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Review Series

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Reparative T lymphocytes in organ injury

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Acute organ injuries such as acute cerebrovascular accidents, myocardial infarction, acute kidney injury, acute lung injury, and others are among the leading causes of death worldwide. Dysregulated or insufficient organ repair mechanisms limit restoration of homeostasis and contribute to chronic organ failure. Studies reveal that both humans and mice harness potent non-stem cells that are capable of directly or indirectly promoting tissue repair. Specific populations of T lymphocytes have emerged as important reparative cells with context-specific actions. These T cells can resolve inflammation and secrete reparative cytokines and growth factors as well as interact with other immune and stromal cells to promote the complex and active process of tissue repair. This Review focuses on the major populations of T lymphocytes known to mediate tissue repair, their reparative mechanisms, and the diseases in which they have been implicated. Elucidating and harnessing the mechanisms that promote the reparative functions of these T cells could greatly improve organ dysfunction after acute injury.

Introduction

Acute, repeated, and chronic injuries lead to organ dysfunction. In the aftermath of injury, tissue repair and regeneration are essential to restoring organ homeostasis, and defective or insufficient repair mechanisms can lead to permanent organ dysfunction. Tissue repair is an active, complex, and highly regulated process, and tissue response to injury involves a well-studied inflammatory response characterized by influx of immune cells and their activation. However, much less is known about the role of inflammation and the immune system in repair. The importance of inflammation in repair is highlighted by observations that glucocorticoid use, which inhibits immune responses, also impairs repair (1). Moreover, a timely resolution of inflammation is required for repair (2).

T lymphocytes are pivotal for the maintenance of adaptive immune responses, including recognition of pathogens, allergens, and tumor antigens. Moreover, although T lymphocytes coordinate and maintain immunological memory and self-tolerance, they have also been linked to inflammatory and autoimmune diseases (3). For instance, type 2 immune cells involved in allergic inflammation or parasitic infection can also regulate tissue repair (4, 5). Interplay between immune cells (macrophages, type 2 innate lymphoid cells, T cells, etc.) and nonimmune cells (fibroblasts, epithelial cells, endothelial cells, stem cells, etc.) helps to direct their responses to environmental cues, as well as epigenetic and metabolic reprogramming during tissue repair. This Review will focus on the major populations of reparative T cells, describe their role in specific contexts, and present approaches to harness them to enhance tissue repair (Figures 1 and 2).

CD4+Foxp3+ Tregs

Regulatory T cells (Tregs) have emerged as critical orchestrators of resolution of inflammation. These T cells can mediate repair by dampening inflammation, by modulating other important repair cells such as macrophages, and by synthesizing pro-repair molecules such as amphiregulin (AREG) or keratinocyte growth factor (KGF) that directly promote tissue regeneration. In humans and in mice, Tregs constitute 5% to 10% of the total CD4+ pool, or 1% to 2% of peripheral blood lymphocytes. Despite their relatively low frequency, Tregs are among the master regulators of the immune system, with established roles in immune tolerance, homeostasis, and inflammation (6, 7). Treg relevance is highlighted by descriptions of humans who carry mutations in the master transcription factor forkhead box P3 (FOXP3) and exhibit massive multisystem inflammation and autoimmunity (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, or IPEX syndrome) (8–10). A murine counterpart with severe, generalized autoimmunity has been described in scurfy mice (11).

