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Foxp3+ regulatory T cells (Tregs) are essential for preventing autoimmunity and uncontrolled inflammation, and they modulate immune responses during infection and the development of cancer. Accomplishing these tasks requires the widespread distribution of Tregs in both lymphoid and nonlymphoid tissues, and the selective recruitment of Tregs to different tissue sites has emerged as a key checkpoint that controls tissue inflammation in autoimmunity, infection, and cancer development, as well as in the context of allograft acceptance or rejection. Additionally, Tregs are functionally diverse, and it has become clear that some of this diversity segregates with Treg localization to particular tissue sites. In this article, I review the progress in understanding the mechanisms of Treg trafficking and discuss factors controlling their homeostatic maintenance and function in distinct tissue sites. The Journal of Immunology, 2015, 195: 2507–2513.

The discovery of dominant tolerance mediated by different populations of regulatory T cells (Tregs) ~20 y ago initiated a flurry of research into the cellular and molecular basis for the function of these cells. A key discovery occurred when several groups found that the transcription factor Foxp3 is essential for the proper development and function of Tregs (1). Indeed, loss of Treg function due to mutations in Foxp3 results in fatal systemic autoimmunity in both mice and humans, and defects in the development, function, or maintenance of Tregs were implicated in the pathogenesis of a host of autoimmune and inflammatory diseases. Conversely, Tregs can inhibit pathogen clearance and promote chronic infection, and they represent a significant barrier to effective tumor immunotherapy. Therefore, understanding the control of Treg homeostasis and function has significant therapeutic implications.

Based on the discovery of Foxp3 as a master transcription factor, a number of experimental tools were developed that allowed for the precise identification and molecular characterization of Foxp3-expressing cells, resulting in unparalleled insights into the biology of Tregs. A central theme that emerged from these studies is that, like conventional CD4+ Th cells, Tregs are phenotypically and functionally diverse, and their localization and maintenance in different tissue sites are essential for their ability to interact with and modulate their cellular targets. This Brief Review covers recent advances in understanding the control of Treg localization, homeostasis, and function in lymphoid and nonlymphoid tissue sites, with particular emphasis on how manipulation of these pathways could be therapeutically beneficial in the contexts of autoimmune disease, cancer, and transplantation.

Phenotypic and functional diversity of Tregs

Two pathways exist for Treg development. Differentiation of thymic-derived Tregs (tTregs) depends on high-affinity interactions with self-peptide/MHC class II complexes during T cell development in the thymus (2, 3), whereas peripheral-derived Tregs (pTregs) develop in the periphery from naive T cell precursors that upregulate Foxp3 when activated by foreign Ags in tolerogenic conditions. Specifically, activation of naive T cells in the presence of TGF-β and the absence of inflammatory cytokines, such as IFN-γ, IL-4, or IL-6, results in pTreg development (4); as such, pTregs are particularly important for tolerance at mucosal surfaces against commensal microorganisms and harmless environmental Ags. However, definitive markers differentiating tTregs and pTregs have not been identified; thus, in most cases, the relative contributions of tTregs and pTregs to the Treg pool in different tissues and inflammatory settings have not been determined.

Initial analysis of homing receptor expression by Tregs indicated that, rather than having a uniform phenotype, Tregs could be subdivided into distinct populations that expressed adhesion and chemoattractant receptors that would target them to a range of tissues and inflammatory sites (5). These included cells that would be targeted to secondary lymphoid organs, to specific nonlymphoid tissues, such as the skin and intestines, and to sites of Th1-, Th2-, or Th17-mediated inflammatory responses. Accordingly, Tregs are broadly distributed in lymphoid and nonlymphoid tissue sites, even in the absence of any overt inflammation (6), and many studies demonstrated that Tregs function in both lymphoid and nonlymphoid tissues to prevent the initiation of aberrant immune responses or to dampen ongoing inflammatory responses, respectively.

