Feeding the immune system

Philip C. Calder

Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Tremona Road, Southampton SO16 6YD, UK and
National Institute for Health Research, Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Tremona Road, Southampton SO16 6YD, UK

A well-functioning immune system is key to providing good defence against pathogenic organisms and to providing tolerance to non-threatening organisms, to food components and to self. The immune system works by providing an exclusion barrier, by identifying and eliminating pathogens and by identifying and tolerating non-threatening sources of antigens, and by maintaining a memory of immunological encounters. The immune system is complex involving many different cell types distributed throughout the body and many different chemical mediators some of which are involved directly in defence while others have a regulatory role. Babies are born with an immature immune system that fully develops in the first few years of life. Immune competence can decline with ageing. The sub-optimal immune competence that occurs early and late in life increases susceptibility to infection. Undernutrition decreases immune defences, making an individual more susceptible to infection. However, the immune response to an infection can itself impair nutritional status and alter body composition. Practically all forms of immunity are affected by protein–energy malnutrition, but non-specific defences and cell-mediated immunity are most severely affected. Micronutrient deficiencies impair immune function. Here, vitamins A, D and E, and Zn, Fe and Se are discussed. The gut-associated lymphoid tissue is especially important in health and well-being because of its close proximity to a large and diverse population of organisms in the gastrointestinal tract and its exposure to food constituents. Certain probiotic bacteria which modify the gut microbiota enhance immune function in laboratory animals and may do so in human subjects.

Abbreviations: Th, T-helper.

Corresponding author: Professor P. C. Calder, fax +44 2380 795255, email pcc@soton.ac.uk
locations, the cells are organised into discrete lymphoid organs, classified as primary lymphoid organs where immune cells arise and mature (bone marrow and thymus) and secondary lymphoid organs (lymph nodes, spleen and gut-associated lymphoid tissue) where mature immune cells interact and respond to antigens. The immune system has two general functional divisions: the innate (also called natural) immune system and the acquired (also termed specific or adaptive) immune system. A well functioning immune system is key to providing good defence against pathogenic organisms and to providing tolerance to non-threatening organisms, to food components and to self. The immune system works by providing an exclusion barrier, by identifying and eliminating pathogens and by identifying and tolerating non-threatening sources of antigens and by maintaining a memory of immunological encounters. Full details of the components of the immune system, their roles and interactions and the chemical mediators involved can be found in any good quality immunology textbook.\(^{(8,9)}\)

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Fig. 1. (Colour online) Structure and organisation of the gut-associated lymphoid tissue. Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Immunol 3, 331–341, copyright 2003. Antigen might enter through the microfold (M) cells (a), and after transfer to local dendritic cells (DC), might then be presented directly to T cells in the Peyer’s patch (b). Alternatively, antigen or antigen-loaded DC from the Peyer’s patch might gain access to draining lymph (c), with subsequent T-cell recognition in the mesenteric lymph nodes (d). A similar process of antigen or antigen-presenting cell dissemination to mesenteric lymph nodes might occur if antigen enters through the epithelium covering the lamina propria (e). In this case, there is also the possibility that enterocytes might act as local antigen presenting cells (f). In all cases, the antigen-responsive CD4\(^+\) T cells leave the mesenteric lymph nodes in the efferent lymph (g) and after entering the bloodstream through the thoracic duct, exit into the mucosa through vessels in the lamina propria. T cells which have recognised antigen first in the mesenteric lymph node might also disseminate from the bloodstream throughout the peripheral immune system. Antigen might also gain direct access to the bloodstream from the gut (h) and interact with T cells in peripheral lymphoid tissues (i). SED, subepithelial dome; TDA, thymus-dependent area.
The gut-associated immune system

The immune system of the gut, often referred to as the gut-associated lymphoid tissue is extensive and includes the physical barrier of the intestinal wall and its mucosal coating as well as components of the innate and adaptive immune systems. The physical barrier includes acid in the stomach, mucus and tightly connected epithelial cells, which all act to prevent the entry of pathogens. Within the intestinal wall, cells of the immune system are organised into specialised structures, termed Peyer’s patches which are located directly beneath the epithelium in a region called the lamina propria (Fig. 1). This also contains M cells which sample small particles derived from food or from micro-organisms in the gut lumen. The gut-associated immune system not only plays a vital role in providing host defence against pathogens within the gastrointestinal lumen but also in generating tolerogenic responses to harmless micro-organisms and to food components.