Foxp3 is currently the best available marker to identify Tregs, although it can also be transiently expressed in human activated conventional T cells (12). A combination of CD3+CD4+CD127lo CD25hiFoxp3+ is often used to discriminate human Tregs from activated conventional T cells (13). Natural or thymus-derived Tregs (tTregs) can be distinguished from induced/adaptive or peripherally derived Tregs (pTregs). pTregs can be induced from CD4+ conventional T cells by antigenic T cell receptor (TCR) stimulation with low-dose/high-affinity ligands, suboptimal costimulation, and mediators including TGF-β1, IL-2, and retinoic acid (14–16). Helios and neuropilin-1 are enriched in tTregs compared with pTregs (17, 18), but caution should be used to discriminate the Treg population when inflammation or overt T cell activation is present. Another difference is that CpG motifs in conserved noncoding DNA sequence 2 (CNS2), a Treg-specific demethylated region, are demethylated in tTregs, but not in pTregs (19). In contrast, CNS1 at the *Foxp3* locus has an important role in pTreg generation, while CNS3 has potent effects in increasing Treg frequency in the thymus and the periphery (16).
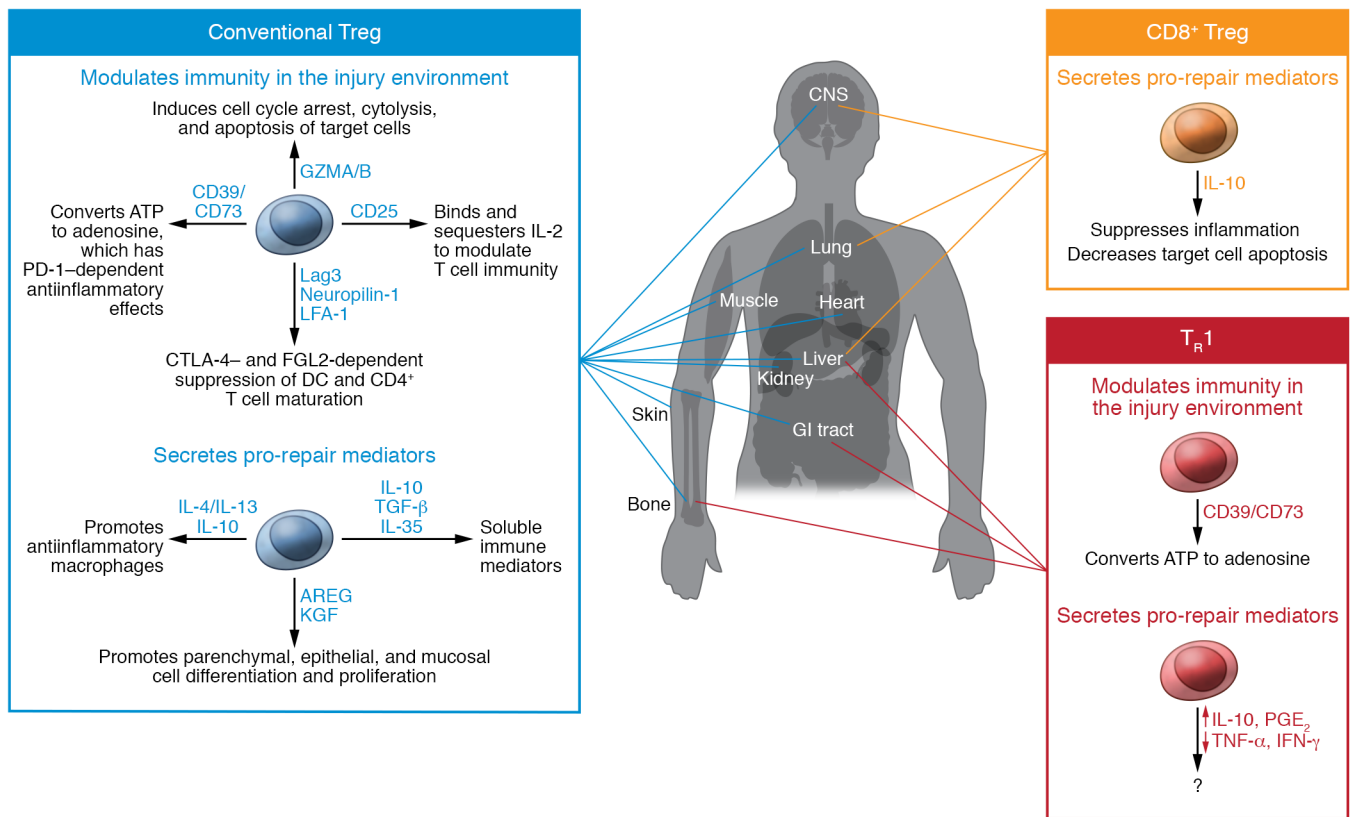
Figure 1. Roles for Treg subsets in repair. Conventional Tregs, CD8+ Tregs, and T_R1 cells can directly influence repair processes by secreting pro-repair mediators. Conventional Tregs and T_R1 cells also regulate other immune processes at the site of injury.

The importance of Tregs in self-tolerance and maintenance of immune homeostasis has been well established, with an emerging literature demonstrating that Tregs harness potent pro-repair functions in a wide range of immune and nonimmune diseases (Table 1). Tregs can exert their pro-repair function in different organs and diverse contexts (Tables 2 and 3). Treg pro-repair mechanisms can include one or more of the following (Figure 1):

Contact-dependent modulation of effector cells. Tregs can dampen immune responses and thus limit overt inflammation to promote a reparative milieu. Among the contact-dependent mechanisms, expression of high levels of inhibitory receptors (e.g., CTLA-4, LAG-3) can downregulate costimulatory molecules on dendritic cells (DCs) (20–22). Tregs can also downregulate the costimulatory molecules CD80 and CD86 in DCs and promote DC production of indoleamine 2,3-dioxygenase, a potent immunosuppressive enzyme, which in turn results in suppression of effector T cells (23, 24). Treg-driven metabolic disruption involves both apoptosis mediated by CD25-dependent cytokine deprivation (25) and immunosuppression mediated by CD39/CD73-generated cAMP via the adenosine–purinergic adenosine A_{2A} receptor (26, 27). While granzyme-induced cytolysis is a key mechanism for NK cells and cytotoxic CD8+ T cells, Tregs can also express granzymes, which have been shown to be important in controlling respiratory syncytial virus–induced lung inflammation (28), in preventing gastrointestinal graft-versus-host disease (GvHD) (29), and as a mechanism underlying self-induced apoptosis after activation (30).

