Clinical and Experimental Allergy

Old Friends for breakfast

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Graham Rook and Laura Rosa Brunet speculate that stimulation of innate immunity with components of saprophytic mycobacteria, lactobacilli and certain helminths (the "Old Friends") will form the basis of treatment in the future by driving both specific and bystander immunoregulation.

We expect patterns of disease to change in parallel with economic development, but the existence of simultaneous increases in diverse chronic inflammatory disorders came as a surprise. Developed countries have more allergic disorders, more autoimmune disease (for example Type 1 diabetes and multiple sclerosis) [1] and more inflammatory bowel disease (IBD; ulcerative colitis and Crohn's disease) [2]. Influenced by the increasing incidence of Th2-mediated allergies, but largely unaware of the simultaneous increases in the Th1-mediated disorders, workers in the field of allergy developed the concept that became known as the Hygiene Hypothesis. This hypothesis, though essentially correct, rapidly spawned three untenable interpretations which delayed its acceptance. However these have now been shown to be unlikely, and a new interpretation, the "Old Friends" mechanism, is looking much more promising.

First it was suggested that diminished exposure to microorganisms in rich developed countries fails to drive Th1 cells, with a consequent over-production of Th2 cells. According to this interpretation the critical issue was Th1/Th2 balance. This notion ignored both the simultaneous increases in Th1-mediated chronic inflammatory disorders and the presence of IFN-γ both in asthma and in atopic dermatitis. It is now clear that the critical balance is not Th1/Th2 but rather $T_{reg}/T_{effector}$. All three groups of chronic inflammatory disorder, whether mediated by Th1 or Th2 effectors, are characterised by immune responses to forbidden targets. It is the role of regulatory T cells to stop such unwanted responses, and the imbalance between T_{reg} and $T_{effector}$ in allergic individuals has now been definitively documented [3].

Secondly, it was suggested that we must suffer true infections such as tuberculosis or the childhood virus infections, in order to be protected from chronic inflammatory disorders. This view seems to have arisen spontaneously, with little epidemiological support, and does not make evolutionary sense. The childhood virus infections are recent additions to mankind's environment. Several excellent studies have indicated that these infections do not protect from allergies [4].

Thirdly there was the view, largely created by the media, that home hygiene itself was in some way to blame. Newspaper articles implied that we should avoid standard hygienic practices such as bactericidal compounds in our kitchen cutting boards, and interviewers tried to make us advise listeners to let their children live in squalor. Again, a detailed recent report has rejected this simplistic concept [5].

So what is left? Should the Hygiene Hypothesis be rejected? We suggest that the answer lies in the "Old Friends" mechanism. Certain harmless microorganisms that are part of our evolutionary history, are recognised as "Old Friends" by the innate immune system, so rather than priming aggressive immune responses they prime immunoregulation [6], mediated in part by release of IL-10 and TGF-β. The "Old Friends" do this by causing an unusual pattern of maturation of dendritic cells (DC) [7] such that these retain the ability to drive regulatory T cells (T_{reg}). This in turn leads to two mechanisms that help to control inappropriate inflammation. First, continuing throughput of the "Old Friends" causes continuous background activation of the DC_{reg} and of T_{reg} specific for the Old Friends themselves. The result is a constant background of bystander suppression. Secondly, the presence of DC_{reg} that inevitably sample self, gut contents and allergens, leads to the induction of T_{reg} specific for the three groups of chronic inflammatory disorder. These mechanisms are of course aborted when there are legitimate "danger" signals. For example, Treg function can be turned off by appropriate "danger signals" *in vitro* [8]. Viewed in the light of the Old Friends mechanism it becomes reasonable that polymorphisms of NOD2 (an intracellular receptor for bacterial peptidoglycan) should be linked to increased susceptibility to both Crohn's disease *and* asthma [9]. It is likely that the particular immunoregulatory disorder that develops in an individual deprived of "Old Friends" will depend on other aspects of his genetic background and immunological history.

Three groups of organism (lactobacilli, saprophytic environmental mycobacteria, and some helminths) have been identified as "Old Friends", though there will be many others [6]. Of these, the saprophytic mycobacterium, *M. vaccae*, has received the most detailed immunological study, and it appears to induce in mice exactly the type of T_{reg} (Tr1) that is deficient in allergic humans [3, 10]. The optimum route of exposure to the Old Friends is via the gut, a critical site for induction of DC_{reg} and T_{reg}. Each of these organisms is active in experimental models of at least 2, sometimes all 3 of the groups of inflammatory disorder discussed here, as anticipated if there is a shared underlying mechanism. Similarly each of them has been subjected to encouraging clinical trials in allergic disorders or IBD (discussed in [6]).

So where is this leading? It is probable that a complex pattern of signals is needed to make the innate immune system drive immunoregulation. It needs to be a secret code so that pathogens cannot too easily acquire it. So it might be difficult to replace the Old Friends with single molecules. Moreover, the particular Old Friend needed to restore immunoregulation might depend on the genetic polymorphisms of the individual patient. The pharmacogenetics could be complex to solve and expensive to apply to the individual.

So there are two extreme solutions; the futuristic one and the practical common sense one.

The futuristic solution requires that we identify all the critical molecules and *patterns* of molecules within the Old Friends. Than we must create a wonderful gismo that

documents the patient's genetic polymorphisms, and prescribes a capsule containing a cocktail of agonists for receptors within the innate immune system that will optimally trigger immunoregulation in that individual. Perhaps this will be possible, but as pharmaceutical regulatory requirements get more complex and expensive, the prospect of isolating, synthesising and manufacturing a panel of novel agonists, and taking each of them, and the mixtures, through the regulatory process is a nightmare. Anyway, why recreate organisms that already exist?

The more practical solution is contrary to the thought patterns of the pharmaceutical industry in 2004, but more likely to be achieved, and more likely to work. If the Old Friends used individually as oral treatments are clinically effective, then the objective is achieved. If they are not sufficiently potent, or work only in discrete subsets of patients, then capsules that incorporate multiple Old Friends could be developed. Taken daily, these would evoke both bystander and specific mechanisms of immunoregulation. Taken intermittently they would preferentially evoke immunoregulation by specific T_{reg}. The pharmaceutical industry may not be ready for common-sense solutions, but we suspect that the public would welcome this approach.

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