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PERSPECTIVES ON TOLERANCE TO PARASITIC INFECTIOUS DISEASES

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Abstract

Immune responses to infectious parasitic diseases appear to be simply directed towards killing or clearing the parasite. However, the immunological strategies constitute a complex incorporated network of immune mechanisms to eradicate the parasite itself in addition to preservation of the integrity of host tissues. Resistance and tolerance are believed to be two distinct complementary host defense immune strategies. Mechanisms triggering infectious tolerance to parasitic infections are still poorly recognized but seem to be centered on controlling parasite-induced tissue damage in the infected host. It is becoming obvious that realizing infectious tolerance as a prominent constituent of defense strategy deliver significant conceptions in coexistence of host-parasite relationship. This data may also pave the way to new therapeutic approaches in many parasitosis.

Key words: Immune response, Tolerance, Parasitic infections, Resistance, Review

Introduction

Infectious tolerance to parasitosis is a variety of defense mechanisms that don't employ a direct effect on the parasite itself but are crucial to limit the health and fitness costs resulting from the infection (Martins *et al,* 2014). In 1970 conception of infectious tolerance was originally introduced (Gershon and Kondo, 1971) and later more illustrated was by Herman Waldman (Qin *et al*, 1993). Tolerance is related to immunological non-responsiveness to a particular antigen, and hosts are tolerant to self-antigens (Roitt *et al*, 1993) and to infectious antigens including parasite antigens when the non-responsiveness occurs (Schwartz 2005). So, infectious tolerance (or disease tolerance) should not be confused with immunological tolerance, in which the latter comprises the abolition of self-reactive T cells, although immunological tolerance can still be considered as a disease tolerance mechanism (McCarville and Ayres, 2018).

Review and Discussion

Tolerance to parasites primarily developed and utilized in plants for decades with marked genetic variation of tolerance (Caldwell *et al,* 1958). This evolutionarily defense mechanism is also active in insects (Teixeira *et al,* 2008), animals and man (Gozzelino *et al,* 2012). Tolerance in animals was recognized by attenuated immunity of green monkeys to simian immunodeficiency virus with increased infection rate in them without effecting health (Chahroudi *et al,* 2012)

Resistance versus tolerance: It was crucial to differentiate between two distinct mechanisms that reduce pathogen virulence that impeded the parasitic growth within hosts (Gandon *et al,* 2003) and reduced the tissue damage caused by parasite or immune response tolerance (Martins e*t al,* 2019). The resistance defends the host from the parasite, but tolerance protected him from harm without having direct negative outcome on parasite (Raberg *et al,* 2009). Resistance was measured by inverse of intensity of infection (parasites/host or unit tissue) as a lower intensity indicated more resistant (Simms and Triplett 19940). Tolerance was considered as the gradient of regression of host fitness against load infection as the sharper slope, the lower tolerance (Koskela *et al*, 2002). So, tolerance and resistance are host adaptive mechanisms (Medina and Langmore, 2016). Also, they might have different evolutionary impact since their responses to the parasitosis might imply distinct selective influences (Medzhitov *et al,* 2012). Ayres and Schneider (2008) showed that the bal-

ance of tolerance and the resistance was the chiefly pathogen specific, and they added that provoking tolerance for one pathogen supported resistance against another. Induction of haemeoxygenase1 (HO_1) expression elicited disease tolerance to the malaria erythrocytic stages (Siexas *et al,* 2009) but, it hampered resistance to *Salmonella enterica* serovar Typhimurium (Soares *et al,* 2017). If resistance evolved in a population, parasite prevalence would be reduced, however, if tolerance evolved a positive or neutral effect on parasitic prevalence was ongoing to be displayed (Roy and Kirchner, 2000). Also, when tolerance occurred completely eliminated the parasite-caused damage, with the probability of host-parasite coexistence facilitating change from parasitism to commensalism (Meiklejohn and Blumenstiel, 2018).

The primary mechanisms mediating disease tolerance to the parasitic infections was poorly understood (McCarville and Ayres, 2018). In immunological tolerance, effector Th2 cells enter a state of anergy and fail to develop specific T effector cells.