Secretion of immunosuppressive molecules. Tregs can produce the antiinflammatory molecules IL-10, TGF-β1, and IL-35, with highly variable mechanisms that can be context-specific. In asthma models, Treg-induced IL-10 production by CD4+ effector T cells suppressed allergic inflammation, although the mechanism did not require IL-10 expression in Tregs themselves (31). In other studies, Treg-derived IL-10 was shown to control lung allergic inflammation (32). In contrast, Treg-derived IL-10 was not necessary to resolve lung injury caused by intratracheal lipopolysaccharide (33). Models of renal ischemia/reperfusion and colitis show important roles for production of IL-10 by Tregs (34, 35). The importance of TGF-β1 production by Tregs is controversial; however, membrane-tethered TGF-β has been shown to be immunosuppressive in both allergic and autoimmune diseases (36, 37). IL-35 has been shown to have robust Treg suppressive function in vitro and in vivo and can generate a suppressive population of pTregs (38).

Secretion of pro-repair mediators. Treg-derived AREG, an EGFR ligand, has been shown to exert potent reparative function in models of muscle injury (39), influenza-induced lung injury (40), and colitis (41). Several mediators can induce AREG, including IL-33, cAMP, insulin-like growth factor-1 (IGF-1), TGF-β, and prostaglandin E_2 (42, 43), each of which contributes to rapid upregulation of AREG during inflammation/injury. In contrast to other EGFR ligands, AREG can induce both mitogenic and cell differentiation signals, placing AREG at center stage in coordination of tissue homeostasis and epithelial repair after injury (43). KGF secreted
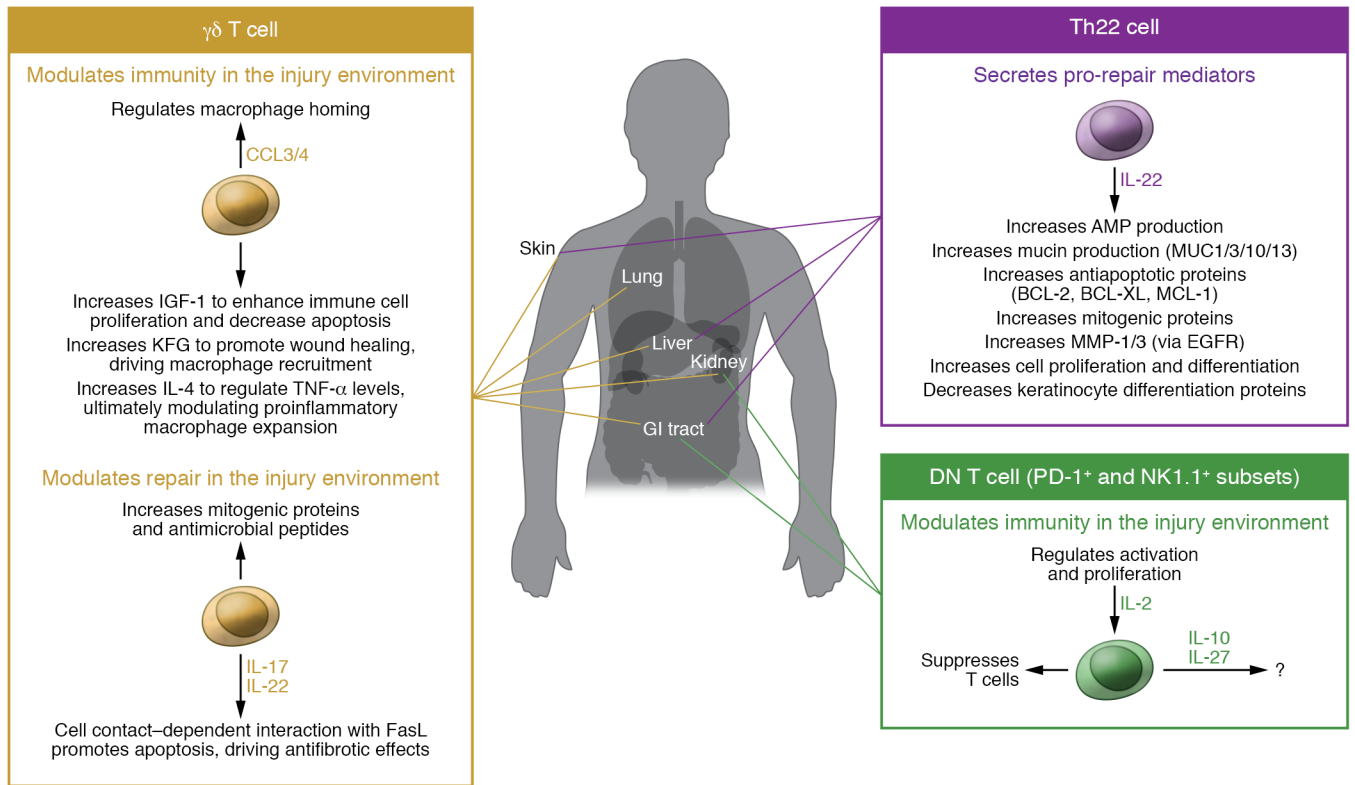
Figure 2. Roles for other T cell subsets in repair. γδ T cells, Th22 cells, and DN T cells influence immunity and repair at the site of injury via a variety of mechanisms.

by activated Tregs has also been shown to be an important factor in promoting alveolar epithelial repair after lung injury (44). Tregs can also promote angiogenesis (45, 46), possibly through enhancement of VEGF production by other cells, as Treg production of angiogenic factors has not been described to date. An additional factor secreted by Tregs is IL-4, which can induce alternative activation and promote a reparative phenotype in human macrophages (47).

