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The parallel paradigm between intestinal transplant inflammation and inflammatory bowel disease

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Abstract

Purpose of review—A significant shift in our understanding of the molecular and cellular basis for inflammatory bowel disease (IBD) mirrors research that has been ongoing in intestinal transplantation. The blurring of lines between these two disease states creates an avenue into potential therapeutic interventions which take advantage of these molecular similarities.

Recent findings—Traditional knowledge of T-cell involvement in IBD has expanded to highlight the role of T helper 17 (Th17) cells as key effector cells. A similar role has been demonstrated in cellular rejection of intestinal allografts. Genetic polymorphism related to the propagation and function of Th17 cells has been found to confer significant risk of developing autoimmune conditions. Interleukin-23, a cytokine identified as crucial to the expansion of Th17 cells, has become a validated molecular target in psoriatic arthritis and IBD, and could become a target for intestinal transplant therapies.

Summary—Intestinal transplant rejection and IBD share a similar phenotype, especially as it relates to key effector cells and gene polymorphisms. Improvements in our understanding of the immune-pathogenesis of IBD, as well as molecular targeting exploiting that knowledge, provide a potential route to improve outcomes for intestinal transplant patients.

Keywords

Crohn's disease; inflammatory bowel disease; intestinal transplantation; T helper 17 cell

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▮▮of outstanding interest

INTRODUCTION

Intestinal transplantation is an important treatment allowing intestinal failure patients to achieve enteral autonomy. Although significant progress has reduced allograft rejection among solid organ transplants over the last decade, intestinal transplantation continues to be hampered by lower longterm survival rates because of rejection [1■■]. As the intestine is the body's largest immunologic organ, its ability to regulate its microbiome requires a complex interaction between both regulatory and effector cell populations. This dynamic interplay is significantly impacted by immunosuppressive medications meant to prevent graft rejection. The resulting loss of immune homeostasis is the hallmark of intestinal allograft rejection and its clinical phenotype is strikingly similar to Crohn's disease. Dysbiosis in the transplanted gut has been shown to be associated with transplant rejection. Recent investigation into large-scale genomic differences between inflammatory bowel disease (IBD) patients and the general population has identified several nuclear polymorphisms thought to be responsible for autoimmunity. This was further validated by in-vivo studies examining the role of a T helper 17 (Th17)/regulatory T (Treg) cell-mediated inflammatory axis, and eventually clinical studies identifying efficacy of interleukin (IL)-23/IL-12 blockade in multiple autoimmune conditions. Extrapolation of IBD-related biological data could be a potential avenue for future targeted therapy in treating intestinal transplant inflammation.

SIGNIFICANCE OF GENETIC POLYMORPHISMS IN INFLAMMATORY BOWEL DISEASE, AUTOIMMUNITY, AND THE INTEGRITY OF THE INTESTINAL MUCOSAL BARRIER

The pathogenesis of IBD is believed to involve a complex interplay between environmental triggers and the immune response in a genetically predisposed individual. The unambiguous patterns of inflammation seen in both Crohn's disease and ulcerative colitis have led to investigations into whether specific gene polymorphisms in the inflammatory response pathways play key roles in triggering the injury that is observed to the intestinal mucosal barrier leading to intestinal autoimmunity. Through genome-wide association studies, 241 loci have been identified as possible points of susceptibility associated with IBD [2,3]. These loci have identified a plethora of immunologic and proinflammatory mechanisms – many of which also appear to play a role in allograft rejection. Given the clinical and pathologic similarities of intestinal allograft rejection to IBD, discoveries in the pathogenesis of one imply operational changes that may occur in both.