The immune system changes over the life course

Newborn babies have an immature immune system. After birth, immunological competence is gained partly as a result of maturation factors present in breast milk and partly as a result of exposure to antigens (from food and from environmental micro-organisms, the latter starting during the birth process itself). Some of the early encounters with antigens play an important role in ensuring tolerance and a breakdown in this system of ‘immune education’ can lead to disease. At the other end of the lifecycle, older people experience a progressive dysregulation of the immune system, leading to decreased acquired immunity and a greater susceptibility to infection. This age-related decline in acquired immunity is termed immunosenescence. An additional consequence of immunosenescence is an impaired response to vaccination. Innate immunity appears to be less affected by ageing than acquired immunity.

Why should nutrition affect immune function?

The immune system is functioning at all times, but specific immunity becomes increasingly active in the presence of pathogens. This results in a significant increase in the demand of the immune system for substrates and nutrients to provide a ready source of energy. This demand can be met from exogenous sources (i.e. from the diet) and/or from endogenous pools. Cells of the immune system are able to utilise glucose, amino acids and fatty acids as fuels for energy generation, which involves electron carriers and a range of coenzymes, which are usually derivatives of vitamins. The final component of the pathway for energy generation (the mitochondrial electron transfer chain) includes electron carriers that have Fe or Cu at their active site. Activation of the immune response induces the production of proteins (including Ig, cytokines, cytokine receptors, adhesion molecules and acute-phase proteins) and lipid-derived mediators (including prostaglandins and leucotrienes). To respond optimally to an immune challenge there must be appropriate enzymic machinery in place for RNA and protein synthesis and their regulation and ample substrate available (including nucleotides for RNA synthesis, the correct mix of amino acids for protein synthesis and PUFA for eicosanoid synthesis). An important component of the immune response is oxidative burst, during which superoxide anion radicals are produced from oxygen in a reaction linked to the oxidation of glucose. The reactive oxygen species produced can be damaging to host tissues and thus antioxidant protective mechanisms are necessary. Among these are the classic antioxidant vitamins (vitamins E and C), glutathione, the antioxidant enzymes superoxide dismutase and catalase, and the glutathione recycling enzyme glutathione peroxidase. The antioxidant enzymes all have metal ions at their active site (Mn, Cu, Zn, Fe and Se). Cellular proliferation is a key component of the immune response, providing amplification and memory: before division there must be replication of DNA and then of all cellular components (proteins, membranes, intracellular organelles, etc.). In addition to energy, this clearly needs a supply of nucleotides (for DNA and RNA synthesis), amino acids (for protein synthesis), fatty acids, bases and phosphate (for phospholipid synthesis) and other lipids (e.g. cholesterol) and cellular components. Some of the cellular building blocks cannot be synthesised in mammalian cells and must come from the diet (e.g. essential fatty acids, essential amino acids and minerals). Amino acids (e.g. arginine) are precursors for synthesis of polyamines, which play roles in regulation of DNA replication and cell division. Various micronutrients (e.g. Fe, folic, Zn and Mg) are also involved in nucleotide and nucleic acid synthesis. Some nutrients, such as vitamins A and D, and their metabolites are direct regulators of gene expression in immune cells and play a key role in the maturation, differentiation and responsiveness of immune cells. Thus, the roles for nutrients in immune function are many and varied and it is easy to appreciate that an adequate and balanced supply of these is essential if an appropriate immune response is to be mounted. In essence, good nutrition creates an environment in which the immune system is able to respond appropriately to a challenge, irrespective of the nature of the challenge. The response may be an active destructive one, or a more passive tolerogenic one.