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Tregs are known to occupy their own homeostatic niche, as evidenced by the ability of small numbers of Tregs to expand dramatically when transferred into Treg-deficient hosts (7). However, the presence of significant populations of Tregs in multiple lymphoid and nonlymphoid organs raises the question of whether Tregs in different tissues are maintained by distinct homeostatic mechanisms. Indeed, despite the incredibly complex patterns of homing receptor expression by Tregs, based on differential expression of the activation marker CD44 and the lymph node homing receptor CD62L, Tregs can be broadly divided into CD44hiCD62L– central Tregs (cTregs) and CD44loCD62Lhi effector Tregs (eTregs) that display distinct homeostatic behaviors (8). Although cTregs are quiescent, express high-levels of antiapoptotic molecules (e.g., Bcl-2 and Mcl-1), and recirculate through the secondary lymphoid tissues, eTregs are highly proliferative, are prone to apoptosis due to decreased expression of Bcl-2 and Mcl-1, and are the dominant Treg population in nonlymphoid tissues. Unlike recirculating cTregs, parabiosis experiments indicated that eTregs in nonlymphoid tissues are largely tissue-resident. Thus, there appears to be a division of labor between cTregs and eTregs that are specialized for functioning either within the secondary lymphoid tissues to inhibit T cell priming or in specific nonlymphoid tissues and inflammatory sites to dampen effector cell responses, respectively (9, 10). However, the function of both cTregs and eTregs likely depends on their precise positioning that facilitates the cellular interactions that promote Treg function and homeostasis.

**Treg function and maintenance in secondary lymphoid organs**

Before exiting the thymus, tTregs upregulate the expression of the homing receptors CD62L and CCR7, which together target these recent thymic emigrants to secondary lymphoid tissues (11). Several imaging studies examined Treg behavior in secondary lymphoid tissues and found that Tregs were highly mobile cells that were present throughout the central T cell zones (12-15). However, in the presence of self-Ag, for instance when islet-Ag-specific Tregs from BDC2.5 TCR-transgenic mice are examined in the pancreatic lymph nodes, Tregs arrested and formed stable contacts with Ag-bearing dendritic cells (DCs) (13). The interactions between Tregs and DCs subsequently prevented the stable interactions between naive T cells and DCs that are required for T cell activation and effector differentiation (12, 13). Thus, a primary mode of Treg function in secondary lymphoid tissues may be through inhibition of DC activation and function, thereby blocking the inappropriate priming of autoreactive T cells. Consistent with this, depletion of Tregs caused a rapid increase in the activation state of DCs in secondary lymphoid tissues (16).

The actual mechanisms by which Tregs control DC activation in secondary lymphoid organs are still not entirely clear. However, Treg expression of CTLA-4 appears to be one important component. Tregs are characterized by constitutive expression of CTLA-4, which, as an inhibitory cell surface receptor, has a higher affinity for the costimulatory ligands CD80 and CD86 than does its costimulatory counterpart CD28 (17). Thus, CTLA-4 expression by Tregs can inhibit DC function by masking CD80 and CD86 or even by stripping CD80 and CD86 out of the membrane of DCs via a process known as trans-endocytosis (18). Additionally, reverse signaling via CTLA-4 interactions with CD80 and CD86 induced DC expression of the immunosuppressive enzyme IDO (19). Consistent with this model, loss of CTLA-4 expression in Tregs resulted in lymphoproliferative disease marked by aberrant T cell activation, as well as severe lymphadenopathy and splenomegaly (20). Interestingly, CTLA-4 also mediates direct interactions between Tregs and effector T cells in lymph nodes, and although the functional importance of these interactions is not clear, they may also contribute to inhibition of T cell priming (15).

In contrast to naive T cells, Tregs in secondary lymphoid organs express low levels of the IL-7R component CD127 (21); therefore, unlike naive T cells, they do not rely on IL-7 for their homeostatic maintenance. Instead, Tregs are characterized by constitutive expression of the high-affinity IL-2R component CD25. Indeed, IL-2 serves many similar functions for Tregs that IL-7 does for naive T cells. For example, like naive T cells that respond to paracrine IL-7 produced by fibroblastic reticular cells (FRCs), Tregs cannot produce their own IL-2; instead, they rely on paracrine IL-2 produced by activated T cells (22, 23). Additionally, just as IL-7 helps to maintain naive T cells without driving robust homeostatic proliferation, IL-2 signaling in Tregs in secondary lymphoid tissues is limited to quiescent cTregs and is not associated with the high level of homeostatic proliferation observed in eTregs (8). Indeed, cTregs are particularly dependent on IL-2 for their homeostatic maintenance, whereas eTreg maintenance and proliferation are largely IL-2-independent. The ability of cTregs to selectively access IL-2 in vivo is due to their CCR7-dependent migration into organized T cell zones in secondary lymphoid tissues (8). Interestingly, FRCs are the primary sources of the CCR7 ligands CCL19 and CCL21 in the secondary lymphoid organs (24). Therefore, it appears that whereas FRCs control naive T cell homeostasis via direct production of IL-7, they indirectly regulate cTreg homeostasis by bringing together CCR7-expressing cTregs, DCs, and effector T cells to facilitate effector T cell activation and paracrine IL-2 cross-talk between effector T cells and Tregs. It should be noted that, in addition to its role in cTreg maintenance, IL-2 influences Treg function. Thus, increasing Treg numbers in IL-2–deficient mice by knocking out the proapoptotic molecule Bim failed to rescue the inflammatory phenotype in these animals, and this was associated with impaired Treg expression of CTLA-4 (25).

