

In utero priming by worms protects against respiratory allergies

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The hygiene hypothesis forms a popular explanation for the increasing prevalence of inflammatory diseases, such as allergies, asthma, and autoimmune diseases, by stating that changes in the environment and lifestyle have resulted in decreased microbial exposure and a relatively weaker development of the regulatory arm of the immune system. Indeed, a number of examples have underscored the association between microbes and disease protection, such as studies on farm microbes, orofecal microorganisms, gut microbiota, and other ancient commensals, such as gut worms. Critical elements for successful protection can be listed as chronicity or sustainability of microbial exposure, severity or intensity of infections, and an early time window of exposure (ie, early colonization or infection at young age).¹ In fact, evidence is accumulating that events that educate the immune system even before birth might already be decisive, suggesting a vital link between maternal immune responses and disease protection in offspring.² The study by Straubinger et al³ in the current issue of the *Journal* contributes to this extended hygiene hypothesis, showing that immune responses provoked by maternal worm infections in mice can protect offspring against the development of experimental allergic airway inflammation after birth. Importantly, this was critically dependent on the phase of maternal schistosome infection: the offspring were protected when schistosome-infected mothers were mated in the T_H1 (prepatent larval infection) or regulatory (chronic infection) but not T_H2 (acute infection) immune phase.³ The authors transferred embryos from *in vitro* fertilized oocytes of initial T_H1 phase-infected mothers into uninfected foster mothers to disentangle whether this mechanism was due to changes at the fetal-maternal interface or germline encoded. This led to abolishment of the protective ef-

fect in offspring, suggesting a crucial role for changes at the fetal-maternal interface. Indeed, phase-specific gene expression and schistosome-specific immune responses were found in placental and decidual tissue. Subsequent mating of IFN- γ -deficient initial T_H1 phase-infected mothers with wild-type fathers yielded susceptible offspring for allergic airway inflammation, confirming that maternal IFN- γ was crucial for inducing protection in the offspring (Fig 1).³

In patients with allergic diseases, type 2 responses are dominant, and early priming of those responses during allergen sensitization forms a clear risk factor for young children to have clinical symptoms. This risk is further increased when the mother already has allergies, asthma, or both, pointing to a strong maternal influence, which probably already starts *in utero*.² During pregnancy, interaction between maternal and fetal cells is possible at the fetal-maternal interface. For example, systemic release of maternal mediators can cross the placenta and subsequently affect the fetus and the fetal bone marrow. Furthermore, embryonic trophoblasts extending from the villous tree of the placenta encounter various types of maternal immune cells at the maternally derived decidua. These include dendritic cells, macrophages, and natural killer cells but also CD4 T cells, such as forkhead box P3-positive regulatory T cells, which will secrete local cytokines and interact with the embryonic trophoblasts.² Multiple mechanisms of immune tolerance can take place during these interactions, which remain to be further elucidated.⁴ One study that directly investigated the role of the cytokine milieu at the fetal-maternal interface in relation to allergies showed a significant correlation between IFN- γ production by decidual cells and cord blood mononuclear cells and found less IFN- γ in cord blood mononuclear cells from neonates of allergic mothers.⁵ Indeed, these reduced neonatal IFN- γ responses have been observed in additional studies, further specifying that maternal allergy influences the local cytokine milieu and thereby fetal immune development.² Interestingly, several epidemiologic studies have suggested that some of the microbial protective effects, such as a microbe-rich farm environment, gut commensals, or parasites, might also already act before birth. For example, a maternal diet composed of farm dairy products was protective in the farm studies and associated with enhanced neonatal IFN- γ and regulatory T-cell responses in farmers' children.⁶ A causal relationship between maternal exposure to farm microbes and protection against respiratory allergies in offspring was demonstrated in a mouse model with the farm bacterium *Acinetobacter lwoffii*.⁷ The asthma protective effect was linked to maternal Toll-like receptor (TLR) activation because knocking out multiple TLRs in the mothers abrogated the protective effect in offspring. Importantly, maternal exposure to *A lwoffii* induced epigenetic changes in T_H1/T_H2 cytokine genes of offspring, leading to an open conformation of the *Ifng* promoter, whereas the *Il4* promoter was closed.

