LEADING ARTICLE

Microbes, immunoregulation, and the gut

G A W Rook, L R Brunet

Two distinct, but rapidly converging, areas of research (the hygiene hypothesis and the study of probiotic/prebiotic effects) have emphasised the need to understand, and ultimately to manipulate, our physiological interactions with commensal flora, and with other transient but harmless organisms from the environment that affect immunoregulatory circuits. The story began with allergic disorders but now inflammatory bowel disease is increasingly involved.

EARLY FORMULATIONS OF THE HYGIENE HYPOTHESIS

The hygiene hypothesis was first proposed in the late 1980s to explain the rise in allergic conditions (reviewed by Rook and colleagues1). The incidence of these disorders in the USA and Europe increased from the late 19th century, and appears to have doubled in some decades, particularly during the 1960s and 1970s. Epidemiological correlations with the modern way of life prompted the assumption that modern hygiene was reducing contact with pathogens that prime T helper 1 (Th1) responses. At that time it was believed that this would result in a compensatory increase in T helper 2 (Th2) activity that characterises allergic disorders. This concept, requiring Th1 inducing infections to control Th2 mediated allergic conditions, arose because of the remarkable compartmentalisation of medical knowledge. Readers of this journal, aware of the simultaneous increase in several Th1 mediated disorders such as Crohn’s disease, type 1 diabetes, and multiple sclerosis, will be sceptical. Indeed, the incidences of several Th1 mediated disorders such as Crohn’s disease, type 1 diabetes, and multiple sclerosis, will be sceptical. Indeed, the incidences of type 1 diabetes, and multiple sclerosis, appear to have exaggerated responses to triggering antigens in animal models.8

IMMUNOREGULATORY DISORDERS

The unifying hypothesis that can explain the simultaneous increase in autoimmunity and inflammatory bowel disease (IBD) (Th1 mediated) and allergies (Th2 mediated) is that modern living conditions can lead to defective maturation of regulatory T cells (Treg) and regulatory antigen presenting cells (APCreg). Therefore, rather than Th1/Th2 balance, the crucial factor is likely to be the effector T cells (Teffector)/Treg balance. In the absence of optimal levels of immunoregulation, the individual may develop a Th1 or a Th2 mediated inflammatory disorder, depending on his/her own particular

TREG DEFECTS IN CHRONIC INFLAMMATORY DISORDERS

If this reinterpretation of the hygiene hypothesis is correct, the increase in human immunoregulatory disorders is at least partly attributable to defective Treg activity. Evidence to confirm this hypothesis has come from studies of allergic disorders,3 multiple sclerosis,4 autoimmune polyglandular syndromes,5 and cow’s milk intolerance.6 It is likely to be true for IBD too, though more difficult to prove. The intestine is always in a state of controlled inflammation, and T cells of the regulatory phenotype are abundant in the guts of patients with IBD.7 Nevertheless, data from animal models of IBD suggest that the problem is likely to be an immunoregulatory one,8 and there is evidence that there is defective induction of oral tolerance in IBD patients.9 Moreover, they have exaggerated responses to bowel flora10 which also appear to be the disease triggering antigens in animal models.9

MICROBIAL EXPOSURE AND IMMUNOREGULATION

How does this Treg orientated concept relate to the original hygiene hypothesis, and why would microbial exposure affect maturation of regulatory pathways? To answer these questions we must first establish what we mean by hygiene.

One interpretation of the word “hygiene” in this context, mostly promoted by the media, assumes that the critical factor is domestic hygiene (bathing, soaps, detergents, antibacterial kitchen cutting boards, etc). However, a comprehensive recent report has shown that the development of these practices in the home does not correlate with the observed changes in the occurrence of immunoregulatory disorders.11

Abbreviations: IBD, inflammatory bowel disease; Th1, Th2; T helper 1, 2; Treg, regulatory T cell; APC, APCreg, antigen presenting cell/regulatory antigen presenting cell; DC, dendritic cell; TLR, toll-like receptor; KO, gene knockout; IL, interleukin; TGF-β, transforming growth factor β


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A second view is that the critical change is the decreased frequency of infections due to pathogenic organisms. When the data available from the Centres for Disease Control and Prevention for the incidence of some infections are plotted against time, the graphs suggest that some of the decreases did occur during the critical period 1960–1985 when some chronic inflammatory disorders were doubling every decade. However, more detailed analysis of European data reveals that most of the changes in exposure to pathogens took place long before the crucial period. In addition, there is strong epidemiological evidence to suggest that certain pathogens, such as childhood viruses and respiratory infections, cause an increase rather than a decrease in the incidence of allergic disorders. Interestingly, despite the detrimental effect of infections, this study still identified protective effects of being sent to day care, keeping pets, and living on a farm. The latter has been a consistently robust observation, and the protective effect of exposing children to cowsheds is well documented. If childhood infections do not protect and home hygiene does not correlate, what might be the protective factors associated with pets, farms, and day care centres?

