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The Role of Microbial Byproducts in Protection Against Immunological Disorders and the Hygiene Hypothesis

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Abstract: Over the past three decades the incidence of allergic disorders and autoimmune diseases has risen and this trend is particularly prominent in developed nations. The hygiene hypothesis suggests that as a living environment becomes more sanitized, children are not exposed to microbial and parasitic stimulations that were once commonly acquired since early in life, leading to a lack of immune sensitization tending towards T helper 2 (Th2) dominance. This postulation is sufficient to explain allergic disorders, which mostly result from hyper Th2 responses, but inadequate to explain the increase in Th1 or Th17-based autoimmunity. Recent advances in experimental mouse models revealed that stimulation of Toll-like receptors (TLRs) by pathogen-associated molecular patterns could reduce symptoms of allergic airway disease and prevent the onset of autoimmunity. The underlying mechanism for the protective effects of TLR ligands is currently under intense investigation and there are indications that IL-10-producing B cells, regulatory T cells, and innate immune cells play an important role during this process. The finding that early exposure to microbial byproducts contributes to the modulation of immunological disorders may once again modify our interpretation of the hygiene hypothesis.

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Environmental Microorganism and the Immune System

The immune system protects humans against frequent infection by microbial pathogens. This highly evolved protective process employs both the innate and adaptive arms of the immune system to respond rapidly during pathogenic invasion and provide long-lasting and specific immunity against future challenge. It is estimated that an average healthy human being harbors ten times more bacteria than cells in his/her body (most of these microbes residing in the gastrointestinal tract) (Bjorksten, 2004) and impressively these microorganisms are mostly tolerated or ignored by the immune system. It is therefore critical to understand that not all microorganisms in the environment are detected as dangerous entities by the immune system. The homeostatic ecosystem of microorganisms in the body is collectively termed the human microbiome and is thought to play an integral role in shaping our immune system and affecting human health. Scientific investigations aiming to relate the shifting landscape of the human microbiome to environment and lifestyle changes are crucial for uncovering the beneficial role of commensal microorganisms. The Human Microbiome Project (HMP), initiated by the National Institutes of Health represents one of such undertaking (Tumbaugh *et al.*, 2007).

To a large extent, human survival depends on our immune system's ability to co-exist with microbes in the environment. While genetic diversity is the basis for selection and evolutionary adaptation to an environment, it has been suggested that the immune system will also receive input from the environment to ensure proper functioning during the course of a person's life (Rook, 2009). Industrialization and modernization of human lifestyle have eliminated a great portion of the microbial communities from our surroundings through childhood [vaccination](#), frequent antibiotic usage, and much improved hygiene standards. These practices are encouraged based on medical and scientific advances that have saved an immeasurable number of lives by reducing pathogenic infection. It is likely that this rapid change in lifestyle has also unknowingly deprived us of important microbiological stimulation needed to condition the immune system towards tolerance. As a consequence, people have become susceptible to a range of emerging immune system-related diseases that target innocuous antigens ([allergy](#)), self antigens ([autoimmunity](#)) and even commensal intestinal microbes [inflammatory bowel disease (IBD)] that were rarely heard of a few generations ago. Hence many in the medical and scientific community suspect that the lack of early life infection may contribute to immune disorders later in life. In general, these observations and logics fostered the inception of the [hygiene hypothesis](#).

