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Toward a Paradigm to Distinguish Distinct Functions of FOXP3+ Regulatory T Cells

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ABSTRACT

FOXP3+ regulatory T (Treg) cells are a unique subset of CD4+ T cells that classically function as master regulators of immune homeostasis. Besides this canonical suppressive role, which is required to maintain self-tolerance, a growing body of literature has identified Treg cells as critical orchestrators of tissue protection during acute stress and as effector cells that drive repair following tissue injury. Despite substantial interest in these distinct roles, the field has struggled to disentangle Treg cell suppressive functions from those that promote tissue defense and repair. In this article, we will examine the literature in the context of specific physiologic settings, contrasting the suppressive function of Treg cells with their emerging roles in promoting tissue homeostasis and tissue repair. Further, we will discuss a new paradigm differentiating tissue defense from tissue repair—a paradigm needed to translate Treg cell–based therapies to the clinic. ImmunoHorizons, 2021, 5: 944–952.

INTRODUCTION

Regulatory T (Treg) cells were originally described as a distinct subset of CD4+ T cells expressing high levels of the IL-2Rα subunit (CD25) (1). In contrast to classic CD4+ T helper cells, these CD25+ CD4+ T cells are required for the induction and maintenance of peripheral immune tolerance. Further investigations demonstrated that these cells are defined by their expression of the FOXP3 transcription factor, the loss of which in humans and mice results in the development of profound autoimmunity due to a failure of Treg cell development and function: immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome in humans and the scurfy phenotype in mice (2–4). Further studies identified critical roles for Treg cells in the development of tumors and prevention of autoimmune conditions and solid organ allograft rejection, thus illustrating the critical role of these cells in a wide range of human pathologies (5). Over the past two decades, numerous studies have probed the mechanisms that underlie Treg cell–mediated tolerance and immunosuppression. Importantly, these studies also identified unique aspects of Treg cell biology that did not neatly correspond to a view centered on the immune-tolerogenic function of Treg cells, but instead suggested an essential role for these cells in a broad range of other physiologic processes.

Treg cells deploy a diverse array of cytokines, soluble metabolites and mediators, and surface receptors to maintain immune homeostasis (6, 7). A detailed overview of these processes is beyond the scope of this article; however, despite almost two decades of study, the specific mechanisms that Treg cells use to maintain immune homeostasis remain ambiguous in many
pathophysiologic contexts. For instance, Treg cell production of the classic immunomodulatory cytokine IL-10 is dispensable for the development and maintenance of peripheral immune tolerance, but is required for protection from spontaneous colitis (8). The precise mechanisms by which Treg cell–derived IL-10 protects animals from colitis remain unknown; however, the differential requirement for Treg cell–derived IL-10 in different scenarios highlights the context-specific redundant and non-redundant role of particular Treg cell–derived immunomodulatory factors. Importantly, this division of labor has now been identified for numerous Treg cell effector molecules, suggesting that Treg cells use distinct effector programs in particular environmental and physiologic states (9, 10). In addition, early studies of Treg cells primarily focused on their roles in the maintenance of immune tolerance in lymphoid organs. Nevertheless, a growing body of evidence now clearly demonstrates the importance of tissue-localized and -resident Treg cells in a variety of pathophysiologic states (11). Thus, beyond their classic role in maintaining immune tolerance, Treg cells broadly function as modulators of tissue and organ homeostasis.

Following injury to a tissue, organisms go to great lengths to mitigate ongoing damage and effectively repair that damage by regenerating damaged tissue. Although investigators often lump tissue protection and repair as equivalent processes, they represent distinct physiologic events. Tissue protection involves limiting the initial quantity of damage and promoting the formation of a tissue environment that facilitates repair. Repair involves the proliferation, migration, and trans-differentiation of stem-progenitor cells to regenerate damaged tissue (Fig. 1). Recent investigations have identified Treg cells as essential modulators of both tissue protection and tissue repair in a variety of pathophysiologic conditions and tissue types. One crucial question these studies raise is whether Treg cells use distinct effector programs to support tissue protection and repair or if the classic Treg cell immunosuppressive program mediates these effects. The answer to this question carries profound significance because unrestrained Treg cell–mediated immunosuppressive effects may come with clinical risks, such as enhanced risk of infection and malignancy. Further, a one-size-fits-all approach using adoptive transfer of bulk Treg cells may limit the potential efficacy of administering Treg cell subsets that are selected to target specific disease states. Thus, identifying the signals that induce specific tissue-protective and -reparative effector programs is essential for the development of therapies that harness Treg cell homeostatic function without the negative clinical effects associated with unrestrained immunosuppression. In the next section, we will summarize the recently described role for Treg cells in promoting lung protection and repair while highlighting the functional mechanisms that are distinct to specific pathophysiologic contexts.

