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Invited Commentary

Nutrition, immunity and human health

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It is well established that a balanced diet, including the recommended intakes of macronutrients and micronutrients, is essential for maintaining human health. In PubMed, over 76 000 publications related to nutrition and health can be found (when using these two search terms). A well-functioning immune system is also vital for human health, which has been revealed by a similar PubMed analysis using immunity and health as search terms yielding over 24 000 publications. For the immune system to function optimally, similar to the rest of the body, an adequate nutritional status is required. This particular field of nutritional science, linking nutrition and immunity, is, however, relatively new: 50 years ago, in 1972, only sixteen papers were published, but the number has increased to eighty-three in 1992 and 264 in 2012.

The effect of nutritional status on the functionality of the immune system is evident from deficiency states. Protein and energy malnutrition results in secondary immunodeficiency, and vitamin A and Zn deficiencies lead to characteristic infectious complications. The association between other nutrient deficiencies and susceptibility to infectious diseases is becoming more apparent. For example, in a recent study, in patients admitted to a hospital with community-acquired pneumonia, vitamin D deficiency on admission was associated with an increased risk of intensive care admission and 30 d mortality[1]. The administration of vitamin D has been shown to down-regulate sixty-six genes and up-regulate 291 genes, affecting the biological function of more than 160 pathways linked to autoimmune diseases, cancer and CVD[2]. Vitamin D is thus an example of a nutritional compound with a potential immunomodulatory role, although its exact mode of action still needs to be established.

The primary function of the immune system is protection against infectious diseases. The human immune system is extremely complex and because of the enormous variations in micro-organisms (and macro-organisms for that matter) encountered, the immune system cannot rely on a single defence mechanism, but needs different strategies for different classes of micro-organisms. The most straightforward distinction is between humoral immunity, with specific antibodies as effector molecules acting against extracellular bacteria, and cellular immunity for defence against viral infections. Cells and molecules of the innate immune system further con-tribute to the maintenance of internal homeostasis.

Testing the functionality of the immune system is at least an order of magnitude more complicated than the assessment of, for example, heart or lung functions. An estimated number of 1100 genes are directly or indirectly involved in the regulation of the immune system. Of these genes, the human leucocyte antigen (HLA class I (HLA-A, -B and -C) and HLA class II (HLA-DP, -DQ and -DR)) genes are the most polymorphic. The immunocompetence of an individual is thus determined by the particular combination of HLA genes. The second level of individual variation lies in the diversity and composition of the repertoire of antigen-specific T and B lymphocytes. Third and finally, the ability to respond to an infection will be determined by previous (sub)clinical exposure to identical or related micro-organisms, as well as vaccination status. For these reasons, a single biomarker of the immune system that could be used in every person does not exist.

Albers *et al.*[3] analysed seventy-five markers for their suitability to function as a screen for the ability of nutrition to modulate the immune system in the context of health. They selected the most appropriate markers of the immune system as well as a set of criteria for the interpretation of the observed effects. This paper is a logical extension of earlier work in this field[4] and a very useful complement to guidelines from regulatory authorities[5].

The ultimate test for functionality (or improvement of functionality) of the immune system is the survival of an infectious disease. Deliberate exposure to a pathogen in the past has been used to test the efficacy of vaccines. These practices are now being considered unethical. Yet, the ultimate test of a vaccine is to provide protection against natural exposure to the corresponding pathogen, and this approach is still in use. Deliberate exposure to a low dose of pathogen or to an attenuated strain is a way to study the activities of the immune system required for protection. Thus, intranasal application of live pneumococci to healthy adult volunteers[6] and challenge with the virulent ETEC strain H10407[7] are models that can be used to study the *in vivo* response of the immune system to a challenge with live pathogens. While valuable in an experimental setting, these models are too impractical and costly to be used for the assessment of the functionality of the immune system in (nutritional) intervention studies. The paper of Albers *et al.*[3] advocates the use of the assessment of the immune response to vaccination as the next best thing to determine the functionality of the immune system. In particular for influenza[8,9] and pneumococcal vaccinations[10,11], the laboratory techniques for the measurement of the antibody response, as well as response criteria in the general population, have been established and are ready to be incorporated in future studies.

Maintaining normal functioning of the immune system involves not only protection against infectious diseases, but also risk reduction in the development of inflammatory, allergic or autoimmune diseases. The latter aspect, i.e. risk reduction in the development of allergic and autoimmune diseases in the general population certainly, is a challenge for the future.

Randomised controlled trials (RCT) have, over the last 50 years, evolved from investigations of therapeutic (be they pharmaceutical or nutritional) concepts into assessments of the efficacy of drugs. Because of the amount of money involved, most RCT are conducted by the pharmaceutical company producing the drug in question. In order to get a study population as clear as possible, age restrictions (usually 18–65 years), as well as long lists of co-morbidities, as exclusion criteria are being applied. In the end, the study population is no longer likely to be representative of the general population.

Then, how do we study the effect of nutrition on the functionality of the immune system? The subgroups that would benefit most from the improvement of the immune status are the young, the elderly and those with co-morbidities. This can be exemplified by examining the target groups for seasonal influ-enza vaccination in Europe[12] and in the USA: for example, children aged between 6 months and 4 years, individuals aged above 50 years and children and adults with a chronic pulmonary (including asthma), cardiovascular, renal, hepatic, neurological, haematological or metabolic disorder (including diabetes mellitus). Seasonal vaccination is also recommended for individuals on immunosuppressive medication and those with a BMI >40 kg/m^2, as well as for some other, smaller specific subgroups (http://www.cdc.gov/flu/professionals/acip/specificpopulations.htm, accessed 9 May 2013). All these subgroups at risk would probably be excluded from a regular RCT. However, these subgroups are part of the general population. In fact, they represent that part of the general population with the most vulnerable immune system.

The paper of Albers *et al.*[3] provides guidelines on models and outcome parameters on which basic and clinical scientists, those from an industry background with an interest in applying for immune health claims, as well as regulatory authorities could agree upon to be used in future studies. The next, and maybe ultimate, challenge will be to decide on the most appropriate design of these studies.

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