Protein–energy malnutrition and immune function

It is well known that undernutrition impairs the immune system, suppressing immune functions that are required for protection against pathogens and increasing susceptibility to infection. Undernutrition leading to impairment of immune function can be due to insufficient intake of energy and macronutrients and/or due to deficiencies in specific micronutrients. These may occur in combination. There are a number of reviews of the effect of protein–energy malnutrition on aspects of immune function and on susceptibility to infection. Practically all forms of immunity are affected by protein–energy malnutrition but non-specific defences and cell-mediated immunity are more severely affected than humoral (antibody) responses. Barrier function can be impaired by...
protein–energy malnutrition (24,25) which may permit bacterial translocation into the circulation (24,26). Protein–energy malnutrition causes atrophy of primary and secondary lymphoid organs and there is a decline in the number of circulating lymphocytes, in proportion to the extent of malnutrition (27,28). The ability of T-lymphocytes to proliferate is decreased by protein–energy malnutrition as in the synthesis of cytokines central to cell-mediated immune response including IL-2 and interferon-γ (29,30), suggesting a decline in T-helper (Th1)-type responses. There is a lowered ratio of CD4⁺ : CD8⁺ cells in the circulation (31) and the activity of natural killer cells is diminished (32–35). Phagocytic capacity of monocytes and macrophages appears to be unaffected (36,37). The response to a controlled antigenic challenge is reduced by protein–energy malnutrition (38), reflecting the effects on individual cellular components. The numbers of B-cells in the circulation and serum Ig levels appear to be unaffected by malnutrition and may even be increased. The functional consequence of malnutrition-induced immune impairment was shown in a study in malnourished Bangladeshi children in which those with the fewest skin reactions to common bacterial antigens (i.e. the weakest cell-mediated immune response) had the greatest risk of developing diarrhoeal disease (39,40).

The influence of individual micronutrients on immune function

The effects of individual micronutrients on immune function have been identified from studies of deficiency in animals and human subjects and from controlled animal studies in which the nutrient under investigation is included at known levels in the diet. These studies provide good evidence that a number of nutrients are required for an efficient immune response and that deficiency in one or more of them will impair immune function and provide a window of opportunity for pathogens. It seems likely that multiple nutrient deficiencies might have a more significant impact on immune function, and therefore resistance to infection, than a single nutrient deficiency. This section will describe the importance of six selected micronutrients on immune function and susceptibility to infection. These micronutrients have been chosen because each is widely studied and known to be of great importance for immune function and because they are each the focus of much current research activity with significant new discoveries being made.

Vitamin A

There are a number of reviews of the role of vitamin A and its metabolites in the immune system and in host susceptibility to infection (5–7,41–45). Vitamin A deficiency impairs barrier function, alters immune responses and increases susceptibility to a range of infections (5–7,41–45). Vitamin A-deficient mice show breakdown of the gut barrier and impaired mucus secretion (due to loss of mucus-producing goblet cells), both of which would facilitate entry of pathogens (46). Many aspects of innate immunity, in addition to barrier function, are affected by vitamin A (5–7,41–45).

For example, vitamin A controls neutrophil maturation (47) and in vitamin A deficiency, blood neutrophil numbers are increased, although their phagocytic function is impaired (48) resulting in decreased ability to ingest and kill bacteria (49). Natural killer cell activity is diminished by vitamin A deficiency (50). The impact of vitamin A on acquired immunity is less clear, but there is some evidence that vitamin A deficiency alters the balance of Th1 and Th2 cells, decreasing Th2 response, without affecting or, in some studies enhancing, Th1 response (41–45,51). This would suggest that vitamin A will enhance Th1-cell mediated immunity. However, in contrast to this, studies in several experimental models show that vitamin A metabolite retinoic acid decreases Th1-type responses (cytokines, cytokine receptors and the Th1-favouring transcription factor T-bet), while enhancing Th2-type responses (cytokines and the Th2-favouring transcription factor GATA-3) (52–54). Vitamin A also appears to be important in differentiation of regulatory T-cells while suppressing Th17 differentiation (55,56), effects which have implications for control of adverse immune reactions. Retinoic acid seems to promote movement of T-cells to the gut-associated lymphoid tissue (57) and, interestingly, some gut-associated immune cells are able to synthesise retinoic acid (57,58). Vitamin A deficiency can impair response to vaccination, as discussed elsewhere (50). In support of this, vitamin A deficient Indonesian children provided with vitamin A showed a higher antibody response to tetanus vaccination than seen in vitamin A deficient children (59). Vitamin A deficiency is associated with increased morbidity and mortality in children, and appears to predispose to respiratory infections, diarrhoea and severe measles (5–7,41–45). Replenishment of vitamin A in deficient children improves recovery from infectious diseases and decreases mortality (5–7,41–45).

