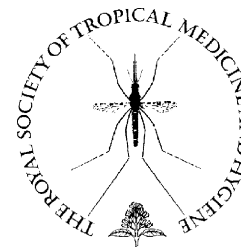




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REVIEW

The hygiene hypothesis and the increasing prevalence of chronic inflammatory disorders

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Received 3 May 2007; received in revised form 23 May 2007; accepted 23 May 2007

KEYWORDS

Regulatory T-cells;
 T_{reg} ;
Allergy;
Autoimmunity;
Hygiene hypothesis;
Helminths;
Mycobacteria

Summary The 'Hygiene' or 'Old Friends' hypothesis suggests that increases in chronic inflammatory disorders (allergies, inflammatory bowel disease and autoimmunity) in developed countries are partly attributable to diminishing exposure to organisms that were part of mammalian evolutionary history. Crucial organisms, including helminths and saprophytic mycobacteria, are recognised by the innate immune system as harmless or, in the case of helminths, as organisms that once established must be tolerated. This recognition then triggers development of regulatory dendritic cells that drive regulatory T-cell responses to the 'Old Friends' themselves and to simultaneously processed 'forbidden' target antigens of the chronic inflammatory disorders.

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The incidence of several chronic inflammatory disorders has been increasing markedly in developed countries. These include allergic disorders (asthma, hay fever), some autoimmune disease (type 1 diabetes, multiple sclerosis (MS)) (Bach, 2002) and inflammatory bowel diseases (IBD) (Sawczenko et al., 2001). The 'Hygiene' or 'Old Friends' hypothesis attributes some of these increases to a failure of immunoregulation caused by diminishing exposure to certain organisms that were part of mammalian evolutionary history. We know that failure of immunoregulatory mechanisms can lead to simultaneous increases in all of these diverse types of pathology, because genetic defects of *Foxp3*, a transcription factor that plays a crucial role in the development

and function of regulatory T-cells (T_{reg}), leads to the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, which includes aspects of all of them (Hori et al., 2003; Wildin et al., 2002).

Clearly, if this view is correct, then there should be evidence for defective regulatory pathways in patients suffering from these disorders. This has been convincingly demonstrated in allergic disorders (Akdis et al., 2004; Karlsson et al., 2004; Perez-Machado et al., 2003) and in some autoimmune diseases (Kriegel et al., 2004; Viglietta et al., 2004). The situation is less clear in IBD because the gut is in a perpetual state of mild inflammation. Nevertheless, defective regulatory pathways are the key aetiological factor in animal models of IBD (Powrie et al., 2003), and tolerance to gut contents (bacteria or ingested material) is broken in human IBD (Duchmann et al., 1995; Kraus et al., 2004).

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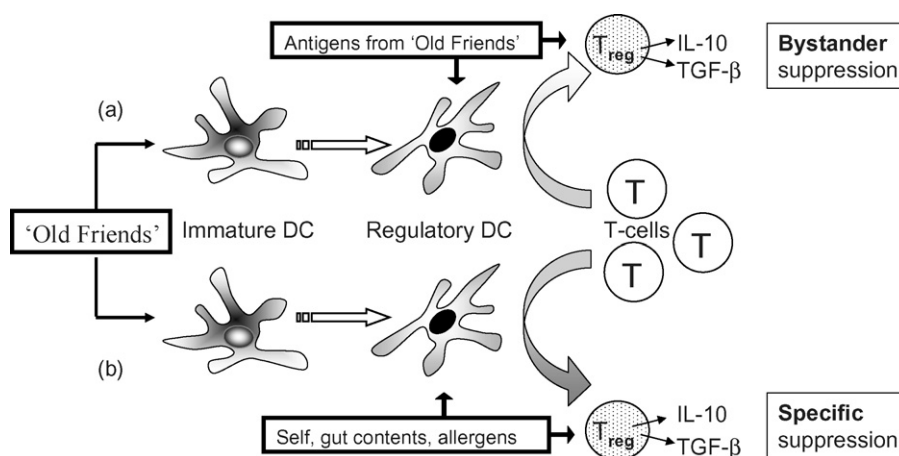