**ACUTE LUNG INJURY AS A MODEL SYSTEM TO DISSECT DISTINCT TREG CELL FUNCTIONS**

As highlighted by the ongoing COVID-19 pandemic and generations of seasonal influenza epidemics and pandemics, damage to the lower respiratory tract following infection (pneumonia) represents a major global cause of morbidity and mortality (12–14). In the context of an ongoing insult, such as a viral infection, the immune system must balance inflammatory responses that limit viral spread with activating the protective and reparative processes that promote lung tissue resilience and regeneration (Fig. 2). Treg cells limit ongoing lung injury and

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**FIGURE 1.** Treg cells promote recovery from lung injury through distinct mechanisms.

Classical Treg cell immunosuppressive functions limit tissue injury by reducing the activation of inflammatory and tissue-destructive immune cells. In addition, Treg cells also limit tissue damage through the induction of tissue-protective programs, such as impairing collagen-producing cell activation and proliferation, polarizing macrophages and monocytes toward anti-inflammatory/prorepair phenotypes, and directly enhancing epithelial resilience. Finally, Treg cells coordinate lung repair through the production of growth factors (GFs) and other soluble mediators that drive epithelial regeneration and vascular recovery. Created with Biorender.com.

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reduce inflammation in mouse models of acute lung injury (ALI) through their production of IL-13, which enhances macrophage efferocytosis (15, 16). Efferocytosis is thought to play a critical role in tissue recovery by removing dead cells while simultaneously activating anti-inflammatory and prorepair programs (17), suggesting that Treg cells may use known immunosuppressive processes to limit the magnitude of injury and initiate repair. In addition, a recent study found that Treg cell–specific production of matrix metallopeptidase 12 reduced the infiltration of neutrophils into the recovering lungs (18). Thus, Treg cells appear to limit active inflammation during acute injury. Another key event in the recovery process is limiting the local fibrostatic response, as a subset of patients develop fibroproliferation following ALI, which impairs respiratory recovery and causes significant long-term morbidity (19). Along with reducing local lung inflammation, Treg cells decrease the recruitment, proliferation, and activity of collagen-producing cells in an animal model of ALI (20). Although we lack a complete understanding of the different signals that promote alveolar repair versus fibrosis, the current data suggest that Treg cells participate in coordinating that decision. Thus, Treg cells shape the trajectory of lung repair early during the course of an injury by reducing inflammation and local fibrosis.

In addition to their functions in mitigating inflammation and fibrosis, multiple recent studies have demonstrated a requirement for Treg cells in tissue protection, and possibly repair, in experimental animal models of pathogen-induced ALI (16, 21). Furthermore, Treg cells are found in the lungs of patients recovering from pneumonia, indicating a probable role for Treg cells in human lung recovery (22, 23). Depletion of Treg cells in mice following induction of ALI with LPS or influenza A virus impairs recovery of lung function and animal survival (16). The precise roles of Treg cells in mediating lung recovery remain uncertain; however, emerging data suggest that Treg cells participate in both initial tissue protection, and later lung repair, using distinct mechanisms from those that mediate immune tolerance or prevent fibrosis. A pivotal study by Arpaia et al. (24) found that Treg cells limited lung injury following influenza A virus infection via a TCR-independent mechanism. Specifically, this study identified Treg cell–intrinsic production of amphiregulin (AREG), a weak epidermal growth factor receptor ligand, as essential for limiting lung damage following intranasal influenza challenge. Interestingly, Treg cell–intrinsic Notch-4 signaling was recently shown to modulate AREG production by Treg cells, suggesting that Notch family ligands produced in the context of lung injury modulate Treg cell function (25). Collectively, both of these studies demonstrate that Treg cell–generated AREG limits the initial severity of lung damage in response to influenza challenge, thus exerting a tissue-protective function. These studies highlight the broad mechanisms by which Treg cells can limit tissue damage and enhance injury resolution, including direct-acting molecules, such as AREG, as well as indirect mechanisms, such as modulation of myeloid cell or fibroblast activity. Thus, future studies must assess the relative importance of these different programs to define the Treg cell tissue-protective module.

