

The immune system is tasked with protection from external threats including bacteria, fungi, and viruses; internally-derived pathology including tumors; and aiding in tissue repair after injury and inflammation. It is crucial that the immune response is commensurate with the threat to the organism; it must be able to respond rapidly, upregulating the number of cells and cytokines involved until the threat has dissipated, while at the same time suppressing this response when the acute phase has resolved. In addition it must minimize the collateral damage to surrounding tissue. If the response is inadequate, the host will succumb to the infection or tumor. Furthermore, if the response is not properly regulated, autoimmunity or massive inflammation will ensue. The immune system as we know it has evolved, beginning with an innate system that allows rapid, non-specific responses to invading pathogens. This is the system used by plants and other primitive organisms. Vertebrates have added the acquired (or adaptive) immune system, which provides specificity, memory, and the ability of the host to acquire responses to invading pathogens over time (1). These two systems are not entirely independent and signals between them are crucial for appropriate immune function.

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In transplant immunology, the role of the acquired immune system has been the primary focus over the last 50 years, although more recently the importance of the innate immune system has been recognized (2). The majority of maintenance immunosuppression and induction therapy has specifically targeted cells and cytokines of the acquired system. This has allowed excellent early results after organ transplantation, with many organs achieving one-year survival rates well above 90%, and half-lives greater than 10 years. Despite that, treatment strategies for chronic rejection remain inadequate, which has brought into question our basic understanding of the mechanisms that account for this phenomenon (3). Improved treatment of acute rejection has not minimized chronic rejection. Lung transplants have particularly poor long-term survivals, despite similar one-year outcomes when compared to other solid organ transplants. As much as 50% of lung transplants are lost due to bronchiolitis obliterans syndrome (BOS) at 5 years (4). BOS remains a poorly understood entity, with few successful treatment modalities other than retransplantation. Although termed chronic rejection, the pathogenesis of BOS appears to be more like an autoimmune disease than the chronic immune damage seen in other organs (5). Recently the term chronic lung allograft dysfunction (CLAD) has been introduced to describe chronic allograft dysfunction, and obstructive CLAD refers specifically to BOS. BOS will be used in this review.

BOS as a Model for Chronic Rejection

This lack of improvement in chronic rejection rates for organs, combined with the knowledge that some recipients will do fine after organ transplantation and suddenly present with chronic rejection years after their transplant has led to the hypothesis that some previously unrecognized mechanisms may be playing a role in long-term immune responses in our patients. Given that lung transplant recipients have such disparate outcomes from other organs, BOS can be used as a model to understand what this unrecognized pathway might be. Chronic rejection of lung transplants has been shown to be dependent on the generation of IL-17 in many animal models (6, 7), and a role for this inflammatory cytokine is well accepted in human BOS as well (8, 9). While not as well recognized in the pathogenesis of rejection of other organs, many studies do identify the presence of IL-17 in rejecting grafts (hearts, kidneys, livers) in animals and humans (10-12). Another feature of chronic rejection in lung transplants is that the process resembles autoimmunity more than an alloimmune response (5, 9). More specifically, acute rejection episodes are associated with alloimmune responses against foreign MHC or other proteins, but chronic rejection is accompanied by a CD4⁺ T cell response to collagen V, a connective tissue self-protein found in normal lung, along with the requirement of IL-17, a cytokine known to be important in most autoimmune diseases (9, 13). Autoimmune response to self-proteins has also been demonstrated in chronic rejection of other organs, including hearts, kidneys, and livers (14-17). Of note, some of these patients had existing autoimmune responses prior to transplant, which may also put a recipient at risk for chronic rejection. This idea that chronic rejection may be partially due to a loss of tolerance to self-proteins would explain its progressive nature and failure of most of our standard treatments to reverse this process. There could be numerous causes for this loss of tolerance, including exposed antigens from

tissue injury at the time of transplant in the setting of an alloimmune response, or a direct immunomodulatory process that disrupts the normal Treg/Teffector cell balance.

