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Mechanisms of the hygiene hypothesis — molecular and otherwise

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The hygiene hypothesis was initially formulated to explain the steep increase in the prevalence of allergies in Western societies observed over the past few decades. It proposes that the microbial environment interfaces with the innate immune system and modulates its ability to impart instructions to adaptive immune responses, particularly when such interactions occur *in utero* and/or in early life. Recent research on the molecular mechanisms of the hygiene hypothesis highlights the role of Toll-like receptor ligands in modulating allergic inflammation and the importance of bacterial products in directing the development of the host's immune system. Genetic analysis, by contrast, clearly shows that the response threshold of the immune system to environmental stimuli is controlled by natural genetic variation and gene–environment interactions, suggesting that the complex interplay between the organism and the environment might not be regulated by a single mechanism.

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Introduction

Few paradigms in immunology have been as pervasive as the hygiene hypothesis. Yet, few paradigms have been so strongly attacked [1,2] or so eloquently praised [3–5]. More than 15 years after the initial formulation of the hypothesis [6], the pro/con debate is still on. This state of affairs stems not only from the broad scope of the hypothesis, its far reaching implications and its multiple flavors but also from often contradictory, always complex, epidemiological and functional findings. The persisting lack of a well-defined mechanistic link between environmental stimuli and immune responses creates a no man's land in which controversy thrives.

In this article, we will review the literature published in the past two years that attempts to sort out the molecular mechanisms of the hygiene hypothesis and we will discuss research directions based on a closer integration between epidemiology, immunology and genetics.

The hygiene hypothesis umbrella

It might be useful to start by clarifying what falls under the umbrella of the hygiene hypothesis [7]. The hypothesis was initially formulated to explain the steep increase in the prevalence of allergies in Western societies observed over the past few decades, and proposed that reduced exposure to infections in early childhood owing to a combination of diminishing family size, improved living standards and higher personal hygiene might result in increased risk of developing allergic disease [6].

As the integration between epidemiology and immunology intensified, the hypothesis converged with the then dominant Th1/Th2 dichotomy to state that hygienic environments typical of Western lifestyles deprive the immune system of stimuli required to boost Th1 responses, leading to a surge in the prevalence of Th2-mediated disease [8]. Once it became clear that the Western world is witnessing an increase in both Th2-mediated allergic disorders and Th1-mediated autoimmune diseases [9], the hygiene hypothesis took on a regulatory twist, stating that evolution endowed our species with immune regulatory mechanisms that are activated by the interaction with the microbial environment and that serve to fine-tune both Th1 and Th2 antigen-driven effector responses [10]. The innate immune system senses the environment and modulates accordingly the T regulatory arm, which looms large as the ultimate keeper of the balance between tolerance and responsiveness. The efficiency of the regulatory interface in its current state would be jeopardized by a decrease in the microbial burden that the immune system has evolved to deal with [11]. Other promising avenues of investigation are currently exploring the role of parasites in this process [4,12].

At the interface between environment and immunity

The strong protective effect of traditional farming environments against allergic sensitization and asthma [13,14] is one of the strongest arguments in favor of the hypothesis and consistently points to bacterial products such as endotoxin [14] and muramic acid [15]. In line with the epidemiologic findings, the search for the molecular

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mechanisms of the hygiene hypothesis has focused mostly on the interactions between bacterial products and Toll-like receptors (TLRs) — the main transducers of microbial signals to the immune system [16] and critical regulators of CD4 T-cell activation [17].

Several animal models have been developed to define how the administration of bacterial stimuli affects antigen-specific immune responses and the development of allergic inflammation. Unfortunately, the results are confusing because no two models are identical in terms of mouse strain, type and dose of antigen, route of antigen administration, type and dose of TLR ligand, and time and route of administration of TLR ligand relative to the antigen. It is fair to say that most groups have reported a protective effect of natural or synthetic TLR2 and/or TLR4 ligands in allergen-induced lung inflammation [18–20], but disease-enhancing effects have been observed as well [21,22[•]]. There is also disagreement as to whether downregulation of Th2-dependent inflammation is [18,20] or is not [19,23] accompanied by a concomitant upregulation of Th1 responses.

Interestingly, the ability to modulate allergic responses is not unique to TLR2/4 ligands. Early life administration of CpG-containing immunostimulatory DNA sequences — agonists of TLR9 — has also been shown to exert a protective effect against allergic inflammation in a murine mode of maternal asthma transmission [24], and the same TLR9 ligand conferred protection against a classic allergen challenge [25]. However, immunostimulatory oligonucleotides failed to inhibit allergic airway responses in a clinical trial [26], which indicates that further work is required before TLR-mediated manipulation of allergen-induced immune responses can be translated into an effective preventive or therapeutic strategy.

