Seminars in Immunology 27 (2015) 300–309

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Nutritional control of immunity: Balancing the metabolic requirements with an appropriate immune function

Veronica De Rosa[a,b,1], Mario Galgani[a,1], Marianna Santopaolo[a,c], Alessandra Colamatteo[b,d], Roberta Laccetti[a,d], Giuseppe Matarese[d,e,*]

[a] Laboratorio di Immunologia, Istituto di Endocrinologia e Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (IEOS-CNR), Napoli 80131, Italy
[b] Unità di NeuroImmunologia, Fondazione Santa Lucia, Roma 00143, Italy
[c] Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università di Napoli "Federico II", Napoli 80131, Italy
[d] Dipartimento di Medicina e Chirurgia, Università di Salerno, Baronissi Campus, Baronissi 84081, Salerno, Italy
[e] IRCCS MultiMedica, Milano 20138, Italy

ARTICLE INFO

Article history:
Received 15 September 2015
Received in revised form 7 October 2015
Accepted 12 October 2015
Available online 29 October 2015

Keywords:
Nutrition
Dietary components
Immune function
Obesity
Gut microbiota
Nutriepigenomics

ABSTRACT

The immune system is a highly integrated network of cells sensitive to a number of environmental factors. Interestingly, recent years have seen a dramatic increase in our understanding of how diet makes a crucial contribution to human health, affecting the immune system, secretion of adipocytokines and metabolic pathways. Recent experimental evidence indicates that diet and its components are able to profoundly influence immune responses, thus affecting the development of inflammatory and autoimmune diseases. This review aims to discuss some of the main topics concerning the impact of nutrients and their relative composition on immune cell development and function that may be particularly important for regulating the balance between inflammatory and tolerogenic processes. We also highlight the effects of diet on commensal bacteria and how changes in the composition of the microbiota alter intestinal and systemic immune homeostasis. Finally, we summarize the effects of dietary compounds on epigenetic mechanisms involved in the regulation of several immune related genes.

1. Introduction

Nutrition has a major influence on immunity and well-being; recent work suggests that lymphoid organs are directly influenced by the environment, especially by diet and products derived from the commensal gut flora (microbiota). In the past few decades, the nutritional change in dietary habits observed in western countries has correlated with an increased incidence of immune dysfunction, such as asthma, allergy and autoimmune diseases, including type 1 diabetes (T1D), multiple sclerosis (MS), rheumatoid arthritis and inflammatory bowel disease (IBD). Dietary components and the relative excess of food intake have a direct influence on lymphoid organs and immune cells, thus modulating their activation and function. Moreover, since lymphoid organs are abundant in the gastrointestinal tract, they are particularly sensitive to nutrient-derived metabolites and products derived from the gut microbiota. Indeed, disruption of the microbiota (dysbiosis), due to the change in diet composition and increased energy-dense food consumption, may be the real driver of the inflammatory conditions observed in industrialized societies. In this review, we examine the main evidence that highlights the role of diet and its components as key factors influencing the immune response and the development of inflammatory diseases. Comprehension of the mechanisms through which nutrients influence immunity is a promising field and may pave the way for the development of new dietary, microbial, and immune-based strategies for improving clinical outcomes.

2. Imprinting immune cell function by maternal and early-life nutrition

The emerging immune system is strongly susceptible to environmental stimuli during embryonic and early-life. Maternal and early-life diet influences the development of the immune system and the balance between the induction of an effector immune response against pathogens and the protective regulatory mechanisms, preventing inflammatory damage of the host [1]. Development of lymphoid organs occurs during embryogenesis in a specific time frame and is chronologically programmed. Secondary

* Corresponding author at: Dipartimento di Medicina e Chirurgia, Università di Salerno, Baronissi Campus, Baronissi 84081, Salerno, Italy.
E-mail address: gmatarese@unisa.it (G. Matarese).
[1] These authors equally contributed to this work.

