The Journal of Immunology

RESEARCH ARTICLE | JULY 01 2021

T Regulatory Cells Influence Decisions between Concomitant Immunity versus Sterile Cure FREE

Juan M. Inclan-Rico; ... et. al

J Immunol (2021) 207 (1): 3–4.
https://doi.org/10.4049/jimmunol.2100338

Pillars of Immunology

The Journal of Immunology

T Regulatory Cells Influence Decisions between Concomitant Immunity versus Sterile Cure

Juan M. Inclan-Rico and De'Broski R. Herbert

Host-protective immunity is dependent upon the generation of inflammatory responses that mediate pathogen clearance, but if left unchecked, it can result in excessive tissue pathology. It is now established that distinct T lymphocyte populations serve inflammatory versus suppressive roles, but these functions are often subverted by pathogens that have evolved countermeasures allowing their chronic persistence. In contrast to acute infections that evoke sterilizing immunity, in which infectious organisms are no longer detectable, some chronic infections can result in the persistence of low amounts of infectious particles, as observed in patients infected with the parasites *Trypanosoma cruzi* or *Toxoplasma gondii* (1, 2). The low-level persistence of pathogens raises the long-standing debate as to whether immunological memory that protects against reinfection requires T cells to be constantly exposed to Ag or live pathogens. During chronic infections, the long-term persistence of reduced pathogenic loads after a primary infection, despite being protected against secondary exposures, is defined as "concomitant immunity" (3). A similar phenomenon has been described in helminth infections with *Schistosoma mansoni* and filarial nematodes, in which infection with adult worms provides effective defense against larval stages (4, 5), suggesting that parasites may represent invaluable experimental systems to study these host-pathogen interactions. Whether concomitant immunity emanated from host manipulation by parasites or is a coevolutionary adaptation of host immune responses that strikes a balance between pathogen clearance and tissue immunopathology has remained an important issue since the 1970s.

To address this and other fundamental questions, the experimental mouse model of infection with the obligate intracellular protozoan *Leishmania major* has been extensively used to investigate the basic tenets of concomitant immunity. Pivotal studies in the late 1980s established that C57BL/6 mice subjected to *L. major* cutaneous infection develop self-resolving lesions that maintain low-level parasite burdens despite the generation of a robust T_H1 response (6, 7). Conversely, *L.* major infection of BALB/c mice results in metastatic lesions and elevated mortality that are associated with T_H2 responses and excessive production of the immunosuppressive cytokine IL-10. Interestingly, human infections with *L. major* do not reflect such contrasting outcomes, but rather present in a broad spectrum of immunopathologies ranging from individuals that develop strong T cell responses and delayed-type hypersensitivity reactions to patients with elevated Ab titers who are unable to control parasite burdens (8, 9). Nonetheless, it is well documented that exposure to viable parasites in a specific skin location, a process referred as "leishmanization"' (10), is highly effective in protecting against natural infections, suggesting that concomitant immunity can develop in *L. major*–infected patients. Together, these findings have motivated studies of the complex dialog stemming from low parasite levels and host immune responses.

Groundbreaking studies by Belkaid et al. in this *Pillars of Immunology* article (https://doi.org/10.1038/nature01152) demonstrated that, along with IFN-γ–producing $CD4^+$ T effector (T_{eff}) cells, skin lesions in *L-major*–infected C57BL/6 mice were enriched with a subset of IL-10–secreting $CD4^+$ T cells. This cell subset also expressed high levels of the IL-2 receptor α-chain (also known as CD25) and CTLA-4, and potently suppressed the proliferation of T_{eff} cells (11). Demonstration that this T regulatory (T_{reg}) cell subset expanded during chronic cutaneous leishmaniasis provoked a number of fundamental questions, many of which remain to this day. One issue was whether T_{reg} cells constituted an evolutionary trade-off between host fitness and parasite survival. It is tempting to propose that leishmania-induced T_{reg} cells mainly function to hold infection-induced inflammation in check, preventing a complete loss of tissue integrity that could lead to secondary bacterial infections, sepsis, and death. Of course, the trade-off to holding inflammation in check is that it favors pathogen persistence. Whether such Darwinian selection emanated from the host or pathogen remains an unanswered question. Perhaps a host-selective process is implicated because IL-10 is central to the mechanism of concomitant immunity. Indeed, Belkaid and colleagues demonstrated that IL-10–deficient mice efficiently cleared all the parasites in the lesion site but with no significant changes in its size (12), suggesting that modulation by leishmania-induced T_{reg} cells may have other effects on disease outcome. Since this work was published, we have now gained a better understanding of the multiple mechanisms by which T_{reg} cells operate including TGF-β and IL-35 secretion, cell-contact molecules such as CTLA-4 and LAG-3, as well as metabolic disruption through IL-2 deprivation and release of adenosine nucleosides (13). As such, it is likely that T_{reg} cells operate via several molecular pathways, and the contribution of these to the outcome of cutaneous leishmaniasis should be further evaluated.