It is notable that many features of BOS are present in native lung disease. Given that inhaled pollution is a major risk factor for native lung disease as well as autoimmunity (18), our laboratory and others began to consider the possibility that exposure to atmospheric pollution is a risk factor for development of BOS. In 2011, a group in Belgium found that lung transplant recipients who lived near major roads were greater than 2 times more likely to develop BOS, compared to those who lived farther away, and displayed inflammatory cytokines in bronchoalveolar lavages. For each 10-fold increase in distance from major roads, hazard ratios and mortality went down for these patients (19). These findings have since been replicated (20, 21).

The Aryl Hydrocarbon Receptor (AHR) and the Immune Response

Although it is known that inhaled pollution can aggravate airway and systemic autoimmune disease, the mechanism for this has not been defined. One possibility includes a role for the AHR. The AHR is a cytosolic receptor first characterized as the receptor for the toxin 2,3,7,8-tetrachlorobenzodioxin (TCDD). Ligands cross the cell-membrane where they bind to the AHR in the cytosol, causing it to travel to the nucleus where it associates with response elements and becomes a transcription factor for various proteins, including cytochrome P450 enzymes (figure 1) (22). Because of its ability to bind to various pollutants in the environment, including polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs) and dioxins, the AHR has traditionally been studied by toxicologists. But its importance in environmental toxicology likely evolved, given that the AHR has been conserved since long before man-made pollutants existed. There are examples of invertebrate organisms that have conserved AHRs that do not bind TCDD and AHR null mice have a physiologic phenotype (patent ductus venosus to the liver), supporting its role in development (23). More recently, a role for this receptor in the immune system has been identified. In 2008 it was reported that certain ligands of the AHR could enhance the differentiation of T cells into regulatory T cells (Tregs), while other ligands of this same receptor enhanced differentiation of Th17 cells (24, 25). This was true both *in vivo* and *in vitro*, and these same ligands could either ameliorate or aggravate models of experimental autoimmune encephalomyelitis (EAE) through this effect on T cell differentiation. We extended this finding to a transplant model, where we were able to either prolong or shorten survival of fully mismatched skin grafts in mice depending on which ligands were injected intraperitoneally (IP) (26). Another study documented the ability of ligands to prolong islet cell transplants in mice (27). This concept that a single receptor could lead to opposite outcomes in T cell differentiation depending on the ligand is truly unprecedented, and numerous high impact reports followed further substantiating this in various murine models (28-31). Over time it has become less clear that specific ligands are “regulatory” while others are “effector”, but instead it seems to depend more on the organ in question, inflammatory milieu, route of ligand exposure, and model being studied (32).

The AHR as a Sensor for the Immune System

Given that the AHR is a receptor that responds to environmental toxins and pollution and that it modulates responses of the acquired immune system, our lab has focused on the concept that the AHR has evolved to serve as a sensor to the environment, facilitating communication with the immune system when a potentially harmful exposure is present in the outside world. In the setting of a toxic exposure, this allows activation of the immune system, causing influx of inflammatory cells and cytokines to protect the organism from localized damage and translocation of endogenous bacteria at the site of the exposure. This is particularly relevant at interface organs, such as the lung, gut, and skin (figure 2A). In the lung, the AHR is activated by inhaled ligands found in atmospheric pollution. In the gut, ligands found both in the diet and as products of the microbiome activate this receptor. In the skin, exposure to ultraviolet light leads to breakdown of tryptophan into a strong AHR ligand (6-formylindolo (3,2-b)carbazole, FICZ) that activates the AHR. All of these interactions have an effect on the local inflammatory state and the presence of immune cells and cytokines found at these interfaces. Additionally, the AHR is intimately associated with the cytokine IL-22 (33); this unique cytokine is secreted by immune cells, but acts on surrounding epithelial cells. In general it is a protective cytokine that improves tight junctions and causes epithelial regeneration. Interestingly, the AHR is required for the production of IL-22 in the overwhelming majority of cases (33, 34) and virtually all ligands we have tested upregulate this cytokine. This further supports the concept that the AHR serves as a sensor to protect the organism in response to a toxic exposure.