Modulation of stromal cells. Tregs can modulate stromal cells to promote repair. Stromal/Treg signaling via the IL-33/ST2 axis has been reported to expand Tregs in injured lungs, muscle, colon, and liver (48–50). Tissue injury leads to release of alarmins, among them IL-33, which can stimulate Tregs through their receptor, stimulation-2 (ST2). IL-33–stimulated Tregs upregulated reparative AREG production by ST2+ Tregs, contributing to the reprogramming of infiltrating macrophages to a pro-repair phenotype (51, 52). IL-33/ST2 signaling can mediate tissue-reparative functions in the resolution phase after injury in different organ systems, although it may play pathological roles in type 2 diseases such as skin and lung allergic pathologies (53–55). Moreover, Treg contact–dependent and –independent cellular interactions with epithelial, endothelial, fibroblast, or other stromal cells can mediate their reparative effector functions. The complexity of Tregs orchestrating repair is highlighted by the migration of these cells to inflamed lungs, where they modulate alveolar macrophage proinflammatory responses, enhance neutrophil clearance by macrophage efferocytosis, and balance effector Th1/Th17 responses while promoting epithelial and endothelial proliferation (33, 40, 56, 57).

Modulation of stem cells. Tregs' pro-repair functions suggest that they may influence tissue-specific stem cell functions. In a model of epithelial regeneration, Tregs were shown to promote hair follicle stem cell differentiation (58). Future work will be needed to determine how Tregs interact with niche-specific stem cells in organ repair.

Intense efforts have been made to use Tregs as immunotherapy for autoimmune diseases and solid organ transplantation, with ongoing trials for type 1 diabetes mellitus (NCT02691247; ClinicalTrials.gov) and GvHD (NCT01937468). Although phase I trials using polyclonal Tregs have demonstrated safety to date, there are unique challenges to developing these therapies, including improving the isolation, expansion, purity, stability, potency, and specificity of Tregs (59). It is anticipated that indications for Treg immunotherapy will expand to include other conditions in which unremitting inflammation or persistent organ damage exists. It has been proposed that chimeric antigen receptors (CARs) or antigen-specific Treg TCRs engineered for a specific organ or disease could be developed as the next generation of cell immunotherapy (60).

Adoptive transfer of expanded Tregs requires time, making them an impractical option during the acute phase of organ injury. Repurposing approved drugs to expand and promote endogenous Tregs represents an alternative option. IL-2/anti–IL-2 complex, IL-33 agonists, mTOR inhibitors (e.g., rapamycin), and DNA methyltransferase inhibitors (e.g., decitabine, azacitidine, etc.) can promote Treg expansion, resolve inflammation, and enhance organ repair (61, 62). In addition, autologous Treg

Table 1. T cell types involved in tissue repair and their markers and functions

Treg populations	Markers	Functions
Conventional Tregs		
tTregs and pTregs	CD4+CD25+Foxp3+→CD3+CD4+CD127loCD25hiFoxp3+ discriminates human Tregs from activated conventional T cells (13)	Repair (see Tables 2 and 3)
		Control (suppress) immune responses including self-antigen tolerance and prevent autoimmune disease (122, 123)
		Regulation of immune responses (124) in: tumor immunity (125), allergy (126), transplant rejection (127), infections (128)
Other Treg subtypes (selection)		
CD8+ Tregs	CD8+CD28−/lo/+	Repair (see Tables 2 and 3)
	CD8+CD122+ (mouse)/CD8+CXCD3+ (human)	Maintain immune homeostasis/tolerance and inhibit autoimmune disease (129, 130)
	Qa-1–restricted CD8+ (mouse)/HLA-E (human)	In cancer: inhibit immune responses (116)
Foxp3− Tregs	T$_R$1→CD4+CD49b+LAG-3+ (65)	Repair (see Tables 2 and 3)
		Induce and maintain antigen tolerance
		Control (suppress) immune responses: GvHD (131), autoimmunity (73), tissue inflammation (73), transplantation (77)
Other reparative T lymphocyte populations		
IL-22+CD4+ T cells (Th22 cells)	IL-22	Repair (see Tables 2 and 3)
	Differentiated from Th cells by absence of IFN-γ, IL-5, and IL-17	Protect against infections (with exceptions) (80, 132)
		Role in cancer initiation and progression (with exceptions) (85, 92)
		Protective and pathogenic role in autoimmune disease (133)
Double-negative (DN) T cells	CD4−CD8−, αβ TCR+	Repair (see Tables 2 and 3)
	There is no specific marker for DN T cells. Other DN populations are also described, e.g., DN γδ T cells, DN NKT cells, DN Tregs	Immune regulation and tolerance: graft tolerance (96), antitumoral potential (98), autoimmunity (97)
		Exceptions: IL-17–producing DN T cells in SLE (99), IL-17– and IL-23–producing DN T cells in bacterial infection (134)
γδ T cells	TCR consists of γ chain and δ chain	Tissue homeostasis and repair (ref. 108 and see Tables 2 and 3)
	Different oligoclonal or monoclonal populations	Located in surface epithelia/mucosa (104)
		Cancer immune response (pro- and antitumor effects) (135)
		Infection defense (136)