"Contact with “old friends” is greatly diminished in rich countries but increased on farms, in cowsheds, and through contact with pets"

The answer might lie in certain relatively harmless microorganisms (including helminths, saprophytic mycobacteria, and lactobacilli) that have been present throughout mammalian evolution. We have called this the “old friends” hypothesis. Contact with “old friends” is greatly diminished in rich countries but increased on farms, in cowsheds, and through contact with pets. A number of reports have provided evidence for this interpretation. Allergic disorders are less frequent in individuals with helminth infections, and atopic sensitisation increases after treatment of intestinal helminths. Similarly, there are less lactobacilli in the guts of children with allergies, and a preliminary clinical study suggests that high doses of lactobacilli may inhibit development of atopic eczema in genetically high risk children. Finally, the saprophytic mycobacterium M vaccae, originally isolated, as its name suggests, from a cow shed, potently drives maturation of Treg that will treat pre-existing allergy in isolated, as its name suggests, from a cow shed, potently.
provide continuous background bystander regulation. However, APCreg will also process and present epitopes from self, allergens, and gut contents, and so drive specific immunoregulation. These mechanisms can be silenced in the presence of appropriate danger signals. In the absence of "old friends", both specific and bystander regulation will be defective. IL-10, interleukin 10; TGF-β, transforming growth factor β.

not only against colitis in IL-10 KO mice but also against collagen arthritis, a mainly Th1 mediated model of autoimmunity.36

"The gut may be the major site for Treg induction even when the probiotic is given subcutaneously."

The fact that probiotics work in models of colitis and arthritis, whether given orally or subcutaneously, is evidence that the important function in this context is not a gut specific one. Once generated, Tregs can travel to other tissues. It is interesting however that the gut may be the major site for Treg induction even when the probiotic is given subcutaneously. Antigens containing bacterial polysaccharides37 38 or whole organisms,39 even when given parenterally, may evoke a pattern of response, detected as IgA secreting cells in peripheral blood, that mimics the response to mucosal immunisation. It seems likely that this is due to cross reactivity with antigens already experienced by the gut associated lymphoid tissue. Moreover, induction of IgA in the gut is heavily dependent on TGF-β which is also closely involved in the maturation of Treg.40

CONCLUSIONS
The "old friends" hypothesis has evolved into a concept similar to that which lies behind attempts to modulate disease by altering the bowel flora. The strong parallels point to the following conclusions. Firstly, we suggest that the strains (whether "old friends" or probiotics; whether bacteria or helminths) used for clinical trials in disorders of immunoregulation (allergies, IBD, autoimmunity) ought to be those which can be shown to drive Treg. Secondly, the particular organism used might need to be tailored to the individual patient. The "old friends" mechanism implies that, in rich countries, we live in an environment that does not only against colitis in IL-10 KO mice but also against collagen arthritis, a mainly Th1 mediated model of autoimmunity.36

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Ultimately, the answer must lie in more rigorous proof that diminishing exposure to these Treg inducing organisms is a factor in the increase in immunoregulatory disorders. If confirmed, we will be able to devise subtle changes to our lifestyles that reconstitute this exposure by the oral route.

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REFERENCES
EDITOR’S QUIZ: GI SNAPSHOT

A rare case of hypalbuminaemic oedema

Clinical presentation
A 35 year old male patient presented massive anasarca, eyelid oedema, and dyspnoea. He also complained of mild diarrhoea and pain in the right calf. Further examination revealed the presence of ascites, bilateral pleural, as well as pericardial effusion. Serum electrophoresis revealed severe hypo- and hypalbuminaemia with dramatically reduced albumin and an increased alpha-2 peak. Tenderness of the right calf was shown to be caused by multiple arterial embolisms on angiography. Due to pronounced acceleration of the erythrocyte sedimentation rate, increased acute phase reactants and presence of ascites, bilateral pleural, as well as pericardial effusion. Serum electrophoresis revealed severe hypo- and hypalbuminaemia.

Question
What is the diagnosis? How should the condition be treated? See page 335 for answer

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