Figure 1 Organisms such as helminths and environmental saprophytes, which are part of mammalian evolutionary history ('Old Friends') and must be tolerated, are detected by pattern recognition receptors on dendritic cells (DC). The DCs mature into regulatory DCs (DC_{reg}) that drive regulatory T-cell (T_{reg}) responses to the antigens of these organisms. (a) The continuing presence of these antigens in the gut flora, in food or resident as parasites such as microfilariae leads to continuous background release of regulatory cytokines from these T_{reg}, exerting bystander suppression of other responses. (b) Meanwhile, the increased numbers of DC_{reg} lead to increased processing by such DCs of self antigens, gut content antigens and allergens. Therefore, the numbers of T_{reg} specifically triggered by these antigens is also increased, downregulating autoimmunity, inflammatory bowel diseases and allergies, respectively.

So why would diminishing exposure to microorganisms lead to a failure to develop adequate immunoregulatory pathways, and which organisms are implicated? The 'Old Friends' hypothesis suggests that the failure is a consequence of diminished exposure to two categories of organisms. First, harmless organisms associated with mud, untreated water and fermenting vegetable matter, such as environmental saprophytic mycobacteria and lactobacilli. These were always a major part of the diets of mammals and early man but are less abundant in chlorinated water and in clean modern supermarket produce. And second, helminth infections that are still common in developing countries but almost completely absent from rich ones. The former need to be tolerated because they are harmless and were constantly present in food and water throughout mammalian evolution. The parasites need to be tolerated because, although not always harmless, once they are established any effort by the immune system to eliminate them is likely to make the situation worse. For instance, a futile effort to destroy microfilariae results in lymphatic blockage and elephantiasis.

The mechanism by which these organisms prime immunoregulation relevant to allergies, autoimmunity and IBD is explained in Figure 1. Rather than provoking aggressive immune responses, these organisms cause a pattern of maturation of dendritic cells (Adams et al., 2004; Smits et al., 2005; van der Kleij et al., 2002) such that these drive T_{reg} rather than Th1 or Th2 effector cells. This in turn leads to two mechanisms that help to control inappropriate inflammation. First, continuing throughput of the 'Old Friends' causes continuous background activation of T_{reg} specific for the Old Friends themselves. The result is a constant background of bystander suppression. Second, these regulatory dendritic cells (DC_{reg}) inevitably sample self, gut contents and allergens, and so induce T_{reg} specific for the illicit target antigens of the three groups of chronic inflammatory

disorder. We do not understand all of the ways in which DC_{reg} and T_{reg} block or terminate inappropriate inflammatory responses, but release of the anti-inflammatory cytokines IL-10 and TGF-β is often involved (Taylor et al., 2006; Wilson et al., 2005; Zuany-Amorim et al., 2002). These inhibitory mechanisms are aborted when there are legitimate 'danger' signals and an aggressive immune response is required (Pasare and Medzhitov, 2003).

The validity of these pathways is supported by clinical trials and experimental models in which microorganisms that are currently 'missing' from the environment in rich countries will treat allergy (Ricklin Gutzwiller et al., 2007; Wilson et al., 2005; Zuany-Amorim et al., 2002), autoimmunity (Zaccane et al., 2003) or intestinal inflammation (Di Giacinto et al., 2005; Summers et al., 2005a, 2005b).

Perhaps the most striking example is a recent experiment of nature. Patients in Argentina suffering from MS were followed up for 4.6 years. It was found that those who developed parasite infections (that were not treated) had significantly fewer exacerbations than those who did not (Correale and Farez, 2007). Moreover, they also developed T_{reg} (CD4⁺, CD25^{hi}, Foxp3⁺) that specifically responded to myelin basic protein. In other words, the presence of the parasite appeared to drive the development of T_{reg} that recognised the autoantigen, as described in Figure 1.

The concept is a simple one that might have considerable implications for future management of changing patterns of disease in rich developed countries.

Funding: None.

Conflicts of interest: G.A.W.R. is a research director of SR Pharma, which owns intellectual property relating to *Mycobacterium vaccae*.

Ethical approval: Not required.

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