Animal models are currently used as a tool to identify the molecules that confer protection from allergic inflammation in a farming environment. Inhalation of extracts of stable dust collected from farms located in rural regions of the Alps (Austria, Germany and Switzerland) during allergen sensitization was found to inhibit the development of airway hyperresponsiveness and airway eosinophilia upon challenge, as well as production of IL-5 and antigen-specific IgG₁ and IgE. Dust extract also suppressed the generation of human dendritic cells *in vitro*. Of note, the biological activity of the dust extract was not exclusively mediated by lipopolysaccharide [27]. Although preliminary and fraught with difficulties related to biochemical deconvolution of the extracts and potential species-specific effects, these studies might help in the identification of the protective factors present in a farming environment, fostering approaches to use these substances as tools to prevent allergic inflammation.

One of the latest analyses of the interactions between environment and immunity highlights the paramount influence that *in utero* exposure to a milieu rich in microbial compounds has on immune responses occurring later in life. Both atopic sensitization and the expression of major innate immune receptor genes (TLR2, TLR4 and CD14) in school-age children were found to be strongly determined by maternal exposure to stables during pregnancy, whereas current exposures had much weaker or no effects [28^{••}]. Interestingly, a dose-response relationship was found between the extent of upregulation of these genes and the number of different farm animal species the mother had encountered in her pregnancy; that is, each additional farm animal species increased the expression of TLR2, TLR4 and CD14. The fact that time of exposure to bacterial ligands relative to sensitization is crucial has been reiterated recently by mouse models showing that mucosal exposure to ovalbumin and/or endotoxin in the neonatal period inhibited allergic responses following subsequent allergen challenge [29].

Some bacteria might be good for your health

Epidemiologic studies indicate that atopic and nonatopic subjects differ in gut flora composition [30], and hygiene-associated deviation in gut microflora has been hypothesized to be one of the key environmental factors underlying development of atopy and asthma in genetically predisposed individuals [4]. However, the mechanistic links between gut flora and immune functions within the host have been unclear. A breakthrough occurred recently with the demonstration that, during colonization of mice with *Bacteroides fragilis* (a ubiquitous gut commensal comprising 2.5% of all bacteria in the human colon [31]), capsular polysaccharide A (PSA) produced by the microorganism directs the cellular and physical maturation of the developing immune system in the host [32^{••}]. PSA can stimulate a surprisingly large fraction of T cells in both mice and humans [33], and its immunomodulatory activities include correcting systemic T-cell deficiencies and Th1/Th2 imbalances and directing lymphoid organogenesis. Probiotic studies with *Lactococcus* and *Bifidobacterium* species suggest that other prominent gut bacteria might produce immunomodulatory molecules [34]. All of these findings have prompted the suggestion that pervasive antibiotic use among children in industrialized countries might lead to clearance of symbionts at an essential point in immune development and result in the absence of molecules with PSA-like activities [32^{••}]. Aberrant immune development without specific direction by this class of immunomodulatory molecules might lead to Th2 cytokine overproduction and the onset of atopic and asthmatic disorders.

The distinction between ‘good’ and ‘bad’ bacteria has been made even more blurred by the demonstration that commensal bacteria are not sequestered by the gut epithelium, but are recognized by TLRs under normal

steady-state conditions. Indeed, the interaction of commensal bacterial products with host microbial pattern recognition receptors plays a crucial role in resistance to epithelial injury and intestinal homeostasis [35]. Because mammalian TLRs recognize products of both pathogenic and commensal bacteria, they might have at least two distinct functions: protection from infection and control of mucosal homeostasis, both of which are dependent on the recognition of microorganisms — pathogens and commensals, respectively. This dual function might explain why some of the TLR-induced gene products, such as inflammatory cytokines and chemokines, are involved in both host defense and tissue repair.

Genes, environment and gene–environment interactions

It is increasingly clear that the molecular mechanisms of the hygiene hypothesis will not be fully understood until we clarify the role played by natural genetic variation in adjusting the response threshold of the immune system to environmental stimuli (see Box 1). In other words,

Box 1 Arguments in the pro/con debate on the hygiene hypothesis

Pro:

The current renaissance (of the hygiene hypothesis) has brought novel microbe-derived therapeutic interventions a long way, with extensive preclinical studies of the protective or therapeutic influence of various microbial exposures, ranging from vaccines to TLR ligand derivatives and from conjugates to microbial extracts. Observations characterizing the renaissance of basic, clinical and translational investigations that refine the hygiene hypothesis suggest that this premise is evolving beyond theory [3].