Vitamin D

There are a number of reviews of the role of vitamin D and its metabolites in the immune system, autoimmunity and host susceptibility to infection (60–65). In this paper, vitamin D refers to the active form of vitamin D (1,25-dihydroxy vitamin D₃). Many immune cells express the cytosolic vitamin D receptor and some can synthesise the active form of vitamin D from its precursor (66,67). These observations suggest that immune cells can both respond to and produce vitamin D indicating that it is likely to have immunoregulatory properties. Indeed, vitamin D can induce macrophages to synthesise anti-microbial peptides (67,68), directly affecting host defence. Individuals with low vitamin D status have been reported to have a higher risk of respiratory tract viral infections (69), while supplementation of Japanese school children with vitamin D for 4 months during winter decreased the risk of influenza by about 40% (70). These studies suggest that vitamin D acts to reduce susceptibility to infection, which may result from improved immune function. However, in contrast, there is a large body of literature showing that vitamin D and its analogues have immunosuppressive effects (71–73). It seems that under physiological conditions vitamin D probably aids immune responses, but that it may also play an active role in prevention of autoimmunity and that there may
even be a therapeutic role for vitamin D in some immune-mediated diseases. Vitamin D acts by binding to its receptor and regulating gene expression in target cells. Its effects include promotion of phagocytosis, superoxide synthesis and bacterial killing, but it is also reported to inhibit T-cell proliferation and production of Th1-type cytokines\(^{(74–84)}\) and of antibodies by B-cells\(^{(85)}\) highlighting the paradoxical nature of its effects. Effects on Th2-type responses are not clear\(^{(86–88)}\) and there may be an increase in numbers of regulatory T-cells\(^{(89,90)}\). Overall, the current evidence suggests that vitamin D is a regulator of immune function but that its effects will depend upon the immunological situation (e.g. health, infectious disease and autoimmune disease).

**Vitamin E**

Vitamin E is the major lipid-soluble antioxidant in the body and is required for protection of membrane lipids from peroxidation. Free radicals and lipid peroxidation are immunosuppressive and hence vitamin E should act to maintain or even to enhance the immune response. There are a number of reviews of the role of vitamin E in the immune system and host susceptibility to infection\(^{(91–94)}\). In laboratory animals, vitamin E deficiency decreases lymphocyte proliferation, natural killer cell activity, specific antibody production following vaccination and phagocytosis by neutrophils\(^{(91–94)}\). Vitamin E deficiency also increases susceptibility of animals to infectious pathogens\(^{(91)}\). Vitamin E supplementation of the diet of laboratory animals enhances antibody production, lymphocyte proliferation, Th1-type cytokine production, natural killer cell activity and macrophage phagocytosis\(^{(91–94)}\). There is a positive association between plasma vitamin E and immune components which can all be increased in numbers of regulatory T-cells\(^{(89,90)}\). Overall, the current evidence suggests that vitamin D is a regulator of immune function but that its effects will depend upon the immunological situation (e.g. health, infectious disease and autoimmune disease).