In addition to its effects on Tregs, IL-2 potentiates effector T cell proliferation and differentiation. This raises the questions of how IL-2 signaling is directed toward different cell types during the development and resolution of immune responses and how this contributes to the pro- or anti-inflammatory functions of IL-2. In the steady-state, high-level expression of CD25 is limited to Tregs; thus, these cells have a competitive advantage for responding to IL-2 (8, 26). However, activated T cells rapidly upregulate CD25, allowing them to compete with Tregs for locally produced IL-2. Additionally, to facilitate IL-2 signaling, effector T cells can form clusters characterized by multifocal, LFA-1–dependent T cell–T cell synapses that allow for direct delivery of IL-2 between the engaged cells (27). In addition to increasing the local concentration of IL-2, it is possible that this synapic cross-talk between effector T cells functions to hide IL-2 from nearby cTregs, thereby helping to potentiate effector cell responses. Thus, synapic versus nonsynapic signaling could help to explain the dual pro- and anti-inflammatory nature of IL-2. In this scenario, IL-2 production following initial T cell activation would act primarily on Tregs, enhancing their function and acting as a brake on self-limiting responses. However, if responding...
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T cells reach a critical density, T cell–T cell synapses can form, leading to direct exchange of IL-2 between effector T cells, thereby promoting their proliferation and function (Fig. 1). Consistent with this model, cTregs can access IL-2 in vivo, even without stimulation by their cognate Ag (and the resulting upregulation of LFA-1 expression and affinity), indicating that, at least in the steady-state, Tregs are unlikely to be receiving IL-2 through synaptic signaling (8, 28). Additionally, IL-2 produced early during viral infection acts predominantly on Tregs and not on responding effector T cells (26). However, various aspects of the timing, extent, and localization of IL-2 signaling in regulatory versus effector T cells during the development of normal and dysregulated immune responses have not been carefully examined; therefore, the extent to which synaptic versus nonsynaptic production/signaling influences the pro- and anti-inflammatory functions of IL-2 is not clear.

**Treg migration, function, and homeostasis in nonlymphoid tissues**

In addition to the ability of cTregs to inhibit T cell priming in the secondary lymphoid tissues, cTregs are widely distributed in nonlymphoid tissues where they can modulate the activity of a variety of effector cell targets to dampen inflammatory responses and prevent collateral tissue damage and autoimmunity. Indeed, cTregs express patterns of adhesion and chemoattractant receptors that are expected to target different cTreg cell subsets to specific nonlymphoid tissues or inflammatory sites, and they highly express immunosuppressive molecules, such as IL-10, that are important for maintaining tolerance in nonlymphoid tissues (10). Nonlymphoid tissues also contain populations of memory Tregs (mTregs) that can develop in response to transient expression or encounter with Ags, such as Ags contacted at barrier surfaces (e.g., the skin) or paternal Ags recognized during allelogeneic pregnancy, and are maintained in the absence of continued Ag recognition (29–31). In many cases, the importance of individual receptors for Treg migration to distinct tissue sites has been demonstrated in vivo, with corresponding impacts on Treg function and immune homeostasis in these sites (32). That Tregs have a fundamental role in controlling autoimmune and inflammatory responses in a wide-range of nonlymphoid tissues has been well established and reviewed elsewhere (33) and, therefore, will only be discussed in this article in the context of specific tissues and inflammatory conditions that demonstrate some of the fundamental principles of Treg migration, function, and homeostasis.

