SCIENCE CHINA
Life Sciences

Special Topic
• Review •

February 2010 Vol.53 No.2: 190–194
doi: 10.1007/s11427-010-0040-5

A new role for T cells in dampening innate inflammatory responses

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Received January 5, 2010; accepted January 15, 2010

Citation: Tang H, Fu Y X. A new role for T cells in dampening innate inflammatory responses. Sci China Life Sci, 2010, 53: 190−194, doi: 10.1007/s11427-010-0040-5

The inflammatory response is an attempt by a host to protect itself against injurious stimuli and initiate the tissue healing process [1,2]. Although the production of both pro- and anti-inflammatory mediators which occurs mainly within tissues is a systemic process, the pathophysiological events of inflammation are usually compartmentalized, being different from organ to organ, and between organs and the peripheral blood [3,4]. Inflammation and consequential tissue injury vary according to the nature of the insults (e.g. burns, hemorrhages, trauma, peritonitis), the cellular composition of each tissue (e.g. the types of phagocytes or endothelial cells), the micro-environment (e.g. the localized presence of GM-CSF in the lungs, low levels of arginine in the liver, presence of endotoxins in the gut), and different modes of leukocyte recruitment. High levels of pro-inflammatory mediators, including interleukin-1 (IL-1), tumor necrosis factor (TNF), gamma interferon (IFN-γ), high mobility group protein-1 (HMGB1), and macrophage migration inhibitory factor (MIF), are produced locally and released into the blood stream to initiate remote organ injury. IL-10 [5] and other anti-inflammatory mediators [6] play essential roles in dampening the inflammatory process. While anti-inflammatory mediators within tissues may not always be sufficient to prevent the initiation of a deleterious inflammatory response in different compartments, the inflammatory response must be actively terminated, because failure to do so results in 'bystander' damage to tissues and diseases. such as arthritis or hepatitis. The underlying mechanisms that control excessive acute inflammatory responses are still poorly understood. The role of the adaptive immune system in acute inflammation is also vague and most studies have focused on how the adaptive immune system activates the innate system to control infection. Recent studies, however, have revealed that adaptive immune cells actively dampen initial innate responses. This raises new questions regarding the role of the adaptive immune system in the acute phase of infection and inflammation.

1 The priming and amplification of the immune system

The immune system of the mammalian host is composed in broad terms of the innate and adaptive immune systems. The innate immune system is evolutionarily conserved among multi-cellular organisms and provides rapid defense against invading microbes and insults within hours——long before the adaptive immune system can mount an antigen-specific response. Cells of the innate immune system recognize microbial structures called pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) which include Toll-like receptors [7,8], retinoic acid-inducible gene I (RIG-I)-like receptors, nucleotide oligomerization domain (NOD)-like receptors [9], and the newly-identified DNA sensors [10–13]. These recognition interactions mobilize the innate immune response, leading

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to upregulation of both major histocompatibility complex (MHC I and II) and co-stimulatory molecules, and secretion of inflammatory cytokines, that together efficiently prime T cells and help to guide the subsequent adaptive response [14]. In a feed-forward activation loop, adaptive immune-cells further drive innate cells to amplify anti-pathogen responses. For example, Type 1 helper T cells (Th1) activate macrophages through both cell-cell contact and IFN-γ secretion [15–17]. Th2 cells activate eosinophils through cytokine release [18–20], and B cells secrete antibodies to activate the cascade of complement proteins, phagocytes, natural killer cells (NK) and mast cells [21–25]. Current understanding, therefore, emphasizes both the sequential activation of the two arms of the immune system and their mutual amplification of responses to eradicate microbes.

2 Conventional T cells temper acute innate inflammation: an unexpected finding

Current understanding is that T cells activate innate cells to clear pathogens. Surprisingly, it has become clear that T cells also take part in regulating the innate immune response during the early phases of infection [26]. Compared with the wild type, T-cell-deficient nude or *Rag1*$^{-/-}$ mice are more susceptible to sub-lethal challenges of either virus infection or TLR agonists. Depletion of both CD4$^+$ and CD8$^+$ T cells in wild type mice or adoptive transfer of T cells to *Rag1*$^{-/-}$ mice effectively suppresses the cytokine storm, indicating that T cells are both necessary and sufficient to control the innate immune response [3,27]. Neutralization of the surge of TNF by soluble TNF receptor antibody, but not of IFN-γ, effectively reduces proinflammatory cytokine levels and rescues the immunodeficient mice. Therefore, the cytokine storm that results from insufficient T-cell numbers seems to account for lethality in both nude and *Rag1*$^{-/-}$ mice. *In vitro* experiments indicate that CD4$^+$ and CD8$^+$ T cells can both effectively reduce the production of inflammatory cytokines by innate cells in response to TLRs, indicating the general suppressive function of T cells [3].