SLE, systemic lupus erythematosus.

function could be enhanced ex vivo for a shorter duration in the presence of these "Treg enhancers" and adoptively transferred back to the host to achieve their pro-repair functions (63).

Type 1 regulatory T cells

Type 1 regulatory T cells (T$_R$1) are a CD4+ population that was initially found to suppress antigen-specific responses to prevent colitis (64). T$_R$1 cells differ from tTregs by their lack of Foxp3 expression and CD25. Both human and mouse T$_R$1 cells express lymphocyte activation gene-3 (LAG-3) and CD49b (65). They can express high levels of regulatory molecules such as OX40 (CD134), glucocorticoid-induced tumor necrosis factor receptor (GITR) (66), and inducible T cell costimulator (ICOS) (67).

T$_R$1 cells' mechanisms of action include suppression of T cell and antigen-presenting cell (APC) responses via secretion of IL-10 and TGF-β (64, 68), death of myeloid APCs via secretion of granzyme and perforin (69), immunomodulation of DC–T cell interactions via secretion of coinhibitory molecules such as CTLA-4, PD-1, and ICOS (70), and production of adenosine through the hydrolysis of ATP by CD39/CD73 expression (71).

T$_R$1 cell–based therapeutics have faced some challenges. They can secrete Th1/Th2 cytokines but have limited clonal expansion ability, likely due to the autocrine effects of IL-10. Culturing T$_R$1 cells in the presence of dexamethasone and vitamin D$_3$ can facilitate differentiation into a regulatory phenotype (72). Their reduced clonal expansion can be overcome by culture in the presence of either IL-10–producing DCs, IL-27, or aryl hydrocarbon receptor (AHR) agonists (73). Although T$_R$1 cells can modulate immune responses primarily by their production of IL-10 and TGF-β, we speculate that these cells have important reparative mechanisms by modulating other cells involved in regeneration. IL-10 has been shown to modulate macrophage phenotype and promote muscle growth and regeneration (74), it mediates mucosal repair by epithelial WNT1-inducible signaling protein (75), and promotes wound healing via fibroblast/STAT3 signaling. Although IL-10 has been administered to patients with inflammatory bowel disease (IBD) and proven to be safe. However, patient outcomes have been disappointing. The short half-life of IL-10, subtherapeutic doses at mucosal surfaces after systemic administration, and variability between individuals in

Table 2. Selection of T cell reparative roles in CNS, heart, lung, and kidney models of injury

Organ	Model	Cell type	Comment on mechanism (reference)
CNS	Cuprizone-induced demyelination	Tregs	Promoted oligodendrocyte differentiation and myelin regeneration via CCN3 (137)
	Spinal cord contusion	Tregs	Promoted M2 macrophages (138)
	Middle cerebral artery occlusion	CD8$^+$ Tregs	IL-10–producing B cell treatment generated a dominant IL-10$^+$CD8$^+$CD122$^+$ Treg population that reduced inflammatory response in brain (118)
Heart	Myocardial infarction	Tregs	CC5R-induced Treg recruitment (139)
			CD39-dependent cardioprotection (140)
			Induced M2-like macrophage differentiation that promoted wound healing (141)
Lung	LPS-induced ALI	Tregs	Decreased macrophage proinflammatory responses and increased efferocytosis (33, 142); CD73$^+$ Tregs promoted adenosine-mediated resolution (143); Tregs inhibited fibrocyte recruitment via CXCL12 reduction (144)
	H5N1 infection		Treg-derived AREG protected against tissue damage (40)
	LPS or left-lung pneumonectomy		Treg-derived KGF increased lung epithelial cell proliferation (44)
	ALI and cell culture		Treg-derived AREG or CD103 increased proliferation of damaged type II AECs and promoted their differentiation into type I AECs (56)
	ALI (H5N1 infection)	CD8$^+$ Tregs	IL-10$^+$Foxp3$^+$CD8$^+$ T cells decreased CD8$^+$ effector T cell responses (119)
	ALI (*Klebsiella pneumoniae* infection)	Th22/IL-22$^+$ T cells	In bronchial/tracheal epithelium, IL-22 increased expression of G-CSF, AMPs, lipocalin 2, CXCL5, polymeric Ig receptor, and mucin 1 (79, 145)
	ALI (LPS injection)	$\gamma\delta$ T cells	$\gamma\delta$ T cell–derived IL-4 regulated proinflammatory M1 macrophage expansion via TNF-α (146)
Kidney	IRI-induced AKI	Tregs	Tregs increase IL-10 (35); CD73$^+$ Tregs provided adenosine-mediated protection (147); PD-L1 and PD-L2 protected from IRI (148); anti–CTLA-4 suppressed Treg-mediated protection (149); antagonists of P2X7R ATP receptors ameliorated AKI (150)
	Cisplatin-induced nephrotoxicity		Tregs decreased TNF-α and IL-1β (151)
	IRI-induced AKI	DN T cells	DN T cells ameliorated ischemic kidney injury and expanded after ischemia, increasing IL-10 and IL-27 (100)