As barrier organs, the skin and the intestines present unique challenges to the immune system. Although both are portals of entry for pathogens, these must be identified among the large number of commensal micro-organisms present in these sites. Additionally, both the skin and intestines are exposed to harmless environmental and food-derived Ags that are contacted or ingested. Breakdown in the appropriate regulation of immune responses in these tissues leads to the development of inflammatory diseases such as psoriasis, atopic dermatitis, contact hypersensitivity, inflammatory bowel disease, and food allergy. Given this immunological balancing act, it is not surprising that, although Tregs are widely distributed in nonlymphoid tissues, both the skin and intestine harbor large populations of specialized Tregs. Moreover, cutaneous and intestinal Tregs use many of the same molecules to access these sites as do their effector cell counterparts. For instance, constitutive Treg migration to the skin requires the chemokine receptor CCR4 and surface expression of carbohydrate ligands for P- and E-selectin that are expressed by vascular endothelial cells in the skin; consequently, Tregs lacking CCR4 or the endothelial selectin ligands fail to properly regulate cutaneous immune responses (6, 34, 35). Treg migration to the intestine is not as well characterized, although, as with effector T cells, it is dependent on the expression of β7 family integrins (α4β7 or αEβ7) (36). Recently, however, the orphan G protein–coupled receptor GPR15 was identified as an essential factor selectively mediating Treg migration to the intestine (37); consequently, loss of GPR15 results in dysregulated intestinal immune responses.

Expression of cutaneous versus intestinal homing receptor expression by Tregs appears to be controlled by specific factors present in the immune environment of these organs and their associated lymphoid tissues. For instance, the intestine harbors a specialized population of CD103 (αE integrin)-positive DCs cells that selectively expresses the RALDH enzymes capable of converting dietary vitamin A into retinoic acid (RA) (38, 39). Signaling through cellular RA receptors, RA drives T cell ex-
pression of the intestinal homing receptors α4β7 integrin and CCR9 (40). Additionally, short-chain fatty acids, such as butyrate produced by commensal bacteria, can promote pTreg differentiation and enhance the proliferation and accumulation of existing intestinal Tregs via signaling through GPR43 (41–43). In contrast to RA and short-chain fatty acids, inflammatory cytokines, such as IL-6, that are produced following recognition of bacterial DNA via TLR9 inhibit pTreg differentiation and function in the intestine (44, 45). This highlights the concept that the abundance and activity of Tregs within the intestine are controlled by a complex regulatory circuit that can monitor the microbiota in the intestine and respond by altering Treg differentiation, homeostasis, migration, and function.

Although the development and homeostasis of cutaneous Tregs are not as well characterized as those of intestinal Tregs, many of the same concepts are thought to apply. The skin is home to a diverse microbial flora, and interaction with these organisms can directly influence the size and functionality of the cutaneous Treg pool, as evidenced by the dramatically elevated numbers of Tregs in the skin of germ-free mice that can dampen responses to cutaneous infection with Leishmania major (46). Moreover, cutaneous Tregs accumulate near invaginations in the epithelium associated with hair follicles that are specific points of interaction between the skin microflora and the cutaneous immune system (47). The signals that direct Treg expression of cutaneous-homing receptors responsible for this positioning have not been precisely defined; however, interaction with cutaneous DCs can promote expression of the fucosyltransferase IV and VII enzymes that generate ligands of P- and E-selectin (48).

In addition to the Treg populations constitutively found in nonlymphoid tissues, eTregs are rapidly recruited to inflamed tissues where they can help to resolve the inflammatory response. The ability of Tregs to access inflamed tissues is due to the wide array of receptors for inflammatory chemokines that they express (5, 33). These include receptors directing cells to sites of Th1-, Th2-, or Th17-mediated inflammatory responses, such as CXCR3, CCR8, and CCR6, as well as more general inflammatory receptors, such as CCR2 and CCR5. In several cases, deficiency in individual receptors has had severe impacts on Treg function during inflammation (49). For instance, loss of CCR6 prevents Treg migration to inflamed joints in a model of rheumatoid arthritis (50, 51), whereas CCR5 broadly helps to direct Treg localization in the contexts of infection, allograft rejection, and inflammatory bowel disease (52–54). In addition to these chemokine receptors, Tregs express surface integrins that influence their localization and function during inflammation. For instance, Tregs express high levels of αLβ2 integrin (LFA-1) and α4β1 integrin (VLA-4); together, these can help to direct Treg migration to inflamed tissue sites (55).