The parasites use different mechanisms to avoid being eliminated by immune system. These mechanisms include suppression, modulation or even blockage of immune pathways which can also lead to attenuation of pathology and tolerance (van Riet, 2007). T regulatory cells (Tregs) might play a role in orchestrating the protective responses of tissues to preserve their wellbeing and function (Waldmann, 2014) the tissue damage caused by the immune responses (Cavassani *et al,* 2006). Similarly, the T cell exhaustion was shown to be a method to elicit disease tolerance in general, yet it can also participate to disease as in case of chronic infections (Wu and Reddy, 2017). Hence, the aiming for T cell exhaustion, either positively or negatively could influence the disease tolerance (McCarville and Ayres, 2018). The chief relationship was demonstrated between the infection and expansion of Tregs cell subset (Finlay *et al,* 2014), which markedly decline after anti-helminthic drug elimination. In humans the activity of Tregs and production of IL-10 closely associated by the isotype switch from pro-allergic/ inflammatory IgE to the non-inflammatory IgG4 (Satoguina *et al,* 2005), which was sharply diminished following treatment (Grogan *et al,* 1996a)

No doubt, the antigen stimulates the new Tregs and expands Tregs memory cells, tolerance can be maintained for long duration (Corthay, 2009). This explained as antigen plays important role in accumulation of antigen-specific regulatory and naive T cells, and that such cells were able to proliferate and accumulate in response to antigen without differentiation into effectors or delivering tissue damage (Lin *et al*, 2002). Redpath *et al.* (2014) reported that IL-10 was imported as an immune-mediator in parasitic infections, particularly for its role in attenuating immune mediated tissue pathology.

Generally, during any infectious process, the host should withstand two main types of tissue damage; direct damage by the pathogen itself and immunopathology. Thus, the tolerance mechanisms would be promoted to reduce both tissue damage types (Wynn *et al,* 1998).

But, in order to sustain parasite-induced immunopathology, different mechanisms are employed. For instance, tolerance may utilize immune strategies targeting toxins of the parasite rather than the parasite itself (Playfair *et al*, 1990). Although specific tolerance mechanisms occupied in direct tissue damage type are still essentially unknown, they are mainly expected to prevent, reduce, or antagonize the pathogen-specific pathological amendments through tissue protection and repair (Medzhitov *et al*, 2012). A specific mechanism may affect resistance and tolerance such as pro-inflammatory cytokines stimulated immune mechanisms to attack the parasite or enhanced resistance, but led to increase in the collateral damage or reduce the tolerance (Raberg *et al,* 2009). Moreover, the tolerance includes immune responses to inhibit any unsuitable host res-

ponses, or limit collateral damage even from the properly organized immune responses (Lübbers *et al,* 2018).

The tolerance strategies can be general i.e. they are protective against nearly all types of tissue stress and injury irrespective of the reason for cell insult e.g. anti-apoptotic and anti-necrotic genes. In contrast, specific tolerance mechanisms are chiefly protective against certain forms of insult and tissue dmage as in the case of erythropoiesis, which was protective chiefly against hemolytic parasites (Medzhitov *et al,* 2012).

Added to the previously mentioned mechanisms, dendritic cells had also been speculated to play an important role in the initiation and modulation of the specific immune responses to promote tolerance effect (Motran *et al,* 2017). In reverse, it was of concern that a dys-regulated tolerance mechanism might produce some sort of pathology such as that occurring with too much tissue repair resulting in fibrosis (Medzhitov *et al,* 2012).

Tolerance capacity among different tissues and physiological processes varied depending on multiple factors including variety of intrinsic damage vulnerability between different tissues, difference in tissue repair capacity, functional autonomy of tissues forming cells and finally the outcomes of specific tissue damage or malfunction (Bente *et al,* 2009). Tolerance to infectious diseases depended on cellular and entire host metabolism, environmental factors and host immunity (McCarville and Ayres, 2018). Genetics are known to affect tolerance as an epigenetic regulator (histone methyltransferase G9) that promoted tolerance to RNA virus infection in *Drosophila* species (Merkling *et al,* 2015), and maggots therapy (El-Tawdy *et al,* 2016), but its exact mechanisms were scarce (Richardson, 2016). Different host strains differed in tolerance slopes of the fitness or health (Sternberg *et al,* 2013).