There is an increasing body of evidence indicating that regulatory T cells (Treg), a subset of CD4$^+$ T cells (CD4$^+$ CD25$^+$FoxP3$^+$), can suppress functions of not only effector T cells but also of innate cells [28–30]. Whereas most studies have indicated that Treg cells minimize tissue damage through pathogen-specific immunity at the late stages of infection [31,32], they may be equally important in hindering innate immunopathology, via either secreting the immunosuppressive cytokine TGF-β to directly inhibit NK cell-mediated cytotoxicity during tumor rejection [28], or by allowing a delayed migration of innate cells and inflammation into the virus-infected tissue [33]. Apart from their long-distance action via secreted cytokines, it is thought that Tregs, just like conventional T cells, may efficiently suppress the cytokine surge by innate immune cells through cell-cell contact *in vitro* [21], although the mechanism of such a response has yet to be determined. To efficiently counteract the vast number of innate immune cells both inside and outside lymphoid tissues, a sufficient number of T cells, and/or B1 cells [34], is required to keep inflammation in check. That sufficient numbers of T cells are required for the control of inflammation has been demonstrated by studies in neonatal mice in which mice challenged with LPS, poly (IC) or virus infection had about 50-fold fewer T cells than those in adult mice, dying of an uncontrolled proinflammatory innate response [35]. Insufficient numbers of neonatal T cells resulted in uncontrolled inflammation and thus caused higher morbidity and mortality. The conclusion that T cell numbers rather than their function is important is in contrast to the often acknowledged dogma that such susceptibility is caused by underdeveloped innate and adaptive immune systems in neonates [36,37]. This is also in sharp contrast to studies on the B1 subset of B cells in newborn mice which inhibits the DC cell-mediated proinflammatory response through secreting IL-10 [34]. The apparent discrepancy in the above studies is due to differences in the TLR agonists used. If the effect of D-galactosamine (D-GalN), a widely used compound that boosts LPS-induced liver injury through macrophages, is excluded, these studies actually come to the same conclusion that adaptive cells (T or B1 cells) play an inhibitory role in the regulation of innate inflammation [3].

Another fundamental advance in our understanding of the suppression of the innate inflammatory response is that cell-cell contact between T cells and innate cells is required and likely requires MHC, yet is independent of antigen specificity or TCR engagement [27]. There has been tremendous interest in searching for potential molecules and/or pathways that might explain the molecular mechanisms of inflammatory regulation by T cells. Several co-inhibitory molecules, such as cytotoxic T lymphocyte antigen (CTLA-4), programmed cell death 1 (PD-1) and B and T lymphocyte attenuator (BTLA), have been implicated in immune homeostasis [38]. Coinhibitory pathways are thought to act in later stages of an adaptive immune response, but whether coinhibition contributes to early innate immunity is unclear. However, engagement of BTLA by herpesvirus entry mediator (HVEM) is critical for negatively regulating early host immunity against intracellular bacteria [39]. Mice lacking HVEM or BTLA are more resistant to Listeria infection than wild type mice, and blockade of the BTLA pathway promotes, while engagement inhibits, early bacterial clearance as early as one day post-infection. This correlates with *BTLA*$^{-/-}$ innate cell-secretion of significantly more proinflammatory cytokines upon stimulation with heat-killed Listeria. Therefore, increased numbers of T cells in BTLA-deficient mice play a critical role in regulating early host innate immunity against infection.

3 Effector and memory T cells dampen the hyperactive inflammasome during late phase of primary responses or on secondary challenges

The inflammasome is a multi-protein complex that mediates the activation of caspase-1 which in turn promotes secretion of the proinflammatory cytokines IL-1 and IL-18, as well as 'pyroptosis', a form of cell death induced by bacterial pathogens. Members of the NLR family, including NLRP1 (commonly called NALP1), NLRP3 (NALP3 or cryopyrin) and NLRC4 (IPAF), and the adaptor ASC are critical components of the inflammasome that link exogenous microbial infection and endogenous 'danger' signals to caspase-1 activation [40–43]. Therefore, the inflammasome plays an important role in both PAMP and DAMP signaling, and is essential for triggering the adaptive immune response [41,44]. Indeed, uncontrolled IL-1β activity is linked to considerable collateral damage in patients with a hyperactive inflammasome [45].