One of the first and most extensively investigated genes that was identified as associated with Crohn's disease is the nucleotide oligomerization domain 2 (NOD2) gene product, which helps the enterocyte respond to luminal antigen attaching to the cell surface. Multiple single nucleotide polymorphisms (SNPs) in NOD2 have been linked to increased risk of developing Crohn's disease through disruption of the mucosal barrier because of alterations in the expression of certain antimicrobial peptides (AMPs). Three SNPs in particular have been identified as susceptibility alleles: SNP 8 (R702W), SNP 12 (G908R), and SNP 13 (L1007fs) [4,5]. As early as 2008, Fishbein *et al.* [6] were able to apply this to the intestinal transplant population and were able to demonstrate and conclude that NOD2 polymorphisms

represented a critical immunological risk factor for intestinal allograft rejection with a significant negative impact on overall patient outcome. Specifically, we demonstrated that there was a higher-than-expected prevalence of mutations in intestinal transplant recipients and a nearly 100- fold increased risk of immunologic graft loss after transplant [6]. These changes were found in association with failure of the enterocyte to appropriately respond with increasing levels of the Crohn's disease-associated AMP human defensin 5. This concept was applied to the intestinal failure population by Guerra *et al.* [7] in 2013 as a higher frequency of NOD2 polymorphisms was noted in individuals with non-Crohn's disease intestinal failure compared with the donor control group, suggesting that NOD2 plays an important role in the maintenance of intestinal immune homeostasis. The failure of the NOD2-deficient phenotype to respond to an insult was postulated to lead to gut failure and loss under stress, impeding intestinal adaptation and leading to intestinal failure [7]. It was further shown that CX3 chemokine receptor 1^+ myeloid cells within the lamina propria support normal Paneth cell function through Wnt5a expression in a NOD2-dependent mechanism [8]. To summarize, one pattern of failure appeared to involve disruption of the normal response to luminal antigen through Paneth cell– enterocyte communication, and production of an appropriate AMP response.

Polymorphisms in autophagy related protein-1 (ATG16L1), a protein with a central role in autophagy and suppressing inflammatory cytokines, have also been described as risk factors for Crohn's disease as variants in ATG16L1 can decrease autophagy [9,10]. The process of degrading and recycling cell components can also be applied to the management of intestinal microbes in Crohn's disease as the clearance of intracellular microorganisms and stress on the endoplasmic reticulum may have implications for gut inflammation seen in IBD [11▪, 12–14]. Typically, turnover of ATG16L1 is dependent on caspase-3 activity; Murthy *et al.* [15] demonstrated that a certain polymorphism (T300A SNP) in ATG16L1 enhances the protein's susceptibility to cleavage by caspase-3, resulting in diminished levels of autophagy. This reduction in turn results in defective clearance of intracellular pathogens, which increases inflammatory cytokine production in times of cellular stress [11▪,15]. As aforementioned, Paneth cells are involved in mucosal defense and produce AMPs, including defensins [16]. In studying the role of autophagy in Crohn's disease, a murine study showed that autophagy compensated for endoplasmic reticulum stress in Paneth cells and when this was lost in *Atg16l1* variants, mice developed intestinal inflammation typically seen in Crohn's disease [17]. Deuring *et al.* [18] reported similar findings of Paneth cell endoplasmic reticulum stress in a human cohort, further substantiating the importance of Paneth cells in the origin of intestinal inflammation in Crohn's disease [17]. Although NOD2 was initially thought only to be involved in the process of intracellular recognition of pathogens in bacterial defense, subsequent investigations of autophagy genes have also shown that NOD2 interacts with ATG16L1 and affects autophagosome formation [19–21]. Given that NOD2 has been validated as a clinically relevant polymorphism in intestinal transplant rejection, it is clear that maintaining intestinal homeostasis is critical to allograft acceptance.

Responding to bacterial pathogens is a functional ecessity for the intestine, with failure leading to invasion of the host and sepsis, a common cause of mortality for intestinal transplant patients. A number of genes have been implicated in the ability of the intestinal