**Iron**

There are a number of reviews of the role of Fe in the immune system and host susceptibility to infection\(^{(115–122)}\). Fe deficiency induces thymus atrophy and has multiple effects on immune function in human subjects\(^{(115–118)}\). The effects are wide ranging and include impairment of respiratory burst and bacterial killing, T-cell proliferation and production of Th1 cytokines\(^{(115–118)}\). However, the relationship between Fe deficiency and susceptibility to infection remains uncertain\(^{(115–122)}\). Indeed, there is evidence that infections caused by organisms that spend part of their life cycle intracellularly, such as plasmodia and mycobacteria, may actually be enhanced by Fe. In children in the tropics, Fe at doses above a particular threshold has been associated with increased risk of malaria and other infections, including pneumonia\(^{(123–126)}\). Thus, Fe intervention in malaria-endemic areas is not advised, particularly high doses in the young, those with compromised immunity (e.g. HIV infection) and during the peak malaria transmission season. Fe treatment for anaemia in a malarious area must be preceded by effective anti-malarial therapy and should be oral. There are different explanations for the detrimental effects of Fe administration on infections. First, Fe overload causes impairment of immune function\(^{(115–118)}\). Second, excess Fe favours damaging inflammation. Third, micro-organisms require Fe and providing it may favour the growth of the pathogen. Perhaps, for the latter reasons, several mechanisms have developed for withholding Fe from a pathogen\(^{(127)}\). Oral Fe supplementation has not been shown to increase risk of infection in non-malarious countries\(^{(118)}\).

**Selenium**

Se is a cofactor for a number of enzymes including some involved in antioxidant defences such as glutathione peroxidase. Therefore, Se may protect against the immunosuppressive effects of oxidative stress, thus acting to enhance immune function. There are a number of reviews of the role of Se in the immune system and host susceptibility to infection\(^{(128–132)}\). Se deficiency in laboratory animals affects both innate and acquired immunity and increases susceptibility to infections. Lower Se concentrations in human subjects have also been linked with...
increased virulence\textsuperscript{(131–133)}, diminished natural killer cell activity\textsuperscript{(133,134)} and increased mycobacterial disease\textsuperscript{(135)}. Se supplementation has been shown to improve various aspects of immune function in human subjects\textsuperscript{(136–138)}, including in the elderly\textsuperscript{(139,140)}. Se supplementation in Western adults with low Se status improved some aspects of their immune response to a poliovirus vaccine\textsuperscript{(141)}.

Probiotics, prebiotics, immunity and infection

Indigenous commensal bacteria within the gastrointestinal tract are believed to play a role in host immune defence by creating a barrier against colonisation by pathogens. Disease and the use of antibiotics can disrupt this barrier, creating an environment that favours the growth of pathogenic organisms. There is now evidence that providing exogenous, live, ‘desirable’ bacteria, termed probiotics, can contribute to maintenance of the host’s gastrointestinal barrier. Probiotic organisms are found in fermented foods including traditionally cultured dairy products and some fermented milks and the most commonly used commercial organisms are lactobacilli and bifidobacteria. These organisms are able to colonise the gut temporarily, making their regular consumption necessary. In addition to creating a physical barrier, some of the products of the metabolism of probiotic bacteria, including lactic acid and antibiotic proteins, can directly inhibit the growth of pathogens\textsuperscript{(142)}. Probiotic bacteria also compete with some pathogenic bacteria for available nutrients. In addition, to these direct interactions between commensal and probiotic organisms on the one hand and pathogens on the other, commensal and probiotic organisms can interact with the host’s gut epithelium and gut-associated immune tissues\textsuperscript{(142)}. These communications with the host may occur through chemicals released from the bacteria or through direct cell–cell contact\textsuperscript{(142)} and it is through these interactions that probiotics are thought to be able to influence immune function, even at sites distant from the gut\textsuperscript{(143)}. Nevertheless, the precise nature of these interactions is not very well understood, although there is significant research activity in this area\textsuperscript{(144)}. A large number of studies have examined the influence of various probiotic organisms, either alone or in combination, on immune function, infection and inflammatory conditions in human subjects\textsuperscript{(145)}. Certain probiotic organisms appear to enhance innate immunity (particularly phagocytosis and natural killer cell activity), but they seem to have a less pronounced effect on acquired immunity. A small number of studies show improved vaccination responses in individuals taking probiotics\textsuperscript{(146,147)}, as extensively reviewed recently\textsuperscript{(148)}. Some studies in children report lower incidence and duration of diarrhoea with certain probiotics\textsuperscript{(145)}. In adults, some studies demonstrate a reduction in the risk of traveller’s diarrhoea in subjects taking probiotics\textsuperscript{(145)} while there is now quite good evidence that probiotics protect against antibiotic-associated diarrhoea\textsuperscript{(149–153)}. There are, however, considerable differences in the effects of different probiotic species and strains and effects observed with one type of probiotic cannot be extrapolated to another.