ALI, acute lung injury; AEC, alveolar epithelial cell; AKI, acute kidney injury; AMP, antimicrobial peptide.

IL-10 receptor or signaling pathway polymorphisms are among possible explanations for the lack of IL-10 efficacy (76).

Therapeutic benefits of T_R1 have been shown in models of colitis, transplantation, and GvHD (64, 77), underscoring the need for IL-10–producing cells and not merely the antiinflammatory cytokine. Administration of antigen-specific T_R1 cells to refractory Crohn's disease patients has been reported to be well tolerated with dose-related efficacy (78).

CD4$^+$IL-22$^+$ cells

IL-22 can be produced by several immune cells, including CD4$^+$ T cells (Th22 cells), innate lymphoid cells (ILC2 cells), and, less commonly, $\gamma\delta$ T cells, natural killer T cells (NKT cells), and CD8$^+$ T cells (79). IL-22 is unique among cytokines, because it is secreted by immune cells, but its action occurs primarily in nonimmune epithelial cells and fibroblasts that express the IL-22 receptor (IL-22R1) (80). CD4$^+$ Th22 cells require RORγt and AHR expression, and they also express CCR10 and CCR4, which can direct them in the skin (81). Other CD4$^+$ populations that can secrete IL-22 include Th1 and Th17 cells (82). The latter express CCR6 and CCR4 and can be found in the intestine, lung, and skin.

IL-22 displays potent protective and reparative functions. It has been well studied in mucosal barriers in the lungs and gastrointestinal tract for its role in protection against bacteria, viruses, and parasites (83). IL-22 plays a role in barrier integrity during invasion of pathogens: IL-22 can work synergistically with other cytokines such as IL-17 to promote the production of endogenous

antimicrobial peptides important in host defense in the skin, airways, and intestine (82). Additionally, IL-22 can promote wound healing by enhancing epithelial migration, differentiation, and proliferation, in part by inducing antiapoptotic molecules (Bcl-2, Bcl-xL) and cell cycle and proliferation proteins (c-Myc, cyclin D1, CDK4) (84–86). IL-22's roles in wound healing (87), pancreatic β cell and liver regeneration (88, 89), protection against lung and liver fibrosis (90, 91), and other functions underscore its widespread importance in tissue protection and repair. However, dysregulated and uncontrolled expression of IL-22 can lead to chronic inflammation and contribute to tissue damage, as seen in psoriasis and atopic dermatitis, and has been linked with the development of several types of neoplasia (92).

A placebo-controlled study to evaluate safety, tolerability, immunogenicity, and pharmacokinetics of intravenous IL-22Fc (an antibody-modified IL-22 fusion protein registered under the name UTTR1147A; NCT02749630) in healthy volunteers, IBD patients, and gastrointestinal GvHD patients (NCT02406651) is under way. Conversely, trials of IL-22 antibody blockade are ongoing for psoriasis and atopic dermatitis (NCT01941537).

CD4$^-$CD8$^-$ double-negative $\alpha\beta$ T cells

CD4$^-$CD8$^-$ double-negative (DN) $\alpha\beta$ T cells are an unconventional subset of T cells with increasingly recognized antiinflammatory and pro-reparative potential. DN T cells can be found in peripheral blood and lymphoid organs in relatively small numbers. However, they represent a substantial fraction

Table 3. Selection of T cell reparative roles in liver, gastrointestinal, muscle, skin, and bone models of injury