immune system to respond to bacterial pathogens and maintain this homeostasis. For instance, IL-23 and its functional receptor, IL-23 receptor (IL-23R), are key mediators in inflammation and differentiation of IL-17 producing Th17 as highlighted in detail below. Many polymorphisms in *IL-23R* typically lead to pro-inflammatory states and are associated with increased risk of IBD [22]. In contrast there are a few variants, specifically G149R, V362I, and R381Q, that lead to loss of protein function by inhibiting receptor maturation and decreasing protein stability and this has been correlated as possibly protective against IBD [23]. Similarly, the signaling of IL-10, a key anti-inflammatory cytokine, involves several gene loci [*IL10, IL10RB,* signal transducer and activator of transcription 3 (*STAT3*), non-receptor tyrosine kinase 2 (*TYK2*)] that may be disrupted in IBD [3,24]. In particular, defects in IL-10 pathway and IL-10R were linked to the early onset phenotype of IBD [25] and this continues to be an area of active investigation. Defects in IL-10 receptor lead to a dysregulated inflammatory immune response with inappropriately high increases in the secretion of tumor necrosis factor α (TNF-α) and other pro-inflammatory cytokines [25]. IL-10 signaling may also be implicated in lineage determination of T-cell subsets, especially Treg cells.

THE ROLE OF T HELPER 17 CELLS IN INFLAMMATORY BOWEL DISEASE, ALLOGRAFT REJECTION, AND THE SIGNIFICANCE OF THE IL-23 RECEPTOR IN T HELPER 17 PROLIFERATION

Striking similarities between IBD and allograft rejection also exist on the cellular effector level. Classical understanding of Th subset involvement in both autoimmunity and allograft rejection has rapidly evolved to now encompass multiple other Th subsets beyond the Th1 and Th2 model [26]. The Th17 cell – a key cell subtype involved in protective immunity against bacterial and fungal infection at the mucosal level – appears to be a key effector of both autoimmunity and rejection [27,28▪]. This cell is driven by the lineage defining transcription factor RAR related orphan receptor (ROR)γt, its activity increased by IL-23 [27], and its main effector function expressed through the production of IL-17A, IL- 17F, IL-21, IL-22, IL-26, IL-8, and chemokine ligand 20. Other cytokine pathways for the induction of Th17 cells include IL-1*b*, IL-6, and IL-21. The role of the Th17 cell has been framed around interactions between itself and the Treg cell compartment, which is involved in protection from autoimmunity and modulation of the immune response [29].

Th17 cells possess polarization plasticity, which leads to significant complexity in fully understanding their molecular behavior in an aberrant autoimmune or posttransplant environment. Polarization can lead to enhanced effector function as well as self-regulation and protection fromuncontrolled inflammation. Specifically, as it relates to autoimmunity, Th17 cells have been found to assume a Th1-like cytokine profile through the expression of interferon (IFN)-γ through a STAT4/T-bet dependent pathway, further contributing to their pro-inflammatory behavior [30▪]. Interestingly, Th17 cells can reciprocally differentiate into counter-regulatory Forkhead box 3^{+} cells, which traditionally define Treg cells, and can even produce the anti-inflammatory cytokine IL-10 [31,32].

The crux of the body's response to this inflammation is the Treg cell. Treg cells are induced in an environment rich with transforming growth factor- *b* and IL-10 and their proliferation helps shut down further induction of Th17 cells [28■]. These cells have been found to be decreased in IBD patients with a concomitant increase in pro-inflammatory effector T cells [31]. Treg cells frequently coexpress other lineage defining transcription factors such as GATA transcription factor 3, T-bet, and RORγt [29,30■] and can assume an effector profile that makes them almost indistinguishable from Th17 cells with expression of IL-17 and IFN-γ, which shows their own predilection for plasticity [33■]. This underscores the significant challenges in targeting a single cytokine or receptor in the treatment of intestinal inflammation.

As stated previously, increased IBD risk has been demonstrated at not only the IL-23 level but also at key downstream signaling steps to include STAT3, Janus kinase 2, TYK2, IL-12B, and RAR related orphan receptor C at the genetic level [34,35]. IL- 23 is traditionally expressed by antigen-presenting cells in the gut. Activation of IL-23R on T cells leads to STAT3/STAT4 dimerization and the initiation of transcription of Th17-related pro-inflammatory genes and cytokine production [35]. Protein and mRNA levels of these cytokines at the mucosal level have been demonstrated to be elevated *in vivo* in IBD patients [31]. IL-23 and IL-6 both have critical roles for altering the balance between Treg cell and Th17 cell response toward unrestrained inflammation.