Interestingly, Tregs in certain nonlymphoid tissues have proposed tissue support functions beyond their well-established roles in immune regulation. These include metabolic regulation by Tregs in visceral adipose tissue (56) and regulation of tissue repair by Tregs in skeletal muscle (57). Although the signals responsible for the development, tissue-specific migration, and maintenance of these resident Treg populations are poorly characterized, Tregs in adipose tissue depend on the transcription factors IRF4 and BATF, as well as the cytokine IL-33 (58). Generally speaking, the homeostatic mechanisms that maintain Tregs in nonlymphoid tissues are distinct from those supporting cTregs. Thus, rather than being IL-2 dependent, eTreg abundance appears to be controlled largely by signals through the TCR and associated costimulatory receptors, such as ICOS (8, 28, 59). Accordingly, deletion of the TCR in mature Tregs or Ab-mediated blockade of ICOSL results in a rapid decline of the eTreg population, whereas IL-2 blockade has little effect on the abundance or proliferation of these cells. The molecular mechanisms by which continued TCR and costimulatory receptor signaling support eTreg homeostasis are poorly understood, but they may involve activation of prosurvival signaling pathways, such as the PI3K pathway that counteracts the proapoptotic functions of Foxp3 (60), and maintenance of the eTreg transcriptional signature, which is dependent, at least in part, on the transcription factor Blimp-1 (28, 61). Additionally, new data indicate that IL-33 is an important homeostatic factor for eTregs in multiple tissue sites (58, 62, 63). In contrast to eTregs, mTregs (by definition) are maintained in nonlymphoid tissues in the absence of cognate Ag stimulation. However, at least in the skin, mTreg maintenance was also IL-2 independent and instead relied on IL-7/IL-7R signaling (64). Additionally, new data indicate that IL-33 is an important homeostatic factor for eTregs in multiple tissue sites (58, 62, 63). Importantly, most eTregs and mTregs retain CD25 expression (albeit generally at lower levels than cTregs) and respond well to IL-2 in vitro and in vivo (8, 64). This strongly indicates that the lack of IL-2 signaling in these cells likely occurs as a result of their localization in tissues and environments that have a low T cell density and lack the cellular organization that facilitates paracrine IL-2 signaling between effector and regulatory T cells. This has important clinical implications, because it suggests that eTregs and mTregs would still be responsive to IL-2-based therapies for boosting Treg abundance.

**Treg homeostasis and migration in disease**

Because the outcome of a given immune response depends, in part, on the relative numbers and function of effector and regulatory cells, understanding Treg migration and homeostasis is important in the contexts of organ-specific autoimmune diseases, transplantation, and cancer development. In each of these settings, therapeutically manipulating Treg function could be beneficial for inducing or restoring tolerance or for promoting effective antitumor responses and successfully implementing new anticancer immunotherapies.

Paradoxically, as a result of the effective recruitment of Tregs to sites of inflammation discussed above, the number and frequency of Tregs are often dramatically elevated in inflammatory infiltrates associated with autoimmune disease in both mice and humans (65–67). However, their inability to control disease indicates that these Tregs are either quantitatively or qualitatively insufficient to fully restore immune tolerance and ameliorate the inflammatory response. Efforts to quantitatively restore Tregs have focused on either expansion of existing Tregs via IL-2 or reinfusion of ex vivo–expanded Tregs. A major hurdle to successful implementation of IL-2–based therapies lies in the fact discussed above: in addition to its effects on Tregs, IL-2 is a potent trophic factor for proinflammatory effector T cells that upregulate CD25 upon activation. As a result, the effectiveness of IL-2 in treating disease in preclinical models of autoimmunity has varied greatly, depending on the dose and timing of administration (68). Although low doses of IL-2 given prior to or early in disease proved effective, higher doses of IL-2 given later exacerbated or accelerated disease development (67,
To promote Treg migration to the intestines via tissue tropism of these infused cells to achieve long-term engraftment and provide substantial clinical benefit. If this is the case, combining Treg infusion with IL-2 therapy to expand the Treg niche may prove to be more efficacious than either therapy alone. Additionally, because eTreg maintenance depends on continued TCR and costimulatory signals, maintenance of Ag-specific Tregs would likely be far more efficient than that of polyclonal Tregs. However, because Treg-derived cytokines, such as TGF-β and IL-35, can promote regulatory function in other T cells (73, 74), Treg infusion may provide long-term clinical benefit, even if the infused cells are present for only a short time via induction of infectious tolerance.