At the time that the studies by Belkaid et al. were published, T_{reg} cells were proposed to suppress the activity of autoreactive

Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA

ORCID: 0000-0002-2449-5365 (D.R.H.).

This work was supported by Grant U01-AI125940 from the National Institutes of Health.

Address correspondence and reprint requests to Dr. De'Broski R. Herbert, University of Pennsylvania, 3800 Spruce Street, Philadelphia, PA 19104-3051. E-mail address: debroski@vet.upenn.edu

Abbreviations used in this article: T_{eff}, T effector; T_{reg}, T regulatory; tT_{reg}, T_{reg} cell derived from the thymus.

T_{eff} cells, leading most to consider that their TCR repertoire recognizes various self-antigens (14). However, the epitope specificity of leishmania-induced T_{reg} cells remained elusive. It is now recognized that T_{reg} cells can be derived from the thymus (tT_{regs}) or induced in the periphery (14). Although this *Pillars of Immunology* article demonstrates that leishmania-induced T_{reg} cells can be recruited from a pre-existing pool in naive mice (11), it is not clear whether leishmania parasites promote the expansion of thymic T_{regs} that are cross-reactive to parasite-derived Ags or if leishmania manipulates the tissue microenvironment to induce the differentiation of peripheral T_{regs}. Alternatively, tissue damage that occurs at the lesion site may result in the release of self-antigens that activate tT_{regs}; considering that skin T_{reg} cells have been shown to facilitate wound healing (15). Furthermore, it is clear now that T_{reg} cells can be further subdivided based on their expression of other transcription factors such as GATA-3 and RORγT, each subset associated with specific functions (16), but how this heterogeneity translates to the regulatory landscape induced in cutaneous leishmaniasis remains to be investigated. This picture becomes even more complex considering the mounting evidence that the tissue-specific properties of skin-resident T_{reg} cells are influenced by skin microbiota, environmental factors, and hair follicle–derived signals (16). Therefore, it is possible that the contribution of T_{reg} cells to the generation of concomitant immunity against cutaneous leishmaniasis represents a unique process that occurs in the skin.

Remarkably, the findings of this *Pillars of Immunology* article not only challenged the dogma that sterilizing immunity is required to generate immune memory, but they also demonstrated that IL-10 and potentially T_{reg} cells are necessary to develop resistance against reinfection with *L. major* (11). On one hand, it can be argued that the low numbers of parasites may function as a persistent source of Ags that is required to maintain a pool of memory T cells. However, long-lived central memory T cells have been shown to survive in the absence of persistent parasite load (9). Alternatively, T_{reg} cells might contribute to the generation of memory T cells via their secretion of IL-10, which has been demonstrated to promote the maturation of memory $CD8^+$ T cells (17, 18). Furthermore, it has become clear that skin-resident memory $CD4^+$ T cells (T_{RM}) are central for protection against *L. major* (19). Therefore, whether coordination between skin-resident T_{reg} and skin-resident memory $CD4^+$ T cells is required for concomitant immunity against cutaneous leishmaniasis needs further investigation. More importantly, understanding the contributions of T_{reg} cells to the development of protective immunity would aid vaccine efforts to combat acute and chronic infections. Particularly now, amid the COVID-19 pandemic, we urgently need to understand the basic mechanisms responsible for the efficacy of SARS-CoV-2 vaccines. Studies focused on understanding how T_{reg} cells facilitate protective immunity could provide critical insight(s) into the controversy over whether naturally infected or vaccinated individuals can develop long-term immunity (>1 y). Although there are still a number of questions to be addressed, this *Pillars of Immunology* article set the stage for an explosion of interest in T_{reg} cell biology in the context of chronic infections that persists today.

Disclosures

The authors have no financial conflicts of interest.