The involvement of Th17 cells in solid organ transplantation has only recently been appreciated [26,36]. We were able to identify the Th17 cell as critical to the propagation of allograft rejection in intestinal transplant patients (manuscript in preparation). We demonstrated at mRNA level that multiple components of the Th17 pathway including IL- 6, IL-23, CCR4, and TNF-α were all upregulated in patients experiencing rejection, as compared with nonrejecting controls. Further studies using polychromatic flow cytometry confirmed that a key effector component in rejection is the $CCR6^{+}$ $CD4^{+}$ Th17 cell through its production of IL-17 and TNF-α. These findings explained the underlying pathophysiologic basis for previously successful clinical use of infliximab for allograft rejection.

Infliximab as a rescue strategy in severe rejection patients has been reported in several small cohorts with clinical response in patients with severe intestinal ulceration and inflammation [37]. Adalimumab, which is a similar biologic with efficacy in IBD patients, has also been reported as utilized successfully but largely in case report format [38]. Thus, targeting TNF-α, a scientifically and clinically validated and attractive target, could be a first step toward precision medicine in the treatment of intestinal allograft rejection that would be superior to currently used nonspecific, lymphocyte-depleting biologics (e.g., thymoglobulin, alemtuzumab), which have significant implications on mutagenesis, occurrence of posttransplant lymphoproliferative disease, and septic complications in solid organ transplant patients.

A key remaining question is whether molecular targeting of the Th17 pathway can be a therapeutic avenue for the treatment of cellular rejection. The monoclonal antibody ustekinumab, which targets and blocks the p40 subunit shared by IL-12 and IL- 23, prevents

binding of these cytokines to their specific receptor complexes on the surface of T cells inhibiting both Th1 and Th17 responses [39]. Importantly, ustekinumab has already been validated as an effective treatment option for moderate to severe Crohn's disease in a large multicenter-controlled trial [40]. This novel biologic is now the subject of much interest in research involving psoriasis, multiple sclerosis, ankylosing spondylitis, and other autoimmune diseases [41,42]. Although currently not utilized in solid organ transplantation, ustekinumab has been experimentally trialed in bone marrow allograft patients and was found to improve overall survival and moderate to severe chronic graft versus host disease free survival [43]. Given its clinically validated efficacy in shutting down Th17 inflammation, ustekinumab can provide a novel therapeutic option for intestinal transplant rejection and inflammation utilizing an alternative pathway to infliximab.

CONCLUSION

A significant stride has been made in the genetic, cellular, and molecular understanding of IBD – leading to expanded therapeutic options and multiple new pathways for further research. Dysregulation of intestinal homeostasis is a complex problem shared by both IBD and intestinal transplant patients. Intestinal transplantation continues to be the least frequent solid organ transplantation performed in the United States. Although less frequent, it is a lifesaving intervention that is plagued by a high rate of rejection with a high rate of graft loss and mortality despite intervention. As our understanding of the molecular and cellular profile of transplant-mediated inflammation is improved and similarities to IBDs are elucidated, novel therapies in IBD should be investigated for efficacy in intestinal transplant rejection.

Specifically, the roles of gene polymorphism and the behavior of Th17 cells as they relate to intestinal autoimmunity can shed new light on the dysregulation of immune homeostasis that is the hallmark of intestinal allograft rejection.

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KEY POINTS

- Numerous genetic polymorphisms that include NOD2, ATG16L1, and IL-23R have been identified in the pathogenesis of IBD and may be significant to the intestinal transplant population.
- Similarly, Th17 cells are also critical to intestinal mucosal defense, autoimmunity, and transplant rejection.
- The IL-23/IL-23R pathway is crucial to Th17-cell proliferation and is a novel therapeutic target in the treatment of autoimmune diseases.
- Applying the latest breakthroughs in understanding and treatment of IBD to the field of intestinal transplantation may open up new pathways for therapies that can improve graft acceptance and patient survival rates.