A recent finding suggests an interesting feedback mechanism that allows T cells to selectively eliminate the bystander effect of the inflammasome [46]. Both effector and memory T cells suppress potentially damaging inflammation, yet leave the primary inflammatory response, crucial for the onset of immunity, intact. Caspase-1 processing and secretion of mature IL-1β by bone marrow-derived macrophages (BMDMs) or bone-marrow-derived dendritic cells (BMDCs) is blocked by *ex vivo* memory and *in vitro*-activated effector $CD4^+$ T cells, but not by naïve, Treg or other T-cell subsets *in vitro*. $CD4^+$ T cells can diminish the inflammasome response to major NLRP3 activators (LPS, monosodium urate crystals, asbestos, alum or nigericin), and NLRC4 activators (*Salmonella typhimurium*), but not to NLRP1 activators (*Bacillus anthracis* lethal toxin). Effector $CD4^+$ T cells appear to promote general BMDM activation, while exclusively blocking caspase-1 activation, but not the caspase-1 independent response to LPS (secretion of CXCL2, IL-12, TNF and IL-6). Therefore, T cells dampen innate immune responses through inhibition of the NLRP1 and NLRP3 inflammasomes.

Antigenic re-stimulation is an essential requisite for inhibition of the inflammasome, and is dependent on direct T/BMDM contact in a 1:1 stoichiometry. As was the case in the suppression of the innate inflammatory cytokines by conventional T cells discussed above [27], TCR engagement is not essential. However, abrogating TNF superfamily members within the T/APC synapse, including RANKL, CD40L, LIGHT, 41BBL, CD30L, and OX40L, can diminish IL-1β secretion upon ATP stimulation. In particular, CD40L, which is upregulated upon $CD4^+$ T-cell activation, suppresses the NLRP3 inflammasome response in a dose-, CD40- and time-dependent manner. The finding that the TNF superfamily turns off the inflammasome is therefore consistent with its established role in shaping the adaptive immune response by acting on innate immune cells [47]. The same *in vitro* functionality can be demonstrated in part by an alum-induced, NLRP3-dependent peritonitis model [41,46]. By monitoring neutrophil and eosinophil influx to the inflamed peritoneum, $CD4^+$ T cells, but not B cells, have a predominant role in suppressing NLRP3-dependent neutrophil influx. Different subsets of T lymphocytes might therefore utilize distinct mechanisms in their suppression of innate responses.

4 Outlook

The purpose of the differentiation and maturation of the immune system is not only to produce an effective immune response to clear pathogens and internal danger signals, but also to regulate the response appropriately. Innate immunity is a phylogenetically ancient defense system, providing efficient and sufficient immunity in invertebrates [48]. In both invertebrates and vertebrates, innate immune responses are tightly regulated by a series of negative regulators at multiple levels to prevent over-reaction and maintain immunological homeostasis [38,49,50]. It is plausible that the innate inflammatory response in invertebrates is either less rampant or is more tightly controlled at various checkpoints of the Toll and IMD (immune deficiency) signaling pathways than in vertebrates. We speculate that, while the immune system becomes more specialized during evolution, the conserved auto-regulatory function of innate inflammatory immunity might be insufficient (quantitatively and/or qualitatively) to meet all the requirements in vertebrates. Therefore, a feedback loop from the adaptive to the innate immune system becomes prominent and evolutionarily advantageous. Rather than being idle in the early phase of infection as previously assumed, the adaptive immune system serves as an indispensable regulator of the innate inflammatory response to PAMPs [3]. In inflammasome activation, lymphocyte infiltration during inflammation acts as a feedback loop, whereby effector or memory T cells edit the quality of the inflammatory mediators produced during the late phases of primary responses or on secondary challenges [46]. During this inhibitory response，full competence in antigen presenting is maintained by APC/T interaction to guarantee efficient T cell re-stimulation, albeit the involvement of MHC is still illusive [27].

Unlike neonatal mice, human newborns have a considerable number of T cells in peripheral blood at birth [51]. However, the proportion of T cells in peripheral blood is lower, especially in infants who are small for gestational age [51–53]. Clinical evidence has shown that extremely high levels of cytokines can be detected in certain infant diseases linked to mild infections [54–58]. Therefore, a lack of T cells would increase the risk of excessive innate activation and consequent immunopathology, higher morbidity and mortality in response to infection. Whether this would

also lead to aberrant inflammasome activation remains to be tested. Recent unexpected results suggesting that T cells of the adaptive immune arm regulate innate responses therefore shed new light on the evolution and interplay of innate and adaptive immunity [59]. Greater understanding of the underlying mechanisms will help us to make better clinical diagnosis and treatment of various infectious and inflammatory diseases in the future.

This work was supported by the National Basic Research Program of China (*Grant Nos. 2006CB910901 and 2009CB522506*) *and the Knowledge Innovative Program of the Chinese Academy of Sciences* (*Grant No. KSCX1-YW-10*).

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