The Original and Changing Definition of the Hygiene Hypothesis

The hygiene hypothesis was first proposed in 1989 by David Strachan's epidemiological analysis on hay fever and household size (Strachan, 1989). In this study, an inverse relationship between the number of older siblings and the prevalence of allergic diseases (hay fever and eczema) was found. The author inferred that childhood infection contracted from siblings, in particular older siblings, might have offered protection later in life against allergy. Subsequently, the hygiene hypothesis was extended to include other allergic maladies and autoimmune diseases (Bach, 2002). Many childhood infections that were once common have become gradually reduced or even eliminated. Simultaneously, there has been a rise in incidence of various immunological disorders in developed nations and among the urban population in developing nations. An increased prevalence of [asthma](#) has been observed in many western countries in the past three decades (Eder *et al.*, 2006) and more recently in developing Asian countries (Leung and Wong, 2008). Unlike asthma, high prevalence of [allergic rhinoconjunctivitis](#) and eczema were not restricted to developed countries. It was found that countries with relatively low asthma incidence such as Nigeria and Ethiopia could have high incidence of one or both allergic rhinoconjunctivitis and eczema. However, low prevalence of these two allergic diseases coincide only with countries with relatively low asthma incidence such as Albania, Georgia, China, India, Indonesia, Uzbekistan, Russia, and Greece [The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, 1998]. Several of these geographic areas continued to see a rising incidence of these allergic disorders during a 5 year period (Asher *et al.*, 2006), suggesting a link to modernization. [Multiple sclerosis](#), an autoimmune inflammatory disease affecting the central nervous system that disproportionately impacts residents of more affluent countries, is inversely correlated with the incidence of parasitic infection (Fleming and Cook, 2006; Milo and Kahana, 2010). [Rheumatoid arthritis](#) in children is increasingly seen and recognized although there is little evidence supporting the notion that this disease is correlated to early life hygienic conditions (Ellis *et al.*, 2010). On the other hand, it was documented that the incidence of [type 1 diabetes \(T1D\)](#) in children and young adults has been increasing steadily in Europe and North America since the mid-1950s (Gale, 2002). The incidence of IBD is growing in developed countries and among individuals with improved sanitation in developing countries, suggesting that environmental conditions strongly influence the onset of IBD (Bernstein *et al.*, 2006; Chouraki *et al.*, 2011; Jakobsen *et al.*, 2009). Another allergic disorder called [eosinophilic esophagitis](#) (EoE) is probably a new disease and its epidemiologic and pathogenic features are just beginning to be understood. EoE was first reported in 1978 but not widely appreciated until the 1990s. The pathogenic site of EoE is by definition in the esophagus and is characterized by dense eosinophilic inflammation, with a concentration of eosinophils in the subepithelial compartment along with subepithelial fibrosis. Mast cells also infiltrate the esophagus during EoE, and the number of eosinophils and mast cells are closely correlated. EoE, other allergic conditions, and asthma often coexist in the same patient. The induction of EoE is likely derived from environmental antigen (food and/or aeroallergens) and experimental models of EoE suggest that indoor insect allergens can trigger EoE (Rayapudi *et al.*, 2010). This notion is supported by the incidence of EoE which can follow seasonal variation, suggesting that pollen and other aeroallergens may play a role in its pathogenesis (Moawad *et al.*, 2010).

One could attribute the higher incidence of these disorders over the years to better diagnosis, improved access to medical facilities, and increased public awareness and these factors may very well contribute to the statistical increase of incidence. A standardized survey across the globe largely corrects for these parameters and it has revealed that asthma remained most prevalent in developed countries (Masoli *et al.*, 2004). Furthermore, diseases that can be easily diagnosed may not be readily explained by improved healthcare standard, such as T1D, that often involve childhood fatality, multiple sclerosis, and IBD.