Martins *et al.* (2014) deduced that tolerance strategy might be an inherent constituent of immunity without direct effect on the parasite itself. This could be exemplified by activation of stress response in patients with hemizygous βS allele (sickle trait), mediating disease tolerance to the malaria infection (Bunn, 2013). Besides, there was a significant decrease of age on tolerance capacity in elderly persons (Raberg, 2014). This might be attributed to the decline in tissue maintenance and repair, associated with marked frailty (Medzhitov *et al,* 2012).

Actually, many novel therapeutic interventions are now aiming to direct the balance of T-cells toward more prominent regulatory control (Waldmann, 2014). Establishing tolerance to parasitic infections could be accomplished through therapeutic targeting of responses controlling the tissue damage such as that targeting labile haem (Larsen *et al,* 2010), which mediates disease tolerance to malaria in mice (Ferreira *et al,* 2007). Indeed, provoking host tolerance via medications or alterations in environmental factors might play a vital role in disease control not only to infections but also to a wide range of disorders (McCarville and Ayres, 2018).

The infectious tolerance to helminthic infections was first encountered via the silent parasite antigen-specific T-cell responses of patients; especially the asymptomatic carriers (Satono *et al,* 1995). Anthelminthic drug elimination from carriers gave rise to a reappearance of antigen-specific responses, proposing that they were actively inhibited during helminthic existence (Grogan *et al*, 1996b). Besides, helminthic infection was assumed to elicit disease tolerance to other major pathogens, such as Mycobacterium tuberculosis as co-infected the TB individuals had higher Tregs abundance than those with TB infection alone (Karo-Atar *et al,* 2021). The different cattle breeds showed variable tolerance to *Fasciola* spp., and infection was estimated by fibrosis score, suggested the genetic and environmental tolerance alterations **(**Hayward *et al,* 2021). The *Fasciola hepatica* & *F. gigantica* execratory-secretory products (FhESPs and FgESPs) were capable of hampering ability of muri-

ne and buffalo DCs and affected capacity to elicit the response (Falcon *et al,* 2010; Mei *et al,* 2020). Similar observations were reported for execratory-secretory products of *Clonorchis sinensis* (Hua *et al*, 2018). The *Trichinella spiralis* (Elhasawy *et al,* 2021) proved to promote tolerogenic properties in host dendritic cells. On murine experimental schistosomaisis Tregs responses controlled Th1 & Th2 responses independent on IL-10 simultaneously associated with control of granuloma formation in chronic infection (Taylor *et al,* 2006).

In hydatidosis, the alveolar echinococcosis (AE) patients, postulated that the metacestode *Echinococcus* species existence was due to immune tolerance that the mainly mediated by specialized Tregs and related cytokines including IL-10 and TGF-β (Haridy *et al,* 2000). It is worth mentioning that increased Tregs activity, immunosuppressive cytokine production, and antigen hyporesponsiveness were all detected in soil-transmitted intestinal nematode infections (Figueiredo *et al,* 2010). Later on, the T cell exhaustion occurred owing to high antigen load (Duck and Mills, 2017). A study done on Soay sheep infected by strongyle nematode displayed the crucial role of tolerance in the defense against parasitic infections and assumed that the tolerance was the variable among the individuals (Johnston *et al,* 2014).

In filariasis, Maizels and Smith (2011) reported that filariasis outcome relied on host immune response and modulation strategy. The filarial ES-62 was speculated to redirect switching of naive DCs to DC2 phenotype, subsequently inducing a strong Th2 response (Goodridge *et al,* 2005). There was increased evidence that LC (Langerhans cells) induced the immune tolerance. But, mechan ism of tolerance was still under interpretation as interaction between L3 stage and LC resulted in priming of naive T cells or altered the LC function allowing L3 to enter the host (Boyd *et al,* 2013). Patients showed elephantiasis and hyper-reactive onchocerciasis diminished Tregs levels compared to asymptomatic carriers (Katawa *et al,* 2015). Moreover, maternal infection where the babies of Haitian *Wuchereria bancrofti* mothers were 2-3 times more likely to become infected, but with decreased level of T-cell reactivity to filarial antigens than babies of normal mothers due to utero toleration to parasite antigens (Mpairwe *et al,* 2014).

