Regulation of inflammatory responses by the commensal microbiota

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ABSTRACT
It is well established that dysregulation of the interactions between the immune system and commensal bacteria is one factor that underpins the development and chronicity of a number of inflammatory diseases. Certain phyla of bacteria within the microbiota have been associated with ‘health’, but the mechanisms by which the presence of these bacteria supports a healthy environment are still being unravelled. Recent evidence indicates that one such mechanism involves the anti-inflammatory properties of fermentation products of fibre, short-chain fatty acids and their signalling through the G-protein coupled receptor GPR43. Recent findings also indicate that, even in health, bacterial communities harbour in the airways, indicating that direct exposure to bacterial products at this site may provide a further explanation for how commensal bacteria can regulate chronic airway inflammation.

A KEY ROLE FOR SHORT-CHAIN FATTY ACIDS IN THE REGULATION OF INFLAMMATORY DISEASES
In recent years it has become clear that changes in the make-up and diversity of commensal bacterial species are associated with chronic diseases ranging from inflammatory bowel disease (IBD) to obesity. Such observations have led to the hypothesis of a mutualistic relationship between commensal bacteria and their mammalian hosts which, when perturbed, results in chronic inflammation. The mechanisms by which commensal bacteria support health and help control inflammation are undoubtedly multifaceted, but new evidence has shed light on one pathway which links diet, the microbiota and systemic inflammation.

Fermentation of dietary fibre by intestinal bacteria has long been known to yield short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate. These are largely produced within the colon and, when applied as enemas, they have shown efficacy as a treatment for IBD. In line with this, increased consumption of fibre is generally considered to be beneficial, particularly in the context of IBD. SCFAs bind to the G-protein coupled receptors 41 and 43 (GPR41, GPR43) which are expressed within the intestine, on adipocytes, in the mesenteric ganglion and on a range of immune cells. Using knockout mice, Maslowski and colleagues have recently shown that acetate signalling through GPR43 is a key regulator of inflammation. In their study they show that axenic mice (which are devoid of all bacteria and consequently SCFA) are highly susceptible to chemical-induced colitis, but that disease can be ameliorated by treatment with acetate. In line with these data, mice deficient in the receptor for acetate (GPR45) were more susceptible to colitis.

To date, most experimental studies investigating health-promoting abilities of commensal bacteria have focused on intestinal inflammation, as one might expect given the immediate proximity of commensal bacteria, dietary factors and the intestinal lamina propria. Importantly, the work of Maslowski et al extended these findings to address whether acetate also influenced GPR43-expressing immune cells present in the periphery. They used a model of arthritis in which autoantibodies against glucose-6-phosphate isomerase are injected into mice resulting in severe joint inflammation, and found that GPR43 knockout mice (unable to respond to SCFAs) or axenic mice (lacking SCFAs) both exhibited exaggerated inflammation. Again, treatment of axenic mice with acetate in the drinking water was able to reverse disease. Notably, the GPR43 knockout mice mounted an exaggerated response in a mouse model of allergic airway inflammation and, supporting this, a separate publication has shown that axenic mice also develop exaggerated Th2-driven allergic airway inflammation. In the latter publication the exaggerated Th2 response in the absence of a microbiota was associated with dysregulated activation states of lung dendritic and macrophage populations; however, the underlying mechanisms and possible role of SCFAs have yet to be explored. Although the exact mechanisms by which SCFAs regulate inflammation remain to be elucidated, treatment of human neutrophils with acetate decreased the expression of proinflammatory receptors such as CXCR2 and C5aR while GPR43-deficient neutrophils exhibited increased production of proinflammatory factors such as reactive oxygen species.

The work by Maslowski and colleagues has brought to the fore a key mechanism linking diet, microbiota and inflammation. In addition to promoting novel strategies for future therapeutics, it highlights how the intestinal microbiota can influence inflammation at peripheral sites including the lung (figure 1). The responsiveness of immune cells to SCFAs via GPR43 is clear, but it is also worthwhile noting that SCFAs such as acetate are energy sources for bacteria themselves. Thus, treatment with acetate—in addition to triggering responses in immune cells directly—might influence the balance of bacterial species in the intestine,
promoting outgrowth of species that confer a protective advantage. Moreover, SCFAs have also been linked with regulating sympathetic nervous system activity and thus their activity might have implications for stress responses and possibly lung function in addition to inflammation.

**LUNG MICROBIOTA: AN EMERGING BUT CONTROVERSIAL FIELD**

Although it is agreed that the airways are repetitively exposed to the normal bacterial flora of the pharynx, it has classically been believed that healthy airways are sterile. Evidence emerging from the use of molecular techniques now indicates that the airways themselves do harbour a bacterial microbiota and that the make-up of this microbial community changes depending upon the health status of the individual. A ‘healthy’ lung, for example, has been associated with bacteria of the Bacteroidetes phylum while Proteobacteria were over-represented in the lungs of individuals with asthma or chronic obstructive pulmonary disease. Currently the field remains divided as to the significance of these early reports of a pulmonary microbiota; however, it is likely that either direct exposure to bacteria or colonisation with distinct bacterial communities could protect the lung from inflammation itself might deter or, on the other hand, perpetuate disease. An alternative perspective is that inflammation itself might determine the diversity of the microbiota; in this case, characterising the microbiota might prove to be a valuable biomarker for resolution of inflammation or infections.

The bacterial load in the airways has been proposed to be in the order of 2000 bacterial genomes per cm² of surface area. Interestingly, this is a similar range to that found in the upper two-thirds of the intestinal tract. Assuming that further evidence supports the presence of a lung-resident microbiota, it will be critical to understand the function and mechanisms through which this microbiota influences inflammation in the lung. Indeed, the presence of a local microbiota may present an alternative explanation for how commensal bacteria can regulate allergic responses in the airways (figure 1). Plausible mechanisms could involve direct recognition of bacterial components (eg, lipopolysaccharide, peptidoglycan) following exposure to local bacterial communities and consequent modulation of immune cells expressing innate receptors for these products (pattern recognition receptors), as already noted for the intestine.

**Summary**

Over recent decades there has been a clear increase in the prevalence of certain inflammatory diseases including asthma and autoimmunity. Over a similar period, changes in diet and urbanisation have occurred which directly influence the constituents, diversity and energy sources of the microbiota. Changes in the microbiota are likely to partially underlie the increased development of diseases, and may additionally be considered as biomarkers that alert clinicians to underlying environmental or genetic predispositions to disease. As links between microbiologists, immunologists and clinicians strengthen, the potential for harnessing the mechanisms currently being discovered allow for design of rational lifestyle intervention strategies (eg, diet or prebiotics), novel therapeutics and predictive diagnostics.

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