The AHR and Chronic Rejection

Given that IL-17 plays an integral role in BOS after lung transplant and that patients exposed to atmospheric pollution are at higher risk for BOS, we hypothesize that chronic exposure to particulate matter (PM) in lung transplant recipients can repeatedly activate the AHR and lead to a deviation of naïve T cells towards Th17 cells and thereby increase the risk of BOS (figure 2B). If this is true, then with every breath a lung transplant recipient takes there would be exposure of the graft immune cells to pollutants and potential immunomodulation. We have characterized components of PM that could be responsible for Th17 deviation in our patients. We recently identified that PAHs represent an ideal candidate for this effect. They are found ubiquitously in PM and are well-defined ligands of the AHR. Samples of PM and PAHs alone were able to enhance Th17 differentiation *in vitro*, dependent on the presence of the AHR (35). Similarly *in vivo*, IL-17 levels in BALs were elevated in mice that inhaled PM samples for a two week period. While we continue to study whether these effects can lead to BOS or similar pathology in a more relevant lung transplant model, we and others have seen aggravation of airway disease after inhalation of PM, leading to physiologic consequences and airway fibrosis.

The AHR and Peripheral/Self Tolerance

The AHR also binds to endogenous ligands present in normal human physiology. Given the ability of ligands of the AHR to enhance Treg differentiation, and the knowledge that tryptophan breakdown products are often ligands of the AHR, we examined whether

metabolites of the enzyme indoleamine 2,3 deoxygenase (IDO) could be relevant ligands. IDO, the rate limiting enzyme for tryptophan metabolism, leads to the generation of kynurenine, a physiologically important protein. IDO is generated by plasmacytoid dendritic cells (pDCs), and is known to be important in pDC-dependent Treg generation (36, 37). We identified that ligands of the AHR lead to the production of IDO by pDCs, and furthermore, kynurenine binds to the AHR on T cells and enhances Treg generation (29). In addition we showed that optimal Treg generation in response to kynurenine or TGF- β also depends on the presence of the AHR. Whether activation of the AHR is required for the achievement of peripheral tolerance in animal models or in humans remains unclear, although it is likely that protocols focused on generating Tregs *ex-vivo* do require the AHR for maximum effect. Kynurenine or other related tryptophan metabolites could also be considered in strategies for maximizing Treg generation or function in both *ex vivo* or *in vivo* peripheral tolerance protocols. In addition, these data further support a role for the AHR in both the maintenance and loss of self-tolerance that could be a mechanism in chronic rejection of a graft. In the steady state after graft “acceptance”, patients on maintenance immunosuppression enjoy stable function and a suppressed immune response to their grafts, which likely includes a role for peripheral Tregs as well as chronic immunosuppressive medications. But over time, if systemic or local AHR activation shifts from the endogenous IDO-dependent regulatory phenotype to the more inflammatory pollution-induced response, a Th17 deviation ensues that leads to chronic graft rejection. Interrogation of this axis may provide a new target for immunomodulation and prevention of graft rejection.

The Role of the AHR in Mucosal Immune Systems

One interesting area of immunity that has grown in attention is the mucosal immune system. At least some of the interest in this has arisen from the recognition of the role of the microbiome and its interaction with cells of the gut, but mucosal immune systems exist in all of the interface organs exposed to the outside environment, including the gut, lung, and skin. Each of these interface organs has a collection of cells that maintain synergy with potentially pathological exposures from the outside, including bacteria and toxins. Interestingly, in both the gut and the skin, the AHR plays an important role in the presence and maintenance of these cells, and it is their responses that help determine the inflammatory state both locally and systemically (figure 3). The importance of the AHR in mucosal immunity is best defined in the gut. Multiple recent studies have defined the necessity for the presence of the AHR and its continued stimulation in the maintenance of the gut immune system (38-41). Specifically, innate lymphoid cells found in the lamina propria (ILC3s, Tregs) and intraepithelial cells (primarily $\gamma\delta$ T cells) in the GI tract in mice are dependent on ligands of the AHR in the diet for their presence. Mice placed on diet devoid of ligands are deficient in these cell types and at risk for bacterial overgrowth and susceptible to pathology in various colitis models. AHR null mice have less IELs in the gut, and when bone marrow from wild-type mice is adoptively transferred to AHR-null Rag mice, these cells are repopulated (but not when AHR-null mice are used as donors) (39). In addition, various bacteria in the microbiome generate ligands of the AHR from tryptophan metabolism that are necessary to maintain a healthy gut mucosa and prevent bacterial and fungal overgrowth and pathological inflammation (42). Gut immune cells, serving as sentinels to the outside environment, have

