Asthma protection with bacteria - science or fiction?

Harald Renz

What is the role of bacterial exposure in asthma protection and prevention? This topic is receiving increasing attention, particularly based on epidemiological findings relating to the ‘hygiene hypothesis’. More than a decade ago the observation was made that infants living in a microbial-rich environment show a high degree of protection, particularly against respiratory allergies and allergic sensitisation. The model situation of the farming environment offers the opportunity to investigate the context of environmental exposures, the effect on immune responses and development of disease phenotypes. That microbes are indeed relevant in triggering the protective immune response was epidemiologically shown initially for exposure to lipopolysaccharide (LPS), a membrane component of Gram-negative bacteria. In that study, an inverse relationship was observed between the natural microbial load (endotoxin load in mattress dust) and the prevalence of asthma, allergic rhinitis and atopic sensitisation. Subsequently, several groups employed models of experimental asthma to study the mechanisms of protection in this regard. These studies provided important information for the context of microbial exposure and asthma protection. First, it was shown that timing of exposure is relevant. If LPS was delivered well before the first contact with the allergen, the immune system was able to mount a clear protective response. In contrast, when LPS was given either simultaneously or even after allergic sensitisation was established, protection was absent, or even in some cases an exacerbation of the inflammatory response was seen. The latter finding is also in line with many clinical observations indicating that acute infections of the upper respiratory tract represent an important trigger for asthma exacerbation. Secondly, dosing is relevant. This finding is not surprising, but further substantiates the epidemiological observations. Thirdly, the route of exposure is relevant. The most consistent findings were observed when the microbial compounds were delivered through the respiratory mucosal tissue.

The next important step forward was the question of whether only LPS would be able to mount such a protective response. Further studies along these lines clearly illustrated that not only Gram-negative but also Gram-positive bacteria were able to provide this protection and this effect is not even restricted to bacterial compounds, since recently it was observed that even the plant product arabinogalactan can induce this protective effect.

Concerning the mucosal aspects, the immune response is initiated by the recognition of microbial compounds by pattern recognition receptors (PRRs). The Toll-like receptor (TLR) family represents one important group of such PRRs which has received a lot of attention recently. TLRs are expressed on a variety of cells, but particularly on airway epithelium, antigen-presenting cells and even cellular subsets of the adaptive immune response in the lung and other organs. It is, therefore, an important question whether activation of TLRs in the airways and the lung would be able to trigger an immune response relevant to asthma protection. This has been tested in a variety of different models with quite consistent outcomes. Activation of TLR2 via synthetic lipopeptides, stimulation of TLR2/4 heterodimers by peptidoglycans, stimulation of TLR4 via LPS, direct activation of TLR3 with poly(I:C) and TLR7 by the compound R848, and activation of TLR9 by DNA extracted from Bordetella pertussis were all able to trigger the protective immune response. However, the underlying mechanisms show substantial differences. Although in most studies the protection was directly or indirectly linked to the stimulation of a T helper 1 (Th1) immune response, protection via activation of TLR3 and TLR7 was related to the production of interleukin 12 (IL-12) and IL-10. These data already indicate that there are most probably different immunological pathways associated with and leading to asthma protection. Clearly, the main pathway in this regard is the activation and stimulation of a Th2-counteracting Th1 immune response with high levels of interferon γ. However, alternative mechanisms via triggering of anti-inflammatory responses and activation of regulatory T cells must also be considered.

That TLRs are indeed important receptors associated with allergy and asthma protection was again delineated from epidemiological (sub)studies. It was shown that children from a farming environment have increased levels of TLR2, TLR4 and CD14 mRNA, and the exposure to an increased number of animal species in this environment is also associated with higher TLR expression levels.

In this context, the paper by Nembrini et al in Thorax (see page 755) adds important additional information. First, the investigators were able to demonstrate that Escherichia coli also delivers this protection. The investigators then went on to demonstrate that TLR4 activation (most probably via LPS) provides an important signal in this regard. This also shows the relevance of mucosal delivery and the interaction with PRRs. It is an important finding that the mechanism of protection is related to the recruitment of γδ-T cells and that neither the Th1 immune response nor regulatory T cells or dendritic cells, nor indeed tumour necrosis factor α was able to overcome the protection or to deliver protective signals. Therefore, this study further underscores that a variety of different mechanisms are able to impact phenotype development in the lung.

From all these observations, several important questions now remain outstanding. Is there any bacterial compound or bacterial strain which does not exhibit such a protective effect when delivered in an appropriate setting and with an appropriate protocol? How important are quantitative exposures over time and what is the duration of the exposure needed to mount a sustainable protective response? How safe is this mode of protection and can it be pharmaceutically industrialised to a level that can be offered as an ‘asthma vaccine’ to the general population, or to at least a subset with high risks? Answering these and other questions will finally prove the concept which was initiated by the hygiene hypothesis. This line of research has clearly now reached a level of translational sciences and must be tested now in clinical studies.

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Three important studies on acute exacerbations of chronic obstructive pulmonary disease (ECOPD) have increased circulating platelet—monocyte aggregates—a potential specific pathogenic mechanism of atherosclerosis. These aggregates further increase during exacerbations, suggesting a plausible biological mechanism to explain the increased cardiovascular risk seen in ECOPD. Taken together, these studies confirm the view that ECOPD episodes requiring hospitalisation must be considered very severe events in the natural course of the disease because they are associated with such important outcomes as increased risk of mortality, reduced health status, impaired lung function, muscle weakness, and cardiovascular complications. The studies also suggest that the increased risk of death is often due to acute cardiovascular involvement, and they highlight the limitations of the current definition of ECOPD and the need to move towards a more comprehensive definition, diagnostic approach and treatment.

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