In the application of Treg-based cellular therapies, a second important factor to consider is the ability of the infused cells to migrate to the appropriate tissues after transfer. The complexity of Treg migration during suppression of unwanted immune responses is highlighted by a study demonstrating, in an islet allograft model, that suppression by transferred Tregs required their choreographed and sequential migration from the tissue, the abundance of homeostatic factors that govern their activity in a given tissue site is a function of their migration to that tissue, the expression of CXCR3 and facilitate Treg localization to sites of Th1-mediated inflammation where the CXCR3 ligands CXCL9 and CXCL10 are abundantly produced (76, 77).

Qualitatively, Treg function can be compromised in inflamed tissues by cytokines such as IL-1, IL-6, or type-1 IFNs that either directly inhibit Tregs or promote effector T cell resistance to suppression by Tregs (45, 78–80). Additionally, the inflammatory environment can promote Treg instability and the differentiation of Foxp3+ ex-Tregs, which, as a result of their autoreactivity and production of effector cytokines, may actually contribute to disease pathology and exacerbation (81). This represents a significant barrier to effective implementation of Treg-based immunotherapies and suggests that combination therapies aimed at simultaneously inhibiting inflammatory cytokines and boosting Treg function have the greatest chance of therapeutic efficacy in blocking unwanted immune responses (82).

In addition to positively promoting Treg migration and accumulation in inflamed tissues to dampen autoimmunity and prevent graft rejection, inhibition of Treg function in tumors is key to initiating robust antitumor responses and could help to improve the efficacy of cellular tumor immunotherapy. That Tregs actively inhibit effective antitumor immune responses is supported by data demonstrating that Treg accumulation within some tumors is associated with poor clinical prognosis and that depletion of Tregs can promote tumor rejection in animal models (83). Additionally, new immunomodulatory therapies for cancer treatment, such as pembrolizumab (anti-PD1) and ipilimumab (anti-CTLA4), target molecules prominently expressed by Tregs and may function, in part, by inhibiting Tregs. However, therapies generally targeting Tregs are likely to encounter side effects related to loss of tolerance and development of autoimmune or inflammatory diseases, as observed with the development of inflammatory bowel disease in melanoma patients treated with anti-CTLA4 (84). Thus, specifically inhibiting Treg migration into the tumor as an adjunct to cellular immunotherapy may be advantageous. Indeed, the homing receptors used by Tregs and effector CD8+ T cells to access some tumors may be distinct, thereby providing the opportunity to selectively disrupt Treg migration and boost antitumor immunity. Specifically, Treg infiltration into several tumor types appears to be dependent on CCR4 (85–87), whose ligands CCL17 and/or CCL22 can be produced by tumor cells themselves or by tumor-associated macrophages. Importantly, CCR4 is generally not highly expressed or used by effector CD8+ T cells, suggesting that targeting CCR4 may selectively inhibit Treg function in certain tumors, thereby boosting antitumor immune responses (87, 88). Similarly, inhibiting CCR10-mediated recruitment of Tregs to tumors could be used to augment antitumor immunity (89).

**Conclusions**

Because of the potent impact that Tregs have on the development of immunity versus tolerance, the manipulation of Treg activity has tremendous therapeutic potential. Although much progress has been made, realizing this potential requires a better understanding of the basic mechanisms of Treg biology. Because Treg activity in a given tissue site is a function of their migration to that tissue, the abundance of homeostatic factors that govern their proliferation and survival, and the presence of cytokines and other factors that promote or inhibit their function, a better understanding of each of these processes will allow for the manipulation of endogenous Tregs, as well as improve the prospects of Treg-based cellular therapies.

**Disclosures**

The author has no financial conflicts of interest.

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