Beyond tissue protection, emerging data suggest a causal role for Treg cells in directly promoting lung repair through a variety of mechanisms. Multiple studies have shown that Treg cells directly communicate with lung stem cells to promote the recovery of damaged lung epithelium by enhancing the proliferation and differentiation of lung epithelial cell progenitors (26, 27). How Treg cells communicate with stem cells is an active area of investigation (28), and initial evidence suggests that Treg cells can alter stem-progenitor cell function through direct mechanisms (e.g., epidermal growth factor receptor ligand generation, discussed above) as well as indirect mechanisms. As an example of an indirect mechanism, during the recovery phase of ALI, alveolar type II epithelial cells exhibit a heightened response to IFN signaling when Treg cells are depleted (29). Further, blockade of IFN-γ partially rescues lung recovery in this model, which correlates with decreases in B cell and inflammatory macrophage infiltration into the recovering lung. These data support a system in which Treg cells mediate changes in lung-localized immune cells that then promote repair independent of direct Treg–epithelial cell communication. In

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**FIGURE 2. Lung injury and recovery consist of distinct physiologic phases that require discrete Treg cell functions.**

Initial tissue injury results in direct pathogen-mediated damage of lung tissue. These inciting events are followed by a period of predominantly immune-mediated tissue damage that continues even after removal of the offending insult (i.e., pathogen clearance). During this ensuing period, reparative processes are activated, yet maximal tissue regeneration will not occur during ongoing inflammation. Treg cells likely use distinct functional programs during these phases; however, few studies have specifically identified specific effector pathways that are required during each phase. Future studies must harness existing genetic tools that allow for modulation of Treg cell function in time and space to identify context-specific tissue-protective and -regenerative Treg cell programs. Time scale shown for common murine influenza models of viral pneumonia. ERT2, tamoxifen-sensitive mutated ligand-binding domain of the human estrogen receptor α. Created with Biorender.com.
addition to the epithelium, Treg cells also function as important modulators of endothelial cells (30, 31), which must also regenerate following lung injury. A recent study by our group found that aged mice exhibited decreased endothelial cell regeneration following influenza infection. We found that this effect was Treg cell–dependent and Treg cell–autonomous, as heterochronic adoptive transfer of young Treg cells into aged mice following influenza viral clearance resulted in a rescue of the aged phenotype compared with an isochronic (age-aligned) adoptive transfer control condition (32). Furthermore, as an ALI progresses, the hyperactive inflammatory response promotes the formation of a hypercoagulable state that drives substantial fibrin deposition and thrombus formation in the lung vasculature (33, 34). Interestingly, a novel study recently demonstrated that Treg cells play crucial roles in clot resolution, potentially through modulation of monocyte activity within the thrombus. Specifically, a subset of Treg cells produces secreted protein acidic and rich in cysteine (SPARC), which enhances production of matrix metalloproteases by clot-localized monocytes (35). Combined, these studies highlight the diverse prorepair mechanisms that Treg cells employ during recovery following lung injury.

UNANSWERED QUESTIONS REGARDING THE DISTINCT FUNCTIONS OF TREG CELLS FOLLOWING TISSUE INJURY

How should we interpret the results of studies that invoke separate immunosuppressive, tissue-protective, and tissue-reparative functions of Treg cells? The distinction between resolution of inflammation, limitation of ongoing tissue damage, and active repair is more than a semantic issue, carrying important scientific and clinical implications for the timing and efficacy of Treg cell–based interventions. Many studies focusing on Treg cell–mediated repair conclude that improved tissue function relative to control animals at a given time point during or following recovery is evidence of an enhanced Treg cell reparative function. Nevertheless, as discussed above in the context of Treg cell–produced AREG, another plausible explanation for this result is enhanced Treg cell–mediated tissue protection, which limits the quantity of initial tissue damage relative to a control condition. Hence, these studies (24, 25), although elegant, are unable to disentangle the precise role of Treg cell–produced AREG in lung tissue protection (resilience to ongoing injury) from its role in repair (regeneration of damaged tissue). These studies used noninducible Treg cell–conditional genetic interventions that, by definition, preceded the viral insult. This experimental design led to different initial injury patterns comparing mice with Treg cell–specific AREG deficiency versus sufficiency (controls). Because the initial magnitude of tissue injury differed between the experimental and control animals, the necessity of Treg cell–generated AREG in stimulating repair is challenging to determine. Moreover, it is possible that AREG exerts an antiviral role by limiting initial influenza replication in infected epithelial cells, which would result in less viral damage and a diminished burden of damaged lung in need of repair. Hence, these experiments cannot identify the temporal importance of AREG during the course of lung injury, highlighting the experimental care needed to characterize Treg cell tissue-protective versus -reparative functions throughout the duration of an ALI.