Prebiotics are typically, though not exclusively, carbohydrates which are not digestible by mammalian enzymes but which are selectively fermented by gut microbiota, leading to increased numbers of beneficial bacteria within the gut. Prebiotics include inulin-type fructooligosaccharides, galactooligosaccharides and xyloooligosaccharides. The bacteria promoted by prebiotics are often lactobacilli and bifidobacteria. Consequently, prebiotics have the potential to induce the same sorts of immune effects as seen with probiotics, acting through similar mechanisms, although there may also be direct communications between the prebiotics themselves and the host immune cells\textsuperscript{(154)}. There is some evidence for immunomodulatory effects of prebiotics, but many experiments conducted in human subjects are difficult to interpret because prebiotics and probiotics are often used in combination\textsuperscript{(154)}.

Impact of infection on nutrient status

Although a poor nutritional state impairs immunity and predisposes to infections, the immune response to an infection can itself impair nutritional status and alter body composition\textsuperscript{(5,6)}. Thus, there is a bidirectional interaction between nutrition, infection and immunity (Fig. 2). Infection impairs nutritional status and body composition in the following ways (Fig. 3):

(1) Infection causes anorexia with reduced food intake ranging from as little as 5% to an almost complete loss of appetite. This can lead to nutrient deficiencies, even...
if the host is not deficient before the infection, and may make apparent existing borderline deficiencies.

(2) Infection can cause nutrient malabsorption and loss, especially infections that damage the intestinal wall or that cause diarrhoea or vomiting (159).

(3) Infection increases resting energy expenditure, placing a demand on nutrient supply, particularly when coupled with anorexia, diarrhoea and other nutrient losses.

(4) Infection causes altered metabolism and redistribution of nutrients, including both macronutrients (e.g. amino acids) and micronutrients (e.g. vitamin A, Zn and Fe). A catabolic response occurs with all infections and brings about a redistribution of energy substrates for energy and biosynthesis away from skeletal muscle and adipose tissue towards the host immune system and its supporting tissues including the liver. As a result plasma concentrations of vitamin A, Zn and Fe, among others, decrease with infection.

Anorexia, increased energy expenditure and redistribution of nutrients are brought about by host factors (mainly inflammatory cytokines), while malabsorption and mal-digestion are brought about by the pathogen. The result is that an increased nutrient requirement coincides with reduced nutrient intake, reduced nutrient absorption and nutrient losses (Fig. 3).

Summary and conclusions

A well functioning immune system is key to providing good defence against pathogenic organisms and to providing tolerance to non-threatening organisms, to food components and to self. The immune system works by providing an exclusion barrier, by identifying and eliminating pathogens and by identifying and tolerating non-threatening sources of antigens, and by maintaining a memory of immunological encounters. The immune system is complex involving many different cell types distributed throughout the body and many different chemical mediators some of which are involved directly in defence while others have a regulatory role. Babies are born with an immature immune system that fully develops in the first few years of life. This immune maturation requires the presence of specific immune factors and exposure to antigens from food and from micro-organisms. Immune competence can decline with ageing. This process is termed immunosenescence. The sub-optimal immune competence that occurs early and late in life increases susceptibility to infection. Undernutrition impairs immune defences at all stages of the life cycle, although infants and the elderly may be more vulnerable, making an individual more susceptible to infection. However, the immune response to an infection can itself impair nutritional status and alter body composition. Practically all forms of immunity are affected by protein–energy malnutrition, but non-specific defences and cell-mediated immunity are most severely affected. Micronutrient deficiencies impair immune function. The gut-associated lymphoid tissue is especially important in health and well-being because of its close proximity to a large and diverse population of organisms in the gastrointestinal tract and its exposure to food constituents. Probiotic bacteria which modify the gut microbiota may enhance immune function in human subjects lowering the risk of certain infections and improving the response to vaccination.

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