not been examined for their potential role in organ rejection, a topic we are actively studying. However, these cells have great importance in maintaining the integrity of the interface with the microbiome, preventing translocation, coordinating immune responses locally, and play a role in systemic immunity and the balance of systemic regulation and effector response. Furthermore, loss of these immune cells can lead to an inflammatory phenotype (39). In a transplant recipient, changes in diet, health of the gut, or alteration in the microbiome could alter the sentinel cell population in the gut, leading to both a local and systemic inflammatory phenotype, along with sub-clinical translocation accompanied by a chronic immune response. Over time this could throw off the balance of immune “tolerance” that the patient might be in, and stimulate rejection in a patient that was otherwise doing well. Simple supplementation of safe AHR ligands (already found in cruciferous vegetables and many regular diets) could have benefit in terms of maintaining a healthy gut immune interface, and is an area we are actively studying. Other investigators are examining the role of the gut microbiome on transplant outcomes (43, 44), and understanding of the interactions between the gut microbiome and the inflammatory state of transplant recipients, and changes that occur after transplantation, will be a very important area for research and intervention for our patients. Similar findings regarding gut immune cells have been replicated in the skin, where IELs are dependent on the presence of the AHR for both homing and survival (39). Unlike the gut, the skin responds to bacteria present on its surface, but also to UV light. As mentioned previously, UV light metabolizes tryptophan in the skin into FICZ, a well-characterized ligand of the AHR. Conceptually this is another scenario where a sensor to a potentially toxic exposure like UV light that can activate the immune system may be beneficial, to limit translocation of endogenous bacteria present on the skin after UV-related damage and help repair disruption of cells with IL-22. Over time, however, significant UV exposure could lead to an inflammatory phenotype that could play a role in rejection of an otherwise stable graft.

The field of organ transplantation has made great progress in early graft outcome and treatment of acute rejection. Future gains in long term survival will require a better understanding of what factors cause shifts in the inflammatory state of recipients that can lead to organ pathology and graft loss despite long periods of graft acceptance. Many of the features of chronic rejection of grafts resemble autoimmunity. Over time, exposures to inflammatory signals through inhalation of pollution, proteins in the diet, and exposure to UV light may be shifting the systemic response from one of self-tolerance and graft acceptance to an inflammatory response, leading to graft loss. Better understanding of this will allow new targets for intervention to prolong graft acceptance.

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Abbreviations

BOS bronchiolitis obliterans syndrome

CLAD	chronic lung allograft dysfunction
AHR	aryl hydrocarbon receptor
TCDD	2,3,7,8-tetrachlorobenzodioxin
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
EAE	experimental autoimmune encephalomyelitis
FICZ	6-formylindolo (3,2-b)carbazole
PM	particulate matter
IDO	indoleamine 2,3 deoxygenase
ILC3	group 3 innate lymphoid cells
IEL	intraepithelial lymphocytes

