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Invited Review

Cestode regulation of inflammation and inflammatory diseases

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ABSTRACT

Helminth parasites are masters of immune regulation; a likely prerequisite for long-term survival by circumventing their hosts' attempt to eradicate them. From a translational perspective, knowledge of immune events as a response to infection with a helminth parasite could be used to reduce the intensity of unwanted inflammatory reactions. Substantial data have accumulated showing that inflammatory reactions that promote a variety of auto-inflammatory diseases are dampened as a consequence of infection with helminth parasites, via either the mobilization of an anti-worm spectrum of immune events or by the direct effect of secretory/excretory bioactive immunomodulatory molecules released from the parasite. However, many issues are outstanding in the definition of the mechanism(s) by which infection with helminth parasites can affect the outcome, positively or negatively, of concomitant disease. We focus on a subgroup of this complex group of metazoan parasites, the cestodes, summarizing studies from rodent models that illustrate if, and by what mechanisms, infection with tapeworms ameliorate or exaggerate disease in their host. The ability of infection with cestodes, or other classes of helminth, to worsen a disease course or confer susceptibility to intracellular pathogens should be carefully considered in the context of 'helminth therapy'. In addition, poorly characterised cestode extracts can regulate murine and human immunocyte function, yet the impact of these in the context of autoimmune or allergic diseases is poorly understood. Thus, studies with cestodes, as representative helminths, have helped cement the concept that infection with parasitic helminths can inhibit concomitant disease; however, issues relating to long-term effects, potential side-effects, mixed pathogen infections and purification of immunomodulatory molecules from the parasite remain as challenges that need to be addressed in order to achieve the use of helminths as anti-inflammatory agents for human diseases.

1. Introduction

The twentieth century was a period of tremendous change with significant improvements in public health and sanitation, awareness of mechanisms of disease transmission, widespread use of antibiotics, and improved medical practices and vaccination strategies. The benefits of these changes are readily apparent in westernised societies in the form of reduced infant mortality and increases in lifespan. One may ask whether this came at a cost. Epidemiological data indicate that since ~1950 there have been rapid increases in the incidences of autoimmune and idiopathic inflammatory diseases such as diabetes, multiple sclerosis, rheumatoid arthritis (RA), allergic disease and inflammatory bowel disease (IBD) (Abdel-Nasser et al., 1997; Bach, 2002). These increases are too rapid to be explained solely on the basis of genetic changes (although a genetic predisposition is likely important in all of these maladies (Waterman et al., 2011)), and so the question arises as to whether there is an environmental component to this issue (Rook, 2012). For instance, has the eradication of helminth parasites in North America contributed to the rise in auto-inflammatory disease (Elliott et al., 2000): put another way, does infection with helminth parasites affect the outcome of co-morbidities? This is a testable hypothesis. Indeed, as evidenced in this article there are overwhelming data, primarily from animal (mostly murine) models, in support of infection with helminth parasites reducing the severity of disease in a variety of organs, including those remote from the site of infection: brain, colon, joints, lung and pancreas (Table 1) and (McKay, 2009).

In this review we restrict our commentary to a consideration of the impact of tapeworms on the outcome of concomitant disease. There is a paucity of data in this area, but those available support the concept that the analysis of helminth-rodent model systems will yield new approaches to treat inflammatory disease (see Table 2).

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Table 1
Modulation of concomitant disease by infection with helminth parasites in rodent model systems.

Species	Effect of infection on disease	Proposed mechanism of action	Reference
Nematodes			
Ascaris suum	Chronic infection reduces ragweed-triggered allergic eye disease in mice	Mobilization of $CD4^+CD25^+$ T cells	Schopf et al. (2005)
Heligmosomoides polygyrus	Inhibition of colitis in piroxicam-treated IL-10 deficient mice	Increases in IL-13 and $Foxp3^+$ mRNA indicating regulating T cells; IL-10 mediated suppression of IL-17 production	Elliott et al. (2004)
	Inhibition of murine TNBS-induced colitis	Skewing towards TH2 cytokines: IL-10	Setiawan et al. (2007)
	Inhibition of *Helicobacter felis*-associated gastric atrophy in mice	Reduced expression of IFNγ, TNFα, IL-1β	Fox et al. (2000)
	Amelioration of spontaneous arthritis (and kidney damage) in MRL/*lpr* mice	Skewing of cytokines towards Th2-type	Salinas-Carmona et al. (2009)
	Suppression of a murine model of asthma	Induction of $CD4^+CD25^+Foxp3^+$ regulatory T cells and IL-10 production	Wilson et al. (2005)
	Suppression of experimental allergic airway inflammation	Induction of $CD4^+CD25^+Foxp3^+$ regulatory T cells; IL-10 not involved	Kitagaki et al. (2006)
		$CD4^-CD19^+CD23^{hi}$ mesenteric lymph node B cells	Wilson et al. (2010)
	Suppression of EAE autoimmune disease in mice	$CD4^-CD19^+$ $CD23^{hi}$ mesenteric lymph node B cells	Wilson et al. (2010)
	Inhibition of peanut induced allergic responses in mice	Reduced IL-13 output from T cells; involvement of IL-10	Bashir et al. (2002)
Litomosoides sigmodontis	Inhibition of allergic airway inflammation and hyper-reactivity in mice	Mobilization of regulatory T cells and TGFβ	Dittrich et al. (2008)
Nippostrongylus brasiliensis	Amelioration of spontaneous arthritis (and kidney damage) in MRL/lpr mice	Skewing of cytokines towards TH2-type	Salinas-Carmona et al. (2009)
	Suppression of allergen-induced airway inflammation in mice	Involvement of IL-10	Wohlleben et al. (2004)
Trichinella pseudospiralis	Reduction in EAE symptoms in mice	Decreased pro-inflammatory cytokine mRNA expression in spinal cord: reduced TH1 and TH17 in spleen	Wu et al. (2010)
Trichinella spiralis	Inhibition of murine TNBS-induced colitis	Skewing towards TH2; reduced IFNγ	Khan et al. (2002)
	Reduced severity of EAE in rats	Induction of $CD4^+CD25^+Foxp3^+$ regulatory T cells	Gruden-Movsesijan et al. (2010)
	Inhibition of T1D in NOD mice	Skewing towards TH2 response	Saunders et al. (2007)
	Inhibition or allergic airways inflammation	Correlated with increased IL-10, TGFβ and regulatory T cells in the lungs	Park et al. (2011)
Trematodes			
Fasicola hepatica	Delays EAE onset in mice	Reduction of TH1 and TH17 responses via TGFβ	Walsh et al. (2009)
Schistosoma japonicum	Attenuated CIA development in DBA/1 mice	Skewing towards TH2; reduced TH17	Song et al. (2011)
Schistosoma mansoni	Inhibition of DSS-induced colitis	Mobilization of an immunosuppressive/immunoregulatory macrophage phenotype	Smith et al. (2007)
	Inhibition of TNBS-induced colitis in rats	Modulation of colonic cytokine levels	Moreels et al. (2004)
	Protection against anaphylaxis	IL-10 producing (IL-4 deficient) B cells	Mangan et al. (2004)
	Prevention and reversal of allergic airways inflammation in mice	IL-1- producing $CD1d^{high}$ regulatory B cells and $Foxp3^+$ T regulatory cells	Amu et al. (2010), van der Vlugt et al. (2012)
	Reduction in severity of EAE in mice	Suppression of IL-12p40 production	Sewell et al. (2003)
	Prevention of T1D in NOD mice	Generation of TH2 response	Cooke et al. (1999)
	Chronic, high density infection alleviates murine allergic airway inflammation	Suppression of antigen-induced cytokines; increased IL-10 from B cells and $CD4^+$ T cells	Smits and Yazdanbakhsh (2007)
	Suppression of CIA in mice	Down-regulation of Th1 cytokines, IL-1β and NFκB in the paw; increased IL-4 and IL-10	Osada et al. (2009)
S. mansoni (male cercariae)	Protects mice from allergen-induced airway hyper-responsiveness	Reduced IL-5, increased IL-10 and evidence for B cell involvement	Mangan et al. (2006)
S. mansoni (eggs, ip.)	Inhibition of murine TNBS-induced colitis	Skewing of cytokines towards TH2; IL-10	Elliott et al. (2003)
	Reduction in the severity of EAE in mice	Skewing of cytokines towards TH2	La Flamme et al. (2003)
Cestodes			
Hymenolepis diminuta	Inhibition of DSS colitis associated symptoms	Not determined	Reardon et al. (2001)
	Inhibition of murine DNBS colitis	Participation of IL-10	Hunter et al. (2005)
	Conferred protection against FCA-induced mono-arthritis	IL-10 and adaptive $CD4^+$ T cell response	Shi et al. (2011)
Taenia crassiceps	Reduced hyperglucemia in T1D murine model	Decreased levels of TNFα and increased IL-4	Espinoza-Jimenez et al. (2010)
	Blockade of EAE development in mice	Inhibition of MOG_{35-55} specific IL-17 production and proliferation	Reyes et al. (2011a)

CIA, collagen-induced arthritis; DNBS, dinitrobenzene sulphonic acid; DSS, dextran sodium sulphate; EAE, experimental autoimmune encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; NOD, non-obese diabetic; T1D, Type 1 diabetes; TGF, transforming growth factor; TH, T helper cell; TNBS, trinitrobenzene sulphonic acid.

2. Tapeworm parasites

The Cestoda (or tapeworms) is a complex group of organisms that are, with few exceptions, united by two common features: an elongated tape-like body and the absence of an alimentary canal. Their tegument serves as both a protective layer and an absorptive surface, and the worms tend to reside in the alimentary canals of their definitive hosts or the ducts of associated viscera. All but *Hymenolepis nana* have indirect lifecycles with one or two intermediate hosts that may be invertebrate or vertebrate, and warm- or cold-blooded. Taxonomically, the class is divided into the Cestodaria (lack segments) and the segmented Eucestodaria which is composed of a number of orders, predominantly the Tetraphyllidea, the Trypanorhyncha, the Pseudophyllidea and the Cyclophyllidea (definitive hosts are birds or mammals).