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Review

Nutrition and chronic inflammatory rheumatic disease

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ABSTRACT

Nutrition is a major environmental influence on human health. Epidemiological and interventional studies suggest a pathophysiological or therapeutic role, respectively, for nutrition in inflammatory rheumatic diseases (IRDs). Nevertheless, the associations between nutrition and IRDs are often weak and inconsistent, and the available clinical trials on nutrition are methodologically flawed. Experimental evidence is accumulating that micronutrients in the diet may influence intestinal and systemic immune responses via complex interactions involving the gut microbiota. Micronutrients may, therefore, contribute to the pathogenesis of inflammatory diseases. No interventions targeting these interactions for diagnostic, prophylactic, or therapeutic purposes have been developed to date. Moreover, the relevance to human disease of experimental results obtained in animals or in vitro is unclear. Novel high-throughput technologies (-omics) may prove useful for a systems biology approach to these results that takes the complexity of the interactions into account. Concomitant cohort studies combining clinical and laboratory data collected over time may provide new impetus to research into the connections between nutrition and IRDs.

1. Introduction

The gut lining is one of the epithelial barriers located at the interface between multicellular organisms and the environment. The gut contains a vast variety of microorganisms, known as the microbiota, which interacts with the host [1]. The microbiota is composed of eukaryotes, bacteria, and viruses, with over 5 million genes whose biological effects benefit the hosts by ensuring the breakdown and metabolism of otherwise indigestible substances, as well as the synthesis of vitamins and other metabolites [1].

The gut barrier controls the selective passage of substances from the environment to the inside of the body. This function requires close surveillance by the immune system, which is provided by the well-developed and highly specialized gut-associated lymphoid tissue (GALT). A host of antigens continually challenge this tissue, which must ensure tolerance to most of them, while remaining alert to potential insults.

Thus, throughout life, complex interactions occur between dietary metabolites, the gut microbiota, and the host. In the gut, the interaction between the immune system and the environment is mediated by resident microorganisms, and the components of the diet interact with the genetic background of the individual to determine a state of health or disease.

Metabolites can influence the phenotypic range of gene expression via several mechanisms. Some of these mechanisms are epigenetic changes, such as acetylation or methylation of the DNA in histones and other ribonucleoproteins (e.g., folates, S-adenosyl methionine, and vitamin B12). Others consist in regulation of gene transcription by a ligand-receptor complex (e.g., carotenoids and vitamin D) or in activation of intracellular signaling pathways (e.g., long-chain fatty acids [2], antioxidants, and products of bacterial metabolism such as short-