References

1. Flajnik MF, Kasahara M. Origin and evolution of the adaptive immune system: genetic events and selective pressures. *Nature reviews Genetics*. 2010; 11(1):47–59.
2. Solhjoui Z, Athar H, Xu Q, Abdi R. Emerging therapies targeting intra-organ inflammation in transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2015; 15(2):305–11.
3. Lodhi SA, Lamb KE, Meier-Kriesche HU. Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2011; 11(6):1226–35.
4. Hayes D Jr. A review of bronchiolitis obliterans syndrome and therapeutic strategies. *J Cardiothorac Surg*. 2011; 6:92. [PubMed: 21767391]
5. Weber DJ, Wilkes DS. The role of autoimmunity in obliterative bronchiolitis after lung transplantation. *American journal of physiology Lung cellular and molecular physiology*. 2013; 304(5):L307–11. [PubMed: 23262227]
6. Fan L, Benson HL, Vittal R, Mickler EA, Presson R, Fisher AJ, et al. Neutralizing IL-17 Prevents Obliterative Bronchiolitis in Murine Orthotopic Lung Transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2011; 11(5):911–22.
7. Basha HI, Ramachandran S, Tiriveedhi V, Takenaka M, Subramanian V, Nath DS, et al. Critical Role for IL-17A/F in the Immunopathogenesis of Obliterative Airway Disease Induced by Anti-MHC I Antibodies. *Transplantation*. 2013; 95(2):293–300. [PubMed: 23325004]
8. Vanaudenaerde BM, De Vleschauer SI, Vos R, Meyts I, Bullens DM, Reynders V, et al. The role of the IL23/IL17 axis in bronchiolitis obliterans syndrome after lung transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2008; 8(9):1911–20.
9. Burlingham WJ, Love RB, Jankowska-Gan E, Haynes LD, Xu Q, Bobadilla JL, et al. IL-17-dependent cellular immunity to collagen type V predisposes to obliterative bronchiolitis in human lung transplants. *The Journal of clinical investigation*. 2007; 117(11):3498–506. [PubMed: 17965778]
10. Matignon M, Aissat A, Canoui-Poitaine F, Grondin C, Pilon C, Desvaux D, et al. Th-17 Alloimmune Responses in Renal Allograft Biopsies From Recipients of Kidney Transplants Using Extended Criteria Donors During Acute T Cell-Mediated Rejection. *American journal of*

transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015; 15(10):2718–25.

11. Millan O, Rafael-Valdivia L, San Segundo D, Boix F, Castro-Panete MJ, Lopez-Hoyos M, et al. Should IFN-gamma, IL-17 and IL-2 be considered predictive biomarkers of acute rejection in liver and kidney transplant? Results of a multicentric study. *Clinical immunology*. 2014; 154(2):141–54. [PubMed: 25088788]
12. van Besouw NM, Caliskan K, Peeters AM, Klepper M, Dieterich M, Maat LP, et al. Interleukin-17-producing CD4(+) cells home to the graft early after human heart transplantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2015; 34(7):933–40.
13. Bharat A, Fields RC, Steward N, Trulock EP, Patterson GA, Mohanakumar T. CD4+25+ regulatory T cells limit Th1-autoimmunity by inducing IL-10 producing T cells following human lung transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2006; 6(8):1799–808.
14. Dinavahi R, George A, Tretin A, Akalin E, Ames S, Bromberg JS, et al. Antibodies reactive to non-HLA antigens in transplant glomerulopathy. *Journal of the American Society of Nephrology : JASN*. 2011; 22(6):1168–78. [PubMed: 21566057]
15. Kalache S, Dinavahi R, Pinney S, Mehrotra A, Cunningham MW, Heeger PS. Anticardiac myosin immunity and chronic allograft vasculopathy in heart transplant recipients. *Journal of immunology*. 2011; 187(2):1023–30.
16. Dubel L, Farges O, Johanet C, Sebah M, Bismuth H. High incidence of antitissue antibodies in patients experiencing chronic liver allograft rejection. *Transplantation*. 1998; 65(8):1072–5. [PubMed: 9583868]
17. Porcheray F, DeVito J, Yeap BY, Xue L, Dargon I, Paine R, et al. Chronic humoral rejection of human kidney allografts associates with broad autoantibody responses. *Transplantation*. 2010; 89(10):1239–46. [PubMed: 20445487]
18. Ritz SA. Air pollution as a potential contributor to the ‘epidemic’ of autoimmune disease. *Medical hypotheses*. 2010; 74(1):110–7. [PubMed: 19665849]
19. Nawrot TS, Vos R, Jacobs L, Verleden SE, Wauters S, Mertens V, et al. The impact of traffic air pollution on bronchiolitis obliterans syndrome and mortality after lung transplantation. *Thorax*. 2011; 66(9):748–54. [PubMed: 21429899]
20. Verleden SE, Scheers H, Nawrot TS, Vos R, Fierens F, Geenens R, et al. Lymphocytic bronchiolitis after lung transplantation is associated with daily changes in air pollution. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2012; 12(7):1831–8.
21. Bhinder S, Chen H, Sato M, Copes R, Evans GJ, Chow CW, et al. Air pollution and the development of posttransplant chronic lung allograft dysfunction. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2014; 14(12):2749–57.
22. Nguyen LP, Bradfield CA. The search for endogenous activators of the aryl hydrocarbon receptor. *Chemical research in toxicology*. 2008; 21(1):102–16. [PubMed: 18076143]
23. Schmidt JV, Su GH, Reddy JK, Simon MC, Bradfield CA. Characterization of a murine Ahr null allele: involvement of the Ah receptor in hepatic growth and development. *Proc Natl Acad Sci U S A*. 1996; 93(13):6731–6. [PubMed: 8692887]
24. Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, et al. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature*. 2008; 453(7191):65–71. [PubMed: 18362915]
25. Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld JC, et al. The aryl hydrocarbon receptor links T(H)17-cell-mediated autoimmunity to environmental toxins. *Nature*. 2008; 453(7191):106–9. [PubMed: 18362914]
26. Pauly SK, Fechner JH, Zhang X, Torrealba J, Bradfield CA, Mezrich JD. The Aryl Hydrocarbon Receptor Influences Transplant Outcomes in Response to Environmental Signals. *Toxicol Environ Chem*. 2012; 94(6):1175–87. [PubMed: 23002321]