To what extent are classic Treg cell immunosuppressive functions required for recovery from injury versus distinct tissue-protective and –reparative effector programs? Depending on the clinical context, some Treg cell effector functions may cause harm by increasing local and global immunosuppression, as observed in animals and patients recovering from sepsis (36, 37). As detailed above, all established Treg cell functions likely fill essential roles in tissue recovery, but the temporal and environmental contexts in which these distinct programs operate require further investigation. Many of the tools needed to illuminate these differences already exist. A tamoxifen-inducible Cre-recombinase system expressed from the Foxp3 locus is already widely used, allowing for further assessment of the time dependence of distinct Treg cell functions in mice (38) (Fig. 2). Our group used this approach to assess the role of mitochondrial metabolism and DNA methylation in Treg cells during immune system development and maintenance (39, 40). Specifically, our study investigating the role of the epigenetic regulator, UHRF1, highlights the power of this approach. Mice constitutively lacking UHRF1 in Foxp3+ cells from birth display an almost complete lack of mature Treg cells in the periphery secondary to a failure of Treg cell development past the Foxp3+ thymic Treg cell stage. In contrast, inducible loss of UHRF1 in postdevelopmental Treg cells demonstrated a requirement for UHRF1 in the maintenance of Foxp3 expression and Treg cell lineage identity (40). Investigators could use similar strategies to causally differentiate tissue-protective processes from truly reparative mechanisms in mice by altering the expression of transcriptional regulators or effector molecules at specific time points during recovery. For example, in models of influenza, Cre-mediated recombination can be activated 7 or 8 d postinfection, when the virus has already been cleared, thus allowing for the assessment of Treg cell–reparative function during late injury and lung recovery. Besides genetic modifications, the increasing availability of unbiased omics technologies allows investigators to characterize the environmental context that shapes prorepair Treg cells. Specifically, single-cell RNA sequencing combined with unbiased proteomic profiling might be used to serially characterize immune profiles during initial tissue injury and recovery to better detail the immune cell populations that receive and support different Treg cell functions. Importantly, these approaches can be applied directly to patient samples, allowing for a comparison between human and animal immune systems. Finally, much of the work assessing Treg cells in ALI has been performed using artificial immune stimuli, such as LPS or Poly I:C. Although these models have the benefit of providing reproducible degrees of injury, they fail to recapitulate reparative processes in patients. Unlike replicating pulmonary pathogens, the immune system rapidly clears LPS and Poly I:C; thus, these sterile systems may fail to
properly contextualize Treg cell immunosuppressive, tissue-protective, and -reparative functions. To fully understand the dynamic role of Treg cells in recovery from lung injury, physiologic models, such as influenza virus or pneumococcal bacterial infection, need to be used (41, 42).

**SEARCHING FOR A DISTINCT PROREPAIR TREG CELL SUBSET**

Besides their role in host recovery following ALI, Treg cells are required for tissue protection and repair in a variety of extrapulmonary tissues. These discoveries have raised the intriguing possibility that a unique prorepair Treg cell subset may circulate or arise after injury in vivo. This possibility is buttressed by recent studies that have identified shared effector molecules and upstream inducing signals in tissue-protective and -reparative Treg cells in a variety of different tissues and physiologic contexts. For instance, multiple recent studies have identified Treg cell–generated AREG as a critical effector molecule of tissue recovery. Outside the lung, Treg cells produce elevated levels of AREG in response to muscle and kidney injury (43, 44). Importantly, Treg cell–intrinsic AREG production is not required for Treg cell suppressive function in vitro and in vivo (24, 45). Besides AREG, multiple studies have also identified SPARC as a Treg cell–produced prorepair effector molecule in diverse models, including thrombosis resolution and recovery from myocardial infarction (35, 46). In models of acute myocardial damage, Treg cells reduce inflammatory monocyte and macrophage polarization (47), similar to the monocyte-modulating effects of Treg cell–produced SPARC in thrombosis resolution (35). Interestingly, both AREG and SPARC production in Treg cells can be induced by the alarmin, IL-33, and the IL-33R subunit, ST2, has commonly been proposed as a marker of Treg cells (48, 49). This work has grown out of a body of evidence finding that tissue-resident Treg cells exhibit high expression of the transcription factors, GATA binding protein 3 (GATA3) and peroxisome proliferator–activated receptor γ (PPAR-γ). GATA3 is famous for driving the induction of type II immunity in conventional Th cell responses (54), and experimental data suggest it may support a tissue-protective Treg cell subset in vivo (43, 49). Similarly, PPAR-γ is known to be expressed in resident Treg cells from a variety of tissues, including skin, adipose, and colon, and its expression in Treg cells correlates with the expression of tissue-protective molecules, including AREG and IL-10 (48). In a model of ischemic brain injury, in which Treg cells enhance recovery, brain-localized Treg cells express high levels of AREG and PPAR-γ (55). Importantly, despite these studies demonstrating high expression of GATA3 and PPAR-γ, no causal data exist to support the necessity or sufficiency of these transcription factors specifically in repair. In fact, both GATA3 and PPAR-γ are essential for proper Treg cell function in homeostatic conditions (56–59). Whereas GATA3 is known to promote Foxp3 stability in inflammatory environments (58), PPAR-γ is essential for proper homing of nonlymphoid tissue-localized Treg cells (56). These findings demonstrate that although these transcriptional pathways likely play a role in the stability and location of prorepair Treg cells, their expression is unlikely to define a unique tissue-protective or -reparative Treg cell subset.