Childhood Infection, the Commensals, and Protection from Immunological Disorders

If indeed childhood infection could prevent the onset of allergy and [autoimmunity](#) in susceptible individuals, it will be important to identify the microbes or multicellular parasites that are responsible for this protective effect. Proving the hygiene hypothesis in humans mechanistically has been a challenging task for the medical and scientific community. Further complicating this undertaking is the many reports demonstrating that certain infections can trigger or exacerbate autoimmune conditions (Kivity *et al.*, 2009). Nevertheless, human patient studies showed that certain microbes, such as [Helicobacter pylori](#) and [helminth](#) infection, correlate with lower incidence of specific autoimmunity, namely IBD (Kamradt, 2005; Lidar *et al.*, 2009; Vare *et al.*, 2001). Parasitic infestation with helminthes is endemic in many third world countries. Advances in sanitation and public health campaigns have practically eradicated multicellular parasites in Western countries, and coincidentally these areas have the highest incidence of IBD (Bernstein *et al.*, 2006). Pilot clinical trials using eggs of the porcine helminth [Trichuris suis](#) have shown efficacy in inducing remission of Crohn's disease and [ulcerative colitis](#), suggesting that even established IBD can be skewed toward a less injurious phenotype after exposure to helminthes (Summers *et al.*, 2003; 2005). Therefore, it is possible that the lack of exposure to certain parasites early in life may condition the gut immune system to react inappropriately to endogenous gut flora in genetically predisposed individuals. However, it is essential to highlight that although these infections may alleviate autoimmunity, they are not harmless. Living with chronic infection by these organisms could have undesirable immunosuppressive effects that may compromise immunity against other pathogenic infections. On the other hand, it was reported that enteric bacteria are necessary for the onset of IBD in animal models as germ-free [IL-10](#)-deficient mice do not show sign of gut inflammation (Sellon *et al.*, 1998). Therefore, in a genetically susceptible host, the composition of [gut microbiota](#) may determine the onset or prevention of [autoimmune disease](#). In humans, IBD is associated with a decrease in microbial diversity of the gut, with reduction in the number of putative protective bacteria (e.g., [Faecalibacterium prausnitzii](#) in Crohn's disease) and an increase in pathogenic species (such as adhesive [Escherichia coli](#)) (Kang *et al.*, 2010; Schippa *et al.*, 2009). Experimental mouse models of IBD demonstrated that colitis can be induced by colonization of specific bacteria in these models. Transfer of colitogenic bacteria to healthy recipient mice can induce colitis suggesting that alterations in the gut flora in response to environmental factors can cause IBD in a host with genetic susceptibility (Garrett *et al.*, 2010). The relationship between gut flora and the intestinal immune system is dynamic, with bilateral influences from the time of gut colonization at birth. Experimental evidence suggests that the absence of gut flora results in an immature intestinal immune system (Atarashi *et al.*, 2011), and reduced diversity of intestinal flora in early childhood is associated with an increased risk of allergic disease at school age (Bisgaard *et al.*, 2011). As stated above, inflammation is associated with significant changes in the composition of gut flora. Therefore, it is likely that environmental factors greatly influence the diversity and makeup of gut bacteria, and perhaps other microbes as well including those found in lung. Interestingly, infections acquired through oro-fecal route, such as [Toxoplasma gondii](#), [Helicobacter pylori](#), and Hepatitis A virus, showed an inverse correlation to incidence of atopic disorders in the studied population, whereas infections acquired through the respiratory route did not demonstrate such correlation (Matricardi *et al.*, 2000). It is likely that the postnatal colonization of the gut mucosa and the maturation of the gut-associated lymphoid system aided by challenge with environmental microbes have a major role in tolerization towards [Th2](#)-mediated allergy and immune deviation from [Th1](#)-related autoimmunity.

The intestinal microflora is different between individuals and its composition is largely dependent on geographical factors and lifestyle choices. Although no single [commensal bacteria](#) species have been conclusively proven to protect against allergy or autoimmunity, the lack of certain bacterial species was observed with human patients prone to or suffering from immune disorders. Allergic children, as determined by skin prick testing, tend to have less colonization by lactobacilli and [bifidobacteria](#) in the gut (Bjorksten *et al.*, 1999; Kalliomaki *et al.*, 2001). Rectal biopsies from human patients with IBD also showed significantly lower count of bifidobacteria (Mylonaki *et al.*, 2005), suggesting that the presence of this bacterial species could have beneficial effects on the host immune system. The gut microbiota is complex and diverse of which we currently have limited understanding. Although early emphasis has been placed on the study of gut bacteria, the intestine probably also hosts Archaea, fungi, and viruses that have roles in normal physiology and disease. Furthermore, many bacterial species living in the gut are anaerobic, making them difficult to culture and study outside the body. Bifidobacteria may be just one of the many potentially beneficial species, but it opens a window of opportunity whereby gut symbiont-dependent [immunoregulation](#) can be investigated. A recent study conducted by Fujie *et al.* (2011) suggested that a particular strain of bifidobacteria has [Toll-like receptor 2](#) (TLR2)-stimulating properties and is capable of inducing the immunosuppressive cytokine IL-10 from intestinal CD4 T cells. This brings us to a large body of scientific literature attempting at exploiting the immunosuppressive role of TLR family members.