Organ	Model	Cell type	Comment on mechanism (reference)
Liver	Hepatic IRI	Tregs	Mediated decreases in IFN-γ and IL-17 (152)
	Poly:C/d-GalN–induced fulminant hepatitis		Mediated increases in TGF-β and Kupffer cell–derived IL-10 (153)
	Chronic HCV infection[A]		Suppressed T cell proliferation and IFN-γ (154, 155)
	Chronic HCV infection[A]	CD8+ Tregs	IL-10–secreting CD8+ Tregs reduced hepatocellular apoptosis, but impaired viral clearance (120)
	Concavalin A–induced hepatitis	T_R1	Increased IL-10 and decreased TNF-α and IFN-γ (156)
	Concavalin A–induced hepatitis	Th22/IL-22+ T cells	Mediated STAT3-dependent increases in antiapoptotic and mitogenic proteins (88)
	HBV infection[A] (mice and humans)		Proinflammatory role in HBV viral infection (157)
	CCl4-induced liver fibrosis	γδ T cells	CCR6-dependent recruitment of IL-17+IL-22+ γδ T cells reduced hepatic inflammation and fibrosis (158)
GI	Intestinal epithelial carcinoma cells	Th22/IL-22+ T cells	Increased expression of AMPs (79)
	Colonic epithelial cells		Upregulated mucin 1, 3, 10, and 13 (159)
	Human adenocarcinoma cells[A]		Upregulated the AMP β-defensin and IL-8 (160)
	Intestinal IELs	γδ T cells	γδ T cell–derived KFG promotes epithelial maintenance and repair (105, 109, 161)
Muscle	Cardiotoxin-induced injury	Tregs	Decreased IFN-γ production by NK and effector T cells, leading to decrease in MHC-II+ macrophages (162)
	Dystrophy model		Treg-derived AREG enhanced satellite cell differentiation and muscle repair (51)
Skin	Wound healing	Tregs	Decreased IFN-γ production by effector T cells, reduced M1 macrophage accumulation, increased EGFR expression, reduced infiltration and increased apoptosis of neutrophils to shorten the inflammatory response (163)
	Human keratinocytes[A]	Th22/IL-22+ T cells	IL-22 in T cell dermatosis patient skin (164); increased AMPs/proinflammatory gene expression and decreased keratinocyte differentiation gene expression (165); mediated psoriasis-like morphological changes (166); slight elevation in CXCL1, 2, 5, and 8 (167); slight decrease in CCL22 and increase in IL-20 (168)
	Mouse skin	γδ T cells	Murine DETCs have multiple roles in epithelial homeostasis (104, 109, 169, 170); produced KGFs to indirectly drive macrophage recruitment (110); produced IGF-1, increasing survival of epithelial cells in wounds (111); regulated keratinocyte AMP production (107)
	Human skin[A]		Human γδ T and αβ T cells produced IGF-1, an epithelial growth and survival factor (106)
Bone	Bone fracture healing	Tregs	Decreased osteoclast differentiation via TGF-β, IL-4, and cell-cell contact (171, 172); (in)directly promoted osteoblast differentiation by inhibiting conventional T cells (173, 174)

AMPs, antimicrobial proteins; HCV, hepatitis C virus; GI, gastrointestinal; IEL, intraepithelial lymphocyte. [A]Human data.

in nonlymphoid tissues, e.g., lung, liver, and kidney (93), and can be detected in high numbers in mucosal tissue, e.g., gut epithelia (94) and female reproductive tract (95). Their potential in immune regulation has been described in various settings: graft tolerance (96), autoimmunity (97), and cancer (ref. 98 and Table 1). The predominant antiinflammatory mechanisms ascribed to DN T cells are secretion of IL-10 (97) and cytolysis by granzymes and perforins (98). However, in systemic lupus erythematosus, IL-17–producing DN cells have been associated with an adverse effect (ref. 99 and Table 1).

In mouse kidneys, a large proportion (~25%) of T cells are DN αβ T cells, which are also prominent in human kidneys, but to a lesser extent. Two different types of renal DN αβ T cells have been described: an MHC-independent programmed cell death protein-1 receptor+ (PD-1+) subset and an MHC class I–dependent NK1.1+ subset. DN αβ T cells ameliorate ischemic kidney injury and expand after ischemia. More specifically, the PD-1 subset is highly responsive under ischemia/reperfusion injury (IRI) conditions (100, 101).

IL-2 is required for DN αβ cell activation and function as well as DN αβ cell proliferation during the steady state (101). In vitro T cell function is suppressed by DN αβ T cells (100). Additionally, kidney-resident DN αβ T cells showed sizable expression of the antiinflammatory cytokines IL-10 and IL-27 in steady state at the mRNA and protein levels. Three hours after IRI, an increase of IL-10 and a decrease of IL-27 were found (ref. 100 and Table 2).

Other data suggest an aggravation of inflammatory processes by DN αβ T cells. In a stroke mouse model, DN cells were found to cause an exacerbation of ischemic brain injury (102). However, this study did not distinguish different DN T cell subtypes, so the analyzed population might not be limited to DN T cells with αβ TCR. To date, no specific marker has been found for DN T cells, which makes it difficult to compare different studies and easy for results to be misinterpreted owing to possible contamination of other immune cell types.

Thus, DN αβ T cells are a very promising T cell subset to put the brakes on inflammation and accelerate repair. Recently, adoptive transfer of allogeneic DN T cells has been shown to be safe

and efficacious for potential treatment for patients with acute myeloid leukemia and could be considered as a cellular therapy to accelerate organ repair (103).