It is increasingly clear that CD4+ Foxp3+ cells comprise a heterogeneous population of cells that possess distinct functions (60). However, as presented above, the evidence for the existence of a unique reparative Treg cell subset remains ambiguous, thus raising the question of what other data could determine whether a distinct prorepair Treg cell subset actually exists. For one, the precise role of Foxp3 and TCR signaling in prorepair function needs to be further elucidated. In the lung, AREG production by Treg cells does not require TCR signaling, suggesting that some tissue-protective processes may be modulated by alternative, Ag-independent environmental signals (24). In contrast, a recent study demonstrated that following muscle injury, Treg cells clonally expand in muscle tissue, and that the functional activities of these cells depends on TCR specificity (61). These paradoxical findings suggest that distinct signals in different tissues modulate tissue-protective and -reparative Treg cell effector programs, highlighting the importance of future studies characterizing the role of the TCR, IL-33R, and other upstream signaling pathways in diverse physiologic contexts. In addition, the role of the Foxp3 transcription factor itself in the reparative Treg cell phenotype remains unclear. Recent data have demonstrated that some specific Foxp3 mutations are dispensable for homeostatic immune function yet result in impaired Treg cell function in specific immunologic contexts, such as aging (62, 63). Future studies could harness these mutants as natural experiments to causally determine the role of Foxp3 in tissue protection and repair.

Another critical objective for the field must be identifying the developmental origin of putative, prorepair Treg cells. Treg cells are classically split into two major groups based on their origins. Thymus-derived Treg (tTreg) cells develop from CD4+ single-positive thymocytes and express Foxp3 early in life, whereas peripheral Treg (pTreg) cells develop from naive CD4+ T cells outside of the thymus (64). Although markers, such as HELIOS and NRP1, have been proposed to differentiate these subsets, in actuality, no specific marker combination perfectly separates these cells based on their developmental origin (65–67). However, strong evidence suggests that pTreg cells and tTreg cells occupy unique immunologic niches, with pTreg cells playing a role in maintaining homeostasis at mucosal
surfaces (68–70). One function of pTreg cells at these barrier sites is the regulation of the local microbiome in animals and humans (70, 71). Interestingly, alterations in the gut and lung microbiome are known to alter the recovery of animals following influenza challenge (72–74), implying a potential role for microbiome-mediated modulation of pTreg cell function as a mechanism of tissue protection and recovery. In addition to their developmental origin, Treg cells are distinguished by their site of residency (11). As discussed above, recent studies have identified resident Treg cells as crucial mediators of tissue homeostasis in a variety of organs. Some studies have suggested that these tissue-resident cells adopt a repair-like phenotype at baseline (48, 49). However, whether these cells expand following insult and function as the developmental pool for reparative Treg cells during and after an insult is less clear. In addition, the relative contribution of tissue-resident Treg cells that limit organ-specific autoimmunity, and whether this contribution represents a distinct tissue-resident Treg cell function, remains undetermined. Experimentally, the question of the origin of prorepair Treg cells can be addressed using shielded chimera experiments to specifically deplete Treg cell populations from the periphery while leaving local resident populations intact (75–77). Differentiating whether prorepair Treg cells come from pTreg or tTreg cellular origins is more challenging experimentally due to the relative lack of straightforward model systems that exist to modulate a specific subset. However, animals lacking the conserved noncoding sequence 1 of the Foxp3 locus selectively lack pTreg cells and could serve as a tool to identify the relative importance of these subsets in injury models (78). In addition, thymectomy Treg cell–conditional inducible knockout mice could aid in differentiating the developmental time frame of tissue-protective and prorepair Treg cell subsets. Finally, a recent study by Andrews and colleagues (79) demonstrated the potential utility of a novel, multistep recombination approach that allows for Cre-recombinase expression specifically in CD4⁺ helper T cells without measurable recombinase activity in Treg cells. A comparable approach could be developed for Treg cells, which may allow for specific, spatial targeting of tissue-resident Treg cells and could be used to dissect the functional differences between tissue-resident, lymphoid-resident, and circulating Treg cells. Identifying the origin of the reparative Treg cell subset has important clinical implications, especially for Treg cell transfer–based therapy regimens. Thus, these experiments should be a priority for the field going forward.