Toll-like Receptor Stimulation and Protection from Immunological Disorders

Toll-like receptors are a family of membrane receptors that recognize a wide variety of microorganism-derived molecular moieties. The TLR ligands are

collectively termed [pathogen-associated molecular patterns](#) (PAMPs), some of which include lipopolysaccharides (LPS) found on [gram-negative bacteria](#) membrane and the double-stranded RNA produced during virus reproductive cycle (Kopp and Medzhitov, 2003). Toll-like receptors can be found primarily on professional antigen presenting cells (APCs), and dendritic cells and macrophages in particular express a subset of these receptors either on cell surface or intracellularly (Iwasaki and Medzhitov, 2004). The APCs are constantly surveying the body for potential threats, and one way that the presence of foreign intruders activates APCs is by engaging TLRs on these cells. The activation of TLRs is often associated with inflammation and the priming of the adaptive immune system. Therefore, many TLR ligands are used as adjuvants to enhance the immunogenicity of a given vaccine.

Besides being commonly used as immunity booster, TLR ligands can effectively inhibit allergy and autoimmunity in many animal models. In two separate [allergic asthma](#) studies performed on different mouse strains [Balb/c and non-obese diabetic (NOD) mice], it was found that all TLR ligands tested, including P40 (TLR2), Poly(I:C) (TLR3), LPS (TLR4), and R848 (TLR7), are able to inhibit multiple parameters of allergic airway disease towards a model antigen ovalbumin (Aumeunier *et al.*, 2010; Sel *et al.*, 2007). In these studies, a single dose of each TLR ligand administered systemically by intraperitoneal injection either before sensitization (Sel *et al.*, 2007) or before aerosol challenge (Aumeunier *et al.*, 2010) with ovalbumin markedly reduced [IL-4](#) and [IL-5](#) levels and [eosinophilia](#) in bronchoalveolar lavage fluid. In addition, goblet cell hyperplasia (Sel *et al.*, 2007) and airway obstruction (Aumeunier *et al.*, 2010) were relieved in the lungs of TLR ligand-treated animals. A ligand for TLR9, the CpG-ODN, was also reported to inhibit pulmonary allergy in several studies [reviewed in (Lazarczyk *et al.*, 2005)], suggesting that all TLR ligands affect a common pathway to prevent experimental airway allergy.