Protozoa: Trypanosomiasis *congolense* infected mice showed the Tregs elicited during infection that limited specific type 1 immune responses responsible for the collateral tissue damage, but without any effect on parasite control yielding trypanotolerance (Guilliams *et al*, 2007). The IL-10 inhibited systemic inflammation and mortality in *T. cruzi* infection as IL-10 suppressed release of IFN gamma and macrophage activation (Hunter *et al*, 1997). Production of nitric oxide by perivascular macrophages limited the parasite passage and activated T cells into CNS via preserving BBB integrity (Paling *et al*, 1991). The genetic resistance and tolerance varied with infection intensity, severity or mortality among the different mouse strains (Graefe *et al*, 2003). **A**cylcarnitine metabolism showed that the carnitine supplementation inhibited Chagas disease mortality without parasite burden though alleviating infection-stimulated metabolic disturbances and diminishing cardiac strain (Hossain *et al*, 2020).

In malaria, antibody-mediated neutralization of *P. falciparum* was associated molecular pattern (PAMP) molecules (Riley *et al,* 2006), desensitization of pattern-recognition receptor (PRR)-mediated signaling by repeated stimulation and production of anti-inflammatory mediators (IL-10 & TGF-B) suppressed inflammation (Walther *et al,* 2005). Tregs were detected in malaria infection in mice (Jangpatarapongsa *et al*, 2008) and humans (Goncalves *et al*, 2010). The damaged RBCs via induced erythropoiesis helped the malaria tolerance to the hemolytic pathogens (Medzhitov *et al,* 2012).

The C-thalassaemia didn't affect parasite load, but decreased the tolerogenic disease

(Williams *et al,* 2005). The haemoxygenase1 (HO-1) expression was induced to destroy liberated haeme and afford tolerance to the pathogenicity of all the *Plasmodium* species, and thus, HO-1 gave more cytoprotective role by limiting reactive oxygen species production (Cunnington *et al,* 2012). Silva *et al.* (2020) reported that HO-1 increases disease tolerance without affecting parasite load during the malaria parasite load in the hepatic stage.

Nahrendorf *et al* (2021) also showed that mice immune cells tolerated consequent malaria infections even after complete parasite elimination, as malaria altered the spleen immune cells responses. Also, helminthic co-infection caused moderated inflammatory reactions, subsequently producing decreased disease severity (Dolo *et al,* 2012). Otherwise, the uncomplicated malaria was the commonest among febrile HIV-children rather than febrile non-HIV ones (Amodu-Sanni *et al,* 2020).

In toxoplasmosis, Melchor *et al.* (2020) reported that *Toxoplasma* infected mice lacked the interleukin 1 receptor (IL-1R) axis recovered from the cachectic weight loss and long term survival irrespective of the parasite burden. IL-10-deficient in toxoplasmosis mice displayed an exaggerated inflammatory reaction accompanied by severe disease, necrosis of small intestine, liver cells, cachexia and rapid mortality (Suzuki *et al,* 2000). The IL-10 inhibited IL-12 from *Toxoplasma*-infected macrophages without impact on nitric oxide production or intracellular killing of the parasite (Jankovic *et al*, 2007). Also, genetic studies of predisposition to *T. gondii* in mice showed that entirely distinct loci existed in tolerance and resistance (Johnson *et al*, 2002) approved that the genetic variations occurred in both immune strategies (Raberg *et al,* 2009).

Conclusion and Recommendations

Generally speaking, parasitosis is a worldwide health problem particularly in developing countries.

Adequate identification of parasite virulence regulation by host immunological responses throughout infection as well as, understanding the essential strategies and outcomes of parasitic infectious tolerance in-host defense is a crucial issue for both present and future immunologic studies.

Discrimination between resistance and tolerance needs to be better understood together with the relationship between both, concerning costs to defense mechanisms.

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