http://dx.doi.org/10.1016/j.smim.2015.10.001
1044-5323/

lymphoid organs formation depends on specific lymphoid cells subsets, named lymphoid tissue initiator (LTin) and lymphoid tissue inducer (LTi) cells and can be influenced by nutrient availability that links the nutritional status with the immune response of the host [2,3]. The pathways through which maternal nutrition influences the developing immune system of the child encompass, alterations of the hypothalamic–pituitary–adrenal (HPA) axis, reduction of nutrient availability and altered transfer of immunity from mother to child. Malnutrition is sensed as a stress factor that activates the HPA axis, eliciting high glucocorticoid production; this directly impacts the developing immune system in terms of reduced thymic weight and lymphocyte numbers [1]. Endocrine perturbation, due to altered HPA axis activation secondary to maternal malnutrition, affects the development of B and T lymphocytes at immature stage and immune responses later in life [4]. Indeed, alterations in cytokine expression, antibody production, lymphocyte function and long-term risk of infection have been reported [5–10]. In addition, nutrient deprivation affects the emerging immune system independent of HPA axis activation; for example, vitamin A deficiency during pregnancy can influence lymphocyte number and the size of secondary lymphoid organs (lymph nodes and Peyer's patches) during their development. Genetic ablation of the vitamin A receptor, retinoic acid receptor (RAR)α, results in the development of smaller secondary lymphoid organs, as a consequence of reduced activity of RARα in LTi cells *in utero* [11]. Pre-birth vitamin A deficiency also affects intestinal immunity, by reducing the number of intestinal intraepithelial lymphocytes (IELs), T cell receptor (TCR)αβ and TCRγδ cells, a defect that can be corrected through vitamin A replacement during pregnancy or soon after birth [12]. Additional studies have revealed role for maternal vitamin E and vitamin D in promoting tolerogenic immune responses and a regulatory T (T_{reg}) cell phenotype. Indeed, several studies reported that low vitamin E intake causes increased responsiveness of peripheral blood mononuclear cells (PBMCs), airway inflammation, wheezing and asthma [13,14]. Moreover, supplementation with vitamin D during gestation increased the number of tolerogenic antigen-presenting cells (APCs) in cord blood [15,16]. Low prenatal vitamin D levels may also increase susceptibility to several diseases later in life, *via* specific effects on target organs and through changes in the developing immune system [17]. By contrast, a recent study showed that high levels of endogenous maternal vitamin D3 does not protect offspring from allergic diseases but is associated with an increased risk of allergic disease in offspring after 25 years [18]. In addition to vitamins and folate, maternal omega-3 (α-linoleic acid (ALA), eicosapantaenic acid (EPA) and docohexaenoic acid (DHA)), as well as omega-6 [linoleic acid (LA) and arachidonic acid (AA)] polyunsatured fatty acid (PUFA) consumption has been documented to play a role in immune function. Indeed, Kremmyda et al. [19] showed that fish intake during pregnancy, which provides high levels of omega-3, correlates with reduced interleukine (IL)-4 and IL-13 cytokine production in cord blood, with a consequent reduction in IgE production and T helper (Th)2-type cell differentiation [20,21]. However, another study showed that high doses of omega-3 supplementation during gestation do not influence the outcome of allergic diseases rather reduce the incidence of atopic eczema [22]. During infancy, fish oil supplementation has been shown to increase the production of interferon (IFN)-γ and reduce the levels of IL-10, thus promoting immune system maturation through the induction of Th1 polarization [23].

Breast milk represents the best nutrient supply and the main source of active and passive immunity in early-life. Breast-fed infants have a considerably larger thymus than do formula-fed infants at four months and this is secondary to the presence of immunomodulatory factors present in human milk, such as immunoglobulins, lactoferrin, lysozyme, cytokines, as well as numerous other immunologic factors, including maternal leukocytes [24]. Moreover, breast-feeding enhances the antibody response to vaccines during the first year of life and promotes anti-inflammatory and tolerogenic immune responses in the gut [25–27]. It has been shown that the relative frequency of specific lymphocyte subsets is different in breast-fed children in comparison to formula-fed infants. Specifically, the numbers of natural killer (NK) and $CD8^+$ cells are greater in breast-fed infants, while the percentage of $CD4^+$ cells and the CD4:CD8 ratio are lower than in formula-fed infants [28]. However, contrasting data showed that breast- and formula-fed infants have little differences in antibody response to vaccines [29,30]. Taken together these data suggest more robust maturation of the immune system in breast-fed infants.

The introduction of solid foods (between 4 and 6 months) and an increased diversity of food antigen exposure into the infant's diet were found to correlate with a reduced incidence of food allergy, allergic rhinitis and atopic sensitization up to 6 years [31]. Protein malnutrition, iron and folic acid deficiency are associated with thymic atrophy as a consequence of thymocyte depletion, decreased proliferation and increased apoptosis [32–35]. In summary, current literature supports a crucial role for both maternal and early-life diet in favoring immune system maturation and differentiation and in preventing allergic/atopic diseases.

3. Dietary components influencing immune cell function

In addition to improved hygiene, the change in dietary foodstuffs occurring in the western countries over the past decades correlates with the rise in the incidence of asthma, allergy and autoimmune diseases. Evidence for the effect of dietary components on immune disorders development is continuously emerging. Western individuals preferentially consume energy-dense, processed foods (red meat, sugars, fat and refined wheat) and low amounts of nutrient-rich foods, such as fish, fruits and vegetables; this correlates with a dramatic rise in inflammatory/immune disorders, such as allergy, asthma, cancer, cardiovascular and autoimmune diseases [36–39]. Free fatty acids and other lipids acquired in the modern diet have been proposed to influence several aspects of metabolism and immune function (Fig. 1). They are classified according to their length (number of carbon residues in the lipid backbone), saturation, number and position of the double bonds. Fatty acids that do not have double bonds are termed "saturated", and those having one or more double bonds are called monounsaturated fatty acids (MUFAs) or polyunsaturated fatty acids (PUFAs), respectively. Saturated fatty acids are generally associated with increased inflammation, while unsaturated fatty acids have both pro-inflammatory and anti-inflammatory activity [40,41] (Fig. 1). Saturated fatty acids or their metabolites, mainly present in meat and cheese, activate the nuclear receptors peroxisome proliferator-activated receptors (PPARs), which are widely expressed by immune cells as three different isoforms, PPARα, PPARβ/δ and PPARγ. The activation of PPARα or PPARγ inhibits Th2 responses and allergic asthma through the down-modulation of eosinophils and denditric cells (DCs) activity [42,43]. Activation of PPARγ also controls inflammation through the involvement of IL-10 [44]. In contrast, PPARβ/δ activation does not inhibit airway inflammation in mouse models of disease [45]. Medium chain fatty acids (MCFAs) are saturated fatty acids present in several types of oils, such as coconut oil and palm kernel oil; their consumption induces the production of thymic stromal lymphopoietin, IL-25 and IL-33 by gut epithelial cells and this promotes Th2 cell responses in the periphery, thus increasing allergic and anaphylactic response to peanut antigens [46]. Moreover, MCFA binding to the G-protein coupled receptor (GPR)-84 present on leukocytes directly affects adaptive immune cells differentiation