Plenty of evidence also indicates that TLR ligands are effective at preventing autoimmune [diabetes](#) in genetically susceptible rat and mouse models. The [NOD](#) mice typically became glycosuric in 20 weeks in a [T cell](#)-dependent manner but early treatment with poly(I:C) could prevent the onset of disease (Serreze *et al.*, 1989). In the diabetes-prone BioBreeding (BB) rats, poly(I:C) was able to significantly decrease incidence when administered at low dose; on the contrary, high dose poly(I:C) accelerates the onset of disease (Ewel *et al.*, 1992; Sobel *et al.*, 1998). However, in other instances, as shown in a peptide-induced diabetes model and genetically-engineered mouse model, injection of poly(I:C) exacerbates the disease (Devendra *et al.*, 2005; Moriyama *et al.*, 2002). It is not entirely clear why poly(I:C) can have contrasting effects on the same disease, but it appears likely that very early exposure to low dose poly(I:C), noticeably before the immune system sufficiently "senses" the [autoantigen](#), confers the benefits of disease prevention. In addition to type 1 diabetes, poly(I:C) was also effective at alleviating disease in [experimental autoimmune encephalomyelitis](#) (EAE) and suppressing inflammatory responses during arthritis progression (Touil *et al.*, 2006; Yariina *et al.*, 2007). In both studies, the induction of type I interferons (IFNs) accounted for the suppressive effects of poly(I:C). Furthermore, in a chemical-induced mouse colitis model, the ability of a TLR9 agonist to suppress intestinal inflammation is linked to type I [IFN](#) signaling (Katakura *et al.*, 2005). Incidentally, type I IFNs are also responsible for disease development in the case of poly(I:C)-induced diabetes (Devendra *et al.*, 2005). The dual effects of type I IFNs observed in these studies are not completely understood. Again, the underlying cause may be the timing of type I IFN release relative to self antigen recognition, as the suppressive effects of TLR ligands in these disease models tend to result from pre-treatment prior to disease induction. A comprehensive study using TLR ligands before and after disease onset in the same experimental model will certainly shed light on the molecular mechanism by which type I IFNs achieve opposing regulatory roles on the immune system.

Cellular Mechanisms of the Toll-like Receptor-mediated Protection

Collectively, we have seen that in many instances TLR activation can lead to suppression of immune responses that mediate autoimmunity and allergy. The explanation for these findings is diverse, and many regulatory immune cells have been implicated. Some of the more prominent cell types are regulatory B cells, which can respond to TLR stimulation by producing the suppressive cytokine IL-10. [B cell](#) receptor triggering, CD40 co-stimulation, and TLR activation are capable of inducing IL-10 from B cells (Fillatreau *et al.*, 2008), in particular the B1 cells and splenic B cells with a marginal zone phenotype, which are some of the defined IL-10-producing subsets (Burke *et al.*, 2004; O'Garra *et al.*, 1992). In the EAE model, resolution of the disease depends on the presence of IL-10-producing B cells and TLR/MyD88 signaling in B cells plays an important role in this regard (Fillatreau *et al.*, 2002; Lampropoulou *et al.*, 2008). The suppressive effects of LPS-activated B cells were also demonstrated in autoimmune diabetes; however, IL-10 was not examined in this study, instead these B cells were found to secrete another immunosuppressive cytokine, TGF β (Tian *et al.*, 2001). Precisely how IL-10-producing B cells regulate autoimmune responses and autoreactive T cells *in vivo* remains to be investigated, but *in vitro* data suggest that they may interfere with dendritic cells mediated priming of T cells (Lampropoulou *et al.*, 2008).

One major cell type that controls tolerance towards self antigens, symbiotic intestinal microflora, and harmless environmental antigens is the CD4⁺CD25⁺FoxP3⁺ T regulatory (Treg) cells (Sakaguchi, 2005). There is some evidence that systemic TLR stimulation somewhat increases the frequency of Tregs in the spleen (Aumeunier *et al.*, 2010) and MyD88-deficient animals tend to have lower frequency of Tregs (Sutmoller *et al.*, 2006). However, it is still not clear if TLR-activated Tregs are responsible for the suppressive effects of TLR ligands in most allergy and autoimmunity experimental models. TLR stimulation has major effects on the CD11c^{hi} [dendritic cell](#) (DC) compartment. Typically, MHC molecules and co-stimulatory ligands are upregulated rapidly after TLR activation on DCs, facilitating antigen presentation and the priming of adaptive immune cells. Importantly, Wilson *et al.* (2006) reported that the phagocytic capacity of DCs was significantly reduced hours after systemic TLR stimulation, which may account for suboptimal priming of T cells when the immune system has been previously exposed to TLR ligands. Therefore, TLR activation on the DCs simultaneously reduced the quality of these cells, and perhaps the quantity as well. Therefore, it is possible that in the absence of overt infection, constant and low grade TLR stimulation regulates self reactivity partly by raising the threshold of a successful priming event through regulating the availability and activity of APCs. Altogether, attempts to understand the suppressive effects of TLR ligands have uncovered several downmodulating effects of these molecules on different immune cell types. It is likely that each of them is important for maintaining the state of tolerance to self and innocuous non-self.