γδ T cells

γδ T cells represent a small fraction (1%–5%) of circulating T cells in the blood and secondary lymphoid organs (104), but can be present in higher proportions in epithelial tissues in the skin, gastrointestinal tract, and reproductive tract (105). Thus they are well positioned to be involved in epithelial barrier function, repair, and homeostasis, and there is evidence that they do so in a tissue-specific manner.

The murine skin epidermal layer contains Langerhans cells and T cells. The majority of the T cells arise from highly specialized γδ T cells termed dendritic epidermal T cells (DETCs). Although a human equivalent of DETCs is yet unknown, the human epidermis houses both γδ and αβ T cells (106–108). After sensing stress or damage, activated DETCs produce IGF-1, KGF, and KGF2, which promote keratinocyte proliferation and wound healing. DETCs can also produce IL-17A, which can stimulate the induction of the antimicrobial peptide regenerating islet-derived protein 3γ (REG3γ) and β-defensin, which provide antimicrobial protection and mediate re-epithelialization of the skin (106). In the intestine, γδ intraepithelial lymphocytes have been shown to produce TGF-β1, which reduced the expression of IFN-γ from intestinal αβ cells to dampen inflammation in addition to their role in promoting tissue repair (105, 109–111).

In summary, subsets of γδ T cells are poised to perform tissue-specific roles in inflammation and repair. While the full spectrum of factors that shape γδ T cell activity is not known, specific butyrophilin-like (BTNL) molecules that are expressed in different epithelial tissues could shape, expand, and mature tissue-specific γδ T cells (112).

CD8+ Tregs

It has been several decades since CD8+ Tregs were first described as regulators of immune responses (113). However, the interest in these cells has been relatively muted compared with that in CD4+ Tregs. Different CD8+ Treg subsets have been described, and there is growing evidence of their role in autoimmune diseases, cancer, and chronic infections (114–116).

No specific marker for CD8+ Tregs has been identified to date, making it difficult to compare different studies. The three main subpopulations described and explored are CD28$^{-/lo/+}$CD8+ Tregs (115); CD122+CD8+ Tregs (mouse), CXCR3+CD8+ Tregs (human) (117); and Qa-1–restricted CD8+ Tregs (mouse), HLA-E–restricted CD8+ Tregs (human) (Table 1).

There are limited data regarding the role of CD8+ Tregs in injury and repair. In a murine model of stroke, treatment with IL-10–producing B cells resulted in generation of a dominant IL-10+CD8+CD122+ Treg population that was associated with decreasing inflammatory responses in brain to a greater extent than were CD4+ Tregs. Thus, CD8+ Tregs might have overlapping function with CD4+ Tregs (118).

Nevertheless, functions of CD8+ Tregs might not be entirely beneficial. In an acute lung injury model involving H5N1 influenza virus infection, IL-10+Foxp3+CD8+ T cell–mediated suppression of CD8+ effector T cell responses led to an increase in mortality (119). However, the effects of regulatory functions of IL-10+Foxp3+CD8+ T cells in lung injury versus viral infection have not yet been elucidated (119). Additionally, because of the lack of a specific marker for CD8+ Tregs, the results of different studies cannot be clearly compared and interpreted. In patients with chronic hepatitis C virus infection, IL-10–producing CD8+ T cells have been reported to reduce hepatocellular apoptosis, suggesting that the CD8+ T cells have regulatory functions. However, a detailed immunophenotyping of the CD8+ T cells was not performed in this study (120). Further research will be needed to investigate the role of CD8+ Tregs in injury and repair processes.

Concluding remarks

An emerging body of work supports the important role for T cells in resolution of inflammation and organ repair. The most studied T cell implicated in organ repair has been the CD4+Foxp3+ Treg. However, data support an important role for T_R1 cells, CD8+ Tregs, CD4+IL-22+ T cells, CD4−CD8− DN αβ T cells, and γδ T cells. Other innate lymphoid T cells such as ILC2 cells, invariant NKT cells, and mucosal-associated invariant T (MAIT) cells have important immune-regulatory functions and can display substantial repair and regeneration effects (121). These cells will be covered in another article in this *JCI* Review series on reparative immunology.

Given the relatively low numbers of these T cells compared with their powerful actions, it is likely that they use both soluble and contact-dependent mediators and work through other cell types. Increasing numbers or enhanced function of specific pro-repair T cells will likely represent the next generation of therapeutics for organ repair. This approach will need to be personalized, and several factors will have to be considered, including specific organ involvement, the underlying cause and stage of organ injury (e.g., sterile versus infectious and acute versus chronic), the need for polyclonal versus antigen-specific T cells, their chemokine and homing receptor repertoire (to target the specific injured organ), and mechanisms to modulate their pro-repair T cell lineage commitment via epigenetic and metabolic reprogramming. Ex vivo "conditioning" of autologous specific T cells with repair function (via cytokines, drugs, viral transduction, or gene editing) or expanded engineered T cells (with a reparative armamentarium) will need to be studied as cellular adoptive transfer therapy to promote resolution of inflammation and organ repair.

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