References

1. Brener, Z., and R. T. Gazzinelli. 1997. Immunological control of *Trypanosoma cruzi* infection and pathogenesis of Chagas' disease. *Int. Arch. Allergy Immunol.* 114: 103–110.
2. Melchor, S. J., and S. E. Ewald. 2019. Disease tolerance in *Toxoplasma* infection. *Front. Cell. Infect. Microbiol.* 9: 185.
3. Clyde, D. F., H. Most, V. C. McCarthy, and J. P. Vanderberg. 1973. Immunization of man against sporozite-induced falciparum malaria. *Am. J. Med. Sci.* 266: 169–177.
4. Brown, S. P., and B. T. Grenfell. 2001. An unlikely partnership: parasites, concomitant immunity and host defence. *Proc. Biol. Sci.* 268: 2543–2549.
5. Rajakumar, S., W. Bleiss, S. Hartmann, P. Schierack, A. Marko, and R. Lucius. 2006. Concomitant immunity in a rodent model of filariasis: the infection of Meriones unguiculatus with Acanthocheilonema viteae. *J. Parasitol.* 92: 41–45.
6. Heinzel, F. P., M. D. Sadick, B. J. Holaday, R. L. Coffman, and R. M. Locksley. 1989. Reciprocal expression of interferon gamma or interleukin 4 during the resolution or progression of murine leishmaniasis. Evidence for expansion of distinct helper T cell subsets. *J. Exp. Med.* 169: 59–72.
7. Scott, P., P. Natovitz, R. L. Coffman, E. Pearce, and A. Sher. 1988. Immunoregulation of cutaneous leishmaniasis. T cell lines that transfer protective immunity or exacerbation belong to different T helper subsets and respond to distinct parasite antigens. *J. Exp. Med.* 168: 1675–1684.
8. Scott, P., and F. O. Novais. 2016. Cutaneous leishmaniasis: immune responses in protection and pathogenesis. *Nat. Rev. Immunol.* 16: 581–592.
9. Scott, P. 2020. Long-lived skin-resident memory T cells contribute to concomitant immunity in cutaneous leishmaniasis. *Cold Spring Harb. Perspect. Biol.* 12: a038059.
10. Senekji, H. A., and C. P. Beattie. 1941. Artificial infection and immunization of man with cultures of *Leishmania* tropica. *Trans. R. Soc. Trop. Med. Hyg.* 34: 415–419.
11. Belkaid, Y., C. A. Piccirillo, S. Mendez, E. M. Shevach, and D. L. Sacks. 2002. CD4+CD25+ regulatory T cells control *Leishmania major* persistence and immunity. *Nature* 420: 502–507.
12. Belkaid, Y., K. F. Hoffmann, S. Mendez, S. Kamhawi, M. C. Udey, T. A. Wynn, and D. L. Sacks. 2001. The role of interleukin (IL)-10 in the persistence of *Leishmania major* in the skin after healing and the therapeutic potential of anti-IL-10 receptor antibody for sterile cure. *J. Exp. Med.* 194: 1497–1506.
13. Sakaguchi, S., N. Mikami, J. B. Wing, A. Tanaka, K. Ichiyama, and N. Ohkura. 2020. Regulatory T cells and human disease. *Annu. Rev. Immunol.* 38: 541–566.
14. Sakaguchi, S., N. Sakaguchi, M. Asano, M. Itoh, and M. Toda. 1995. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J. Immunol.* 155: 1151–1164.
15. Boothby, I. C., J. N. Cohen, and M. D. Rosenblum. 2020. Regulatory T cells in skin injury: At the crossroads of tolerance and tissue repair. *Sci. Immunol.* 5: eaaz9631.
16. Whibley, N., A. Tucci, and F. Powrie. 2019. Regulatory T cell adaptation in the intestine and skin. *Nat. Immunol.* 20: 386–396.
17. Cui, W., Y. Liu, J. S. Weinstein, J. Craft, and S. M. Kaech. 2011. An interleukin-21-interleukin-10-STAT3 pathway is critical for functional maturation of memory CD8+ T cells. *Immunity* 35: 792–805.
18. Laidlaw, B. J., W. Cui, R. A. Amezquita, S. M. Gray, T. Guan, Y. Lu, Y. Kobayashi, R. A. Flavell, S. H. Kleinstein, J. Craft, and S. M. Kaech. 2015. Production of IL-10 by CD4(+) regulatory T cells during the resolution of infection promotes the maturation of memory CD8(+) T cells. *Nat. Immunol.* 16: 871–879.
19. Glennie, N. D., V. A. Yeramilli, D. P. Beiting, S. W. Volk, C. T. Weaver, and P. Scott. 2015. Skin-resident memory CD4+ T cells enhance protection against *Leishmania major* infection. *J. Exp. Med.* 212: 1405–1414.