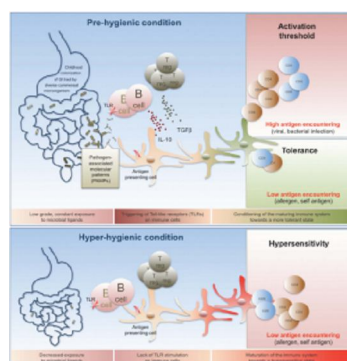


Figure 1. A plausible explanation for the hygiene hypothesis: sensitization of TLR pathways by diverse commensal microorganisms conditions the developing immune system towards a more tolerant state against self antigens and innocuous environmental antigens. In a pre-hygienic living environment (top panel), gut mucosa is colonized by a wide variety of microbes, which constitute a source of diverse PAMP molecules. These microbial ligands stimulate members of the TLR family found on many immune cells, leading to the activation of regulatory cells and the

secretion of immunosuppressive cytokines such as IL-10 and TGF β . As a consequence, the antigen presenting cell compartment is conditioned such that only high antigen encountering events in combination with danger signals (frequently seen in rapidly-proliferating pathogens) are able to trigger a robust immune response. On the contrary, under hyper-hygienic conditions, the gut mucosa is colonized by microorganisms with limited diversity (lower panel). The lack of overall TLR stimulation results in a failure to generate a repertoire of regulatory cells that would benefit the host. As a consequence, the immune system becomes hypersensitive to antigenic stimulation not pertaining to pathogenic invasion.

If indeed early exposure to low grade TLR stimulation could prevent the onset of allergy or autoimmunity in genetically susceptible individuals, this may fit well with the hygiene hypothesis in that childhood or even prenatal exposure to harmless commensal bacteria could be beneficial by conditioning the immune system (**Figure 1**). The challenge remaining is to identify the symbiotic bacterial species that contain TLR ligands that “educate” a growing child’s immune system. A common gut symbiont, *Bacteroides fragilis* could be one such candidate. Introduction of *B. fragilis* into germ free mice, which have Th2 biased immune defects (akin to asthmatic and allergic individuals with Th2-skewing immune responses), was able to restore the immune balance in these animals (Mazmanian *et al.*, 2005). The key molecule on *B. fragilis* with the above-mentioned immunomodulatory effects is a zwitterionic polysaccharide (ZPS) called polysaccharide A (PSA). It was suggested that ZPSs are both TLR2 agonist and T cell antigen (Wack and Gallorini, 2008), and hence many of their biological activities are likely mediated in the presence of APCs. This may still be a long way from suggesting that TLR ligands from commensal bacteria are the most important factor responsible for conditioning a developing immune system towards self tolerance, but this represents a direction worth exploring in the future. The benefit of childhood microbial exposure on reducing the incidence of asthma was clearly demonstrated in a recent epidemiological report. Children raised in farming households were in contact with a wide range of bacterial and fungal species compared to the control group and the greater diversity of environmental microbes is inversely correlated to occurrence of childhood asthma (Ege *et al.*, 2011).

Concluding Remarks

The use of microbial mimics in animal models of allergy and autoimmunity has taught us much about the potential role of microbes in helping us achieve immunological balance. Knowledge gained from animal models was harnessed for the use of TLR ligands in human diseases (Tse and Horner, 2007). However, it is important to constantly remind ourselves that all TLR ligands are also adjuvant that boosts immune responses and this poses a risk when used in humans because they may worsen underlying diseases by provoking an inflammatory response. Ultimately, the understanding of how microbes and their products promote tolerance in a mechanistic sense will prove more valuable, enabling us to potentially shape a lifestyle that prevents the onset of autoimmune diseases and allergy.

Disclosure

The authors declare no conflicts of interest.

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