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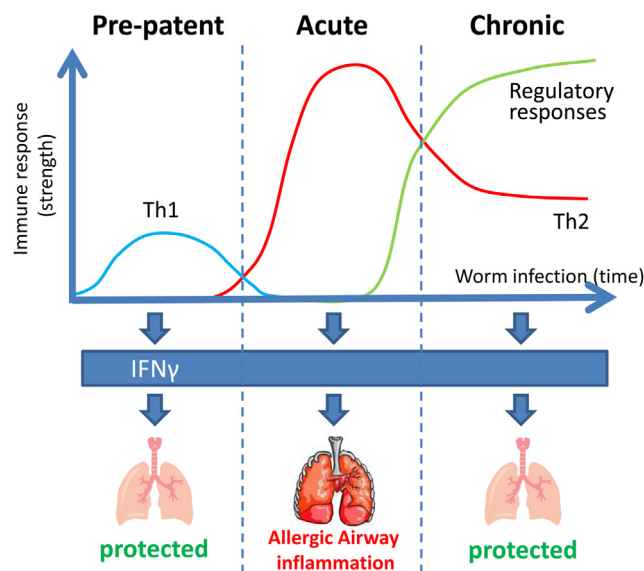


FIG 1. Immune responses provoked by maternal worm infections can protect offspring against the development of allergic airway inflammation after birth, depending on the infection phase. Offspring was protected when schistosome-infected mothers were mated in the T_H1 (prepatent larval infection) or regulatory (chronic infection) but not the T_H2 (acute infection) immune phase. Mating of IFN- γ -deficient, initial T_H1 phase-infected mothers with wild-type fathers yielded susceptible offspring for allergic airway inflammation, confirming that maternal IFN- γ was crucial for inducing protection in the offspring. This study provides an explanation for discrepancies in epidemiologic studies showing a variable degree of allergy or protection in children born to worm-infected mothers.

Epidemiologic studies in worm-endemic areas have also pointed to a role for maternal worm parasites and protection against allergic inflammation in offspring. For example, anti-helminth treatment of Ugandan mothers increased the prevalence of infantile eczema and wheeze compared with that seen in a placebo-controlled group.⁸ The study by Straubinger et al³ now provides a causal link and experimental explanation for the protective effect of maternal worm infections. Helminths are master regulators of the immune system to safeguard their own survival in the host. Helminths not only induce strong type 2 responses, which are presumably important for tissue repair, but also hyperactivate various host regulatory mechanisms.⁹ Mouse models have demonstrated that during infection with *Schistosoma mansoni*, clear stages of different immune responses can be defined. Prepatent infection by *S. mansoni* larvae is linked to a weak T_H1 response. The initiation of egg laying (acute infection) is accompanied by a very strong induction of type 2 responses, whereas during chronic infections, increased regulatory cell counts are found and type 2 responses are reduced.⁹ In particular, during the chronic but not the acute stage of infection, protection against allergic airway inflammation was demonstrated, which was at least in part explained by enhanced regulatory responses. Although protection against allergic responses was not studied during the prepatent infection (associated with weak T_H1 responses), infection with male larvae only, yielding infection without egg-laying worm pairs, also resulted in abolishment of allergic responses in different allergy models. These studies provide a clear link between the type of worm-induced immune responses and protection against respiratory allergies.¹⁰ The

study by Straubinger et al³ confirms that different phases of schistosome infection influence prenatal and early postnatal immune system development, which might lead to protection against allergic airway inflammation. This study not only establishes a clear causal relationship between maternal schistosome infections and protection against respiratory allergies in offspring but also provides an explanation for the contrasting data from cross-sectional or treatment studies in populations with helminth infections and the prevalence of allergic diseases.¹ Essentially, the authors demonstrate that depending on the phase of infection, maternal immune responses, and thereby those of the fetus, can be differentially affected. This might shape the child's susceptibility to have allergies. As such, the findings of this study underline the importance of *in utero* programming by helminth infection as a novel concept and explanation within the expanding hygiene hypothesis.

These findings are exciting and might provide new approaches to prevent or reduce allergic diseases in children at risk. On the basis of microarray and pathway analysis in placental and decidual tissues of protective mothers, several pathways and molecules were increased during protective stages; however, it is yet unclear whether any of these are truly involved or relevant for the protective effect in offspring.³ What is yet unexplored is whether similar or distinct cytokines are also involved during maternal chronic-phase infections. More mechanistic studies should focus on the role of these pathways in the different protective phases and also evaluate the contribution of epigenetic modifications. Particularly from a therapeutic standpoint, it would be very interesting to investigate whether application of single helminth-derived molecules to pregnant mice instead of applying full infections could replicate the protective effect.

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