The research being carried out under the umbrella of the hygiene hypothesis is by no means perfect and does not allow us to give comprehensive advice to our patients, to date. However, the evidence that our modern lifestyle is closely linked to changes in our immune responses to environmental stimuli is growing stronger [4].

A truly unifying concept has not yet emerged, but various pieces of a complex interplay between immune responses of the host, characteristics of the invading microorganism, the level and variety of the environmental exposure, and the interactions between a genetic background and a range of exposures become apparent. Even if today practical implications cannot directly be deduced from these findings, there is great potential for the development of novel preventive and therapeutic strategies in the future [5].

Con:

All clinical epidemiological indications in favor of the hypothesis are based on observational (cross-sectional and cohort) studies and not on observations in randomized controlled intervention studies. In cross-sectional studies, no causal relationships can be assessed with sufficient validity. Also in cohort studies there are validity problems, because the exposure is not determined by chance (by means of randomization) and could be influenced by behavior. Also, behavior might be a confounder because it can be associated with both exposure and outcome [1].

For every exposure studied with regard to the hygiene hypothesis, there are inconsistent findings in relation to asthma. The hygiene hypothesis is not likely to be the sole explanation for the ongoing asthma epidemic in industrialized nations [2].

understanding the hygiene hypothesis requires one to understand the gene–environment interactions that determine the outcome of immune responses. This need is well illustrated by the analysis of genetic variants in CD14 — a component of the TLR signaling complex that facilitates endotoxin responsiveness through the TLR4–MD2 complex but can also associate with a variety of other microbial TLR ligands [36] and even with TLR3, the double-stranded RNA receptor [37].

Many association studies have explored the relationship between CD14–159C>T (also known as CD14/260) — a functional promoter polymorphism [38] — and allergic inflammation. The results of these studies are markedly diverse, ranging from protective to disease-promoting effects, with quite a few reports failing to find an association. What is worse, to the consternation of many, the CD14–159 alleles have been found to have opposite effects, even within the same population (reviewed in [39]). Thus, CD14 provides an excellent example of the consistent inconsistency [40] that marks the genetic analysis of human complex diseases such as allergy and asthma.

Gene–environment interactions offer a method to rationalize this apparent madness. The direction in which CD14–159C>T influences IgE levels and asthma depends on the relevant environmental exposures: cat or dog versus stable animals in a European population [41^{••}], and low versus high endotoxin in subjects of African descent [42^{••}]. In another study, the CD14–260TT genotype protected against atopic dermatitis, but only in children who had a dog at home [43]. Gene–environment interactions have been implicated even more explicitly by evidence of the CD14 genotype-dependent effect of domestic endotoxin exposure on allergic sensitization, eczema and wheeze. Children homozygous for the CD14–159 C allele showed a dose-dependent response to endotoxin: high exposures were associated with a decreased risk of allergic sensitization and eczema, and low exposures with an increased risk relative to the rest of the population. However, in the same children high endotoxin was associated with an increase in non-atopic wheeze. Amongst the remaining children, endotoxin had no effect on sensitization, wheeze or eczema [44^{••}]. The striking conclusion reached by all of these studies is that one and the same polymorphism can be associated with either disease or protection depending on the environment a subject is exposed to. Perhaps the most urgent question raised by these data pertains to the nature of the mechanisms that can turn different environmental exposures into different immune response patterns — what we have called the endotoxin switch [45].

Conclusions

Reflecting on what we do and don't understand about the hygiene hypothesis, Erika Von Mutius, one of the

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epidemiologists most involved in the formulation, validation and elucidation of the hypothesis, recently emphasized the many facets of the hypothesis and wrote that “a truly unifying concept is still missing, but various pieces of a jigsaw puzzle containing a host’s immune response, characteristics of the invading microorganisms, the level and variety of the environmental microbial exposure and a genetic background become apparent” [5]. However, a unifying concept might perhaps be discerned if we take a global look at the field.

The core of the hygiene hypothesis is in the notion that the microbial environment interfaces with the innate immune system and modulates its ability to impart instructions to adaptive immune responses, particularly when such interactions occur *in utero* and/or in early life. This core needs to be now integrated with the pre-eminent role of genetic variation in shaping immune responses to environmental stimuli. Because the introduction of genetics into a field of research typically results in splitting, not unification, we should not be surprised if, the more we learn about the interaction between our genes, our immune system and the environment, the more we find that we need to condition the effects of one to the makeup of the other. By the same token, we surmise that it will not be possible to make progress on one front without simultaneously pushing ahead on the others. Thus, even if we find a unifying concept for the hygiene hypothesis, we might not find a unifying mechanism, because the interactions between environment, genes and immune system are context-dependent. Far from undermining the biological significance of the hypothesis, this reiterates that complex problems, alas (or fortunately), are not amenable to simple solutions.

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