Although the experiments described above provide a road map to causally identify the origin of tissue-protective and -reparative Treg cells in animal models, the field requires alternative approaches to translate these findings to humans. Multiple studies have demonstrated that the cellular epigenetic state correlates with the Treg cell prorepair phenotype, suggesting that epigenetic markers, such as DNA methylation could be used to identify these Treg cell subsets in patients (48, 49). Interestingly, inhibition of DNA methyltransferases, specifically in Treg cells, improves animal recovery in experimental models of ALI (21). Thus, the Treg cell epigenetic state may be used to both identify and promote Treg cell prorepair activity in patients (80). However, investigators must take care when assessing DNA methylation and other epigenetic markers during injury (81). For one, our group has previously demonstrated (39) that mitochondria-generated metabolites shape Treg cell function potentially by altering their DNA methylation profile. Local alterations in nutrient availability are known to impact Treg cell phenotype and function in multiple contexts (82); thus, characterizing metabolic changes in local tissue environments is essential to identifying prorepair signals and cellular phenotypes during injury. In addition, the Treg cell epigenetic state is altered during aging (32, 83); consequently, identification and characterization of tissue-protective and -reparative Treg cells must track these cells across the lifespan of an organism.

Finally, the signals that promote the formation of tissue-protective or -reparative Treg cells must be further elucidated. As discussed above, production of IL-33 appears to play a role in promoting the formation of tissue-protective Treg cells in multiple disease contexts (84). Importantly, in some contexts, IL-33 is directly produced by stromal cells following injury, and impairment in this process, as observed in aged mice, reduces Treg cell infiltration into injured muscle with correspondingly reduced tissue recovery (50). Besides IL-33, another inflammatory cytokine, IL-18, has also been shown to promote Treg cell–mediated production of AREG, suggesting it may also activate a tissue-protective or -reparative Treg cell program (24, 85). Other noncytokine environmental factors can influence Treg cell development and function. For example, microbiome-derived short-chain fatty acids are known to enhance Treg cell differentiation and suppressive function (86–88). Other environmental factors, such as nutrient restriction and tissue hypoxia, also alter Treg cell function as demonstrated in the context of the tumor microenvironment (89–91). These findings highlight how the local microenvironment can profoundly alter Treg cell phenotype and function. Future studies must further investigate how the local metabolic and immunologic environment changes throughout the time course of tissue damage and repair to identify the signals that promote or impede Treg cell protective and reparative function. These studies may also identify unique environmental disruptions that could be targeted to improve Treg cell function in these contexts.

In conclusion, Treg cells serve as critical modulators of immune tolerance and homeostasis. Traditionally, most studies have focused on Treg cell–mediated immunosuppressive activity, whereas an emerging body of data has demonstrated a critical role for Treg cells in tissue protection and repair. The current evidence suggests that Treg cells employ a combination of immunosuppressive as well as distinct tissue-protective and -reparative mechanisms to support these processes. In addition, some studies have also suggested that reparative Treg cells may exist as a unique functional subset. Future studies must carefully work to disentangle the distinct mechanisms used in the context of tissue injury and recovery to identify truly reparative
programs and potential Treg cell subsets. These findings can support the development of therapies that optimize Treg cell phenotype and function in diverse pathophysiologic contexts.

DISCLOSURES

B.D.S. holds United States patent 10,905,706, Compositions and methods to accelerate resolution of acute lung inflammation, and serves on the Scientific Advisory Board of Zoe Biosciences, for which he holds stock options. The other author has no financial conflicts of interest.

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