27. Hauben E, Gregori S, Draghici E, Migliavacca B, Olivieri S, Woisetschlager M, et al. Activation of the aryl hydrocarbon receptor promotes allograft-specific tolerance through direct and dendritic cell-mediated effects on regulatory T cells. *Blood*. 2008; 112(4):1214–22. [PubMed: 18550851]
28. Quintana FJ, Murugaiyan G, Farez MF, Mitsdoerffer M, Tukupah AM, Burns EJ, et al. An endogenous aryl hydrocarbon receptor ligand acts on dendritic cells and T cells to suppress experimental autoimmune encephalomyelitis. *Proc Natl Acad Sci U S A*. 2010; 107(48):20768–73. [PubMed: 21068375]
29. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *Journal of immunology*. 2010; 185(6):3190–8.
30. Gandhi R, Kumar D, Burns EJ, Nadeau M, Dake B, Laroni A, et al. Activation of the aryl hydrocarbon receptor induces human type 1 regulatory T cell-like and Foxp3(+) regulatory T cells. *Nature immunology*. 2010; 11(9):846–53. [PubMed: 20676092]
31. Veldhoen M, Hirota K, Christensen J, O'Garra A, Stockinger B. Natural agonists for aryl hydrocarbon receptor in culture medium are essential for optimal differentiation of Th17 T cells. *J Exp Med*. 2009; 206(1):43–9. [PubMed: 19114668]
32. Duarte JH, Di Meglio P, Hirota K, Ahlfors H, Stockinger B. Differential influences of the aryl hydrocarbon receptor on Th17 mediated responses in vitro and in vivo. *PloS one*. 2013; 8(11):e79819. [PubMed: 24244565]
33. Alam MS, Maekawa Y, Kitamura A, Tanigaki K, Yoshimoto T, Kishihara K, et al. Notch signaling drives IL-22 secretion in CD4+ T cells by stimulating the aryl hydrocarbon receptor. *Proc Natl Acad Sci U S A*. 2010; 107(13):5943–8. [PubMed: 20231432]
34. Basu R, O'Quinn DB, Silberberger DJ, Schoeb TR, Fouser L, Ouyang W, et al. Th22 cells are an important source of IL-22 for host protection against enteropathogenic bacteria. *Immunity*. 2012; 37(6):1061–75. [PubMed: 23200827]
35. van Voorhis M, Knopp S, Julliard W, Fechner JH, Zhang X, Schauer JJ, et al. Exposure to Atmospheric Particulate Matter Enhances Th17 Polarization through the Aryl Hydrocarbon Receptor. *PloS one*. 2013; 8(12):e82545. [PubMed: 24349309]
36. Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B, et al. Prevention of allogeneic fetal rejection by tryptophan catabolism. *Science*. 1998; 281(5380):1191–3. [PubMed: 9712583]
37. Chen W, Liang X, Peterson AJ, Munn DH, Blazar BR. The indoleamine 2,3-dioxygenase pathway is essential for human plasmacytoid dendritic cell-induced adaptive T regulatory cell generation. *Journal of immunology*. 2008; 181(8):5396–404.
38. Kiss EA, Vonarbourg C, Kopfmann S, Hobeika E, Finke D, Esser C, et al. Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. *Science*. 2011; 334(6062):1561–5. [PubMed: 22033518]
39. Li Y, Innocentin S, Withers DR, Roberts NA, Gallagher AR, Grigorieva EF, et al. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell*. 2011; 147(3):629–40. [PubMed: 21999944]
40. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing gammadelta T cells selectively expand in response to pathogen products and environmental signals. *Immunity*. 2009; 31(2):321–30. [PubMed: 19682928]
41. Lee JS, Cella M, McDonald KG, Garlanda C, Kennedy GD, Nukaya M, et al. AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. *Nature immunology*. 2012; 13(2):144–51. [PubMed: 22101730]
42. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity*. 2013; 39(2):372–85. [PubMed: 23973224]
43. Wang W, Xu S, Ren Z, Jiang J, Zheng S. Gut microbiota and allogeneic transplantation. *Journal of translational medicine*. 2015; 13:275. [PubMed: 26298517]
44. Vindigni SM, Surawicz CM. The gut microbiome: a clinically significant player in transplantation? Expert review of clinical immunology. 2015; 11(7):781–3. [PubMed: 26065325]

AHR/ARNT Signaling Pathway

Figure 1. AHR/ARNT Signaling Pathway

The AHR is a cytosolic receptor that is bound to a chaperone protein, ARA9. Ligands cross the cell membrane and bind to the AHR, causing it to shed ARA9 and migrate to the nucleus where it associates with ARNT. This heterodimer then binds to the dioxin response element (DRE) and becomes a transcription factor for the cytochrome P450 enzymes (including Cyp 1a1, Cyp1a2, and Cyp 1b1) and other metabolizing enzymes. Adapted with permission from (22). Copyright 2008 American Chemical Society. AHR, aryl hydrocarbon receptor.

Figure 2.

A (left). The AHR Links the Immune System to Exogenous and Endogenous Exposures.

The AHR serves as a sensor in interface organs including the lung, gut, and skin. In the lung, inhaled pollution contains ligands, including PAHs that bind to the AHR on immune cells and cause a deviation towards Th17 differentiation. In the gut, dietary ligands and breakdown products of tryptophan generated by members of the gut microbiome bind to the receptor on gut immune cells and support the presence of ILC3s and $\gamma\delta$ T cells, which both generate IL-17. In the skin, UV light breaks down tryptophan into an AHR ligand that supports the presence of IELs that generate IL-17. AHR, aryl hydrocarbon receptor.

B (right). Pathologic Exogenous Exposure Can Lead to Autoimmunity and Chronic Transplant Rejection.

While the role of the AHR as a sensor to these exogenous signals is initially protective, over time chronic exposures to inhaled pollutants or UV light may lead to a Th17 deviation in transplanted grafts, including transplanted lungs, and potentially other solid organs. In the gut, changes in diet or the microbiome may lead to a loss of the normal interaction with gut immune cells, leading to a change in immune status of the recipient to an inflammatory phenotype that could shift the balance towards loss of graft acceptance and chronic rejection. AHR, aryl hydrocarbon receptor.

Activation of the AHR is Necessary for Maintenance of a Healthy Mucosal Immune System

Figure 3. Activation of the AHR is Necessary for Maintenance of a Healthy Mucosal Immune System

Cells of the mucosal immune system are dependent on the presence and activation of the AHR for their continued maintenance at this interface with the outside environment. This has been shown best in the gut, where these cells, many of which generate IL-17 and IL-22, interact with signals from bacterial products, dietary ligands, and toxicants to help maintain a healthy balance of effector and regulatory responses. Loss of the AHR or its signaling leads to a loss of these cell populations in both the intraepithelial space and the lamina propria, allowing bacterial overgrowth, inflammatory cytokine profiles, loss of health of cell barriers, and a generalized inflammatory phenotype that could play a role in loss of self-tolerance of the organism, leading to autoimmunity or chronic graft rejection. Figure key:

Cells in lymphoid follicles represent ILCs. Tregs are regulatory T cells. Cells in between the epithelial cells are IELs. In the case of the gut, outside environment represents the lumen, and the inside is the lamina propria. AHR, aryl hydrocarbon receptor.