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Review

Host protective roles of type 2 immunity: Parasite killing and tissue repair, flip sides of the same coin

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ABSTRACT

Metazoan parasites typically induce a type 2 immune response, characterized by T helper 2 (Th2) cells that produce the cytokines IL-4, IL-5 and IL-13 among others. The type 2 response is host protective, reducing the number of parasites either through direct killing in the tissues, or expulsion from the intestine. Type 2 immunity also protects the host against damage mediated by these large extracellular parasites as they migrate through the body. At the center of both the innate and adaptive type 2 immune response, is the IL-4Rα that mediates many of the key effector functions. Here we highlight the striking overlap between the molecules, cells and pathways that mediate both parasite control and tissue repair. We have proposed that adaptive Th2 immunity evolved out of our innate repair pathways to mediate both accelerated repair and parasite control in the face of continual assault from multicellular pathogens. Type 2 cytokines are involved in many aspects of mammalian physiology independent of helminth infection. Therefore understanding the evolutionary relationship between helminth killing and tissue repair should provide new insight into immune mechanisms of tissue protection in the face of physical injury.

1. Introduction

Multicellular metazoan parasites of mammals, also known as helminths, typically induce a Th2-type (type 2) immune response in the infected host. Type 2 immunity is a highly complex multicellular, multifactorial system characterized by the cytokines IL-4, 5, 9, 10 and 13 [1]. These cytokines are produced by Th2 lymphocytes, but also by a range of innate immune cells including basophils, eosinophils, mast cells and innate lymphoid cells (ILCs). The IL-4R alpha chain (IL-4Rα), a component of both the IL-4 and IL-13 receptor, is fundamental to type 2 immune function [1], with expression and engagement of IL-4Rα on immune effector cells (e.g. macrophages, B cells) and tissue cells (e.g. smooth muscle, epithelial cells) dictating the outcome of a type 2 immune response. Details of type 2 immunity are constantly emerging, including the discovery of new cells, such as ILCs, which are central to type 2 immune function. These processes, particularly as they apply to helminth immunity have been reviewed recently [1–3].

The triggers that initiate a type 2 immune response have been under intense investigation for many years with little consensus on the essential pathways that lead to a robust response. However, recently there has been an emerging literature on the critical role of mucosal barriers. In particular, epithelial cells release alarmins, IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [4], all three of which promote Th2 immunity. It is becoming increasingly apparent that we have a robust cytokine alert system to tissue injury that will activate a type 2 immune response in the absence of a more dominant type 1 trigger [5]. Recently, Patel et al. [6] directly linked cellular damage to the induction of protective immunity against a gastrointestinal nematode by demonstrating that release of extracellular adenosine was responsible for inducing the Th2 response. Consistent with this, mast cells, which act as sentinels of injury [7], and other innate cells such as eosinophils and basophils, can readily produce IL-4 which has long been implicated in the generation of a type 2 immune response [8].

Tissue injury alone does not always generate a type 2 response. Additionally, helminth products themselves can induce Th2 responses in the absence of injury [9,10]. Thus, over evolutionary time it seems that mammals have learned to recognize the presence of potentially damaging large multicellular organisms, and initiate a response that largely resembles a reaction to tissue injury. This association between tissue injury and infection with metazoan parasites makes sense. Metazoan parasites do

Abbreviations: IL-4Rα, Interleukin-4 receptor alpha; ILC, innate lymphoid cell; TSLP, thymic stromal lymphopoietin; AAMφ, alternatively activated macrophage.

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not typically replicate in their hosts; instead they enter as larval stages, frequently migrate through tissues to their established niche, grow through developmental stages to sexual maturity, mate and release offspring to infect a new host. Faced with these large tissue migrating invaders, a pro-inflammatory type 1 response, although potentially damaging to the parasite, is even more likely to damage the host. Thus, a response that limited type 1 inflammation and facilitated wound healing would be beneficial. Ideally, this same response, where possible, would contribute to parasite control, either by limiting their numbers, hindering their development, restricting their motility, or preventing new incoming infections. Indeed, this does appear to be the case. The overlap between injury repair pathways and parasite control is striking, as this review will illustrate. The relationship between parasite killing and wound repair is also reflected in the association of fibrosis with helminth infection [11]. The requirement for rapid tissue repair following parasite migration, can necessitate aggressive matrix deposition, the natural consequence of which is formation of scar tissue and fibrosis [12]. IL-13 appears to be the critical type 2 cytokine involved in the fibrotic response, both through direct effects on collagen production and deposition and indirect effects in promoting TGFβ-mediated repair [13]. IL-13 and/or IL-4, which both use the IL-4Rα chain, are also central to resistance against many if not most helminth infections [1].

Infection with the rodent gastrointestinal nematode, *Nippostrongylus brasiliensis* has proved a powerful and useful model to evaluate both control of nematode numbers and repair of damage caused by nematode migration. Throughout this review, *N. brasiliensis* will be used to illustrate the dual function of so many core components of the type 2 immune response, although other models will be described where relevant. As with the related hookworm parasites of man, *N. brasiliensis* larvae invade by penetrating the skin and entering the blood vessels where they are swept to the lung (Fig. 1). Parasites burst from the capillary bed into the lung parenchyma, causing substantial bleeding. Once in the lung, the larvae undergo one molt and within 48 h move into the airways and trachea, where they are coughed up and swallowed by the host. In the gastrointestinal tract parasites reach sexual maturity and produce eggs. Atypical of many helminth infections, *N. brasiliensis* in mice is a relatively acute infection and depending on parasite/host strains, adult worms are expelled from the gut in 1 to 2 weeks. Expulsion is highly Th2 dependent, with a critical role for Stat-6 and the IL-4Rα [14], responses that are also needed for protection from re-infection [15]. Whilst larval migration through the lung causes considerable damage, the tissue is rapidly repaired in a process dependent on type 2 activated macrophages [16]. Nonetheless, the progressive airway remodeling that occurs can lead to deficits in lung function and after some 50 days post infection, the lung in all strains of infected mice exhibit an emphysematous morphology of unknown origin [17,18].

2. Alerting the immune system to injury

IL-33, IL-25 and TSLP alert the immune system to injury and promote the development of a type 2 immune response. Each of these molecules illustrates the intimate relationship between parasite control and injury repair (Fig. 2).

2.1. Interleukin-33

IL-33 is a member of the IL-1 family and its receptor, ST2, is expressed on mast cells, Th2 cells [19], ILC2s [20,21] and can be highly upregulated on macrophages by Th2 cytokines [22]. In keeping with its designation as an alarmin, IL-33 is released in a bioactive form by dying cells [23] and a key mechanism by which mast cells respond to injury is via recognition of IL-33 [7]. IL-33 promotes multiple aspects type 2 immunity [19] and this has been documented in the context of helminth exposure through intravenous administration of *Schistosoma mansoni* eggs, one of the most potent inducers of type 2 immunity known. Mice that lack ST2 fail to develop primary Th2 responses or form Th2-dependent lung granulomas around the eggs [24]. Thus, the evidence that IL-33 acts by alerting the immune system to injury and induces type 2 immune responses is strong. The response elicited by IL-33 also impacts on the repair process and this is documented by accelerated repair of incisional wounds following IL-33 administration [25] and emerging evidence for IL-33 in epithelial restoration and mucosal healing in the gut [26]. The promotion of type 2 cytokines and healing, also means IL-33 contributes to fibrosis in a variety of experimental models [27,28].

As a potent initiator of Th2 responses, it was logical to test the role of IL-33 in *Trichuris muris*, a nematode infection that is strictly dependent on Th2 immunity for parasite expulsion from the intestine. Humphreys et al. [29] demonstrated that IL-33 mRNA was elevated early following infection, and that administration of recombinant IL-33 was sufficient to accelerate clearance of the parasite. The importance of IL-33 for parasite control was also demonstrated for *N. brasiliensis*, where IL-33 is needed in both primary and secondary infection to promote expulsion [30]. The effect on worm expulsion was due to the ability of IL-33 to promote IL-13 production by both ILCs and CD4+ T cells, which in turn increases production of the anti-worm effector molecule RELMβ by intestinal epithelial cells. In this same study, IL-33 deficiency led to greater hemorrhaging at day 3 post infection, along with reduced eosinophil recruitment to the lung. Thus IL-33 is critical for worm expulsion, while also minimizing host damage early in infection [30].

2.2. Interleukin 25

IL-25 is a member of the IL-17 cytokine family produced by epithelial cells, amongst other cell types, and is likely a sensor of epithelial disruption [4]. Like IL-33, IL-25 induces the production of type 2 cytokines by ILCs. As a direct result, type 2 cytokine responses and parasite expulsion are delayed in *N. brasiliensis* infected IL-25 deficient mice [31]. Further, delivery of recombinant IL-25 into RAG-deficient mice is sufficient to mediate parasite expulsion [31,32]. Similarly, when mice normally susceptible to *T. muris* infection were treated with IL-25, they were able to effectively expel the parasite, while IL-25 deficiency on the genetically resistant background prevented worm expulsion [33]. Similar methods revealed that IL-25 protected against infection with *Trichinella spiralis*, including reducing both the worm burden in the intestine and the number of larvae in the muscles [34]. Together these studies demonstrated the potency of IL-25 as an anti-nematode effector. Importantly, in the *T. muris* study, Owyang et al. demonstrated that IL-25 was able to limit the intestinal inflammation and tissue damage in the colon associated with this infection demonstrating the dual roles of this alarmin cytokine [33]. Independently of helminth infection, the anti-inflammatory properties of IL-25 that protect against gut damage are also reflected in studies of type 1 induced colitis [35,36]. Not surprisingly, because of its ability to enhance type 2 responses, IL-25 also promotes allergic responses that themselves can lead to tissue damage and remodeling [37] as well as fibrosis [38], the consequence of aggressive wound repair.

2.3. Thymic stromal lymphopoietin (TSLP)

TSLP is a member of the IL-2 cytokine family expressed predominantly by epithelial cells. Expression of TSLP is constitutive in the lung and gut where it is believed to suppress inflammatory type 1 responses and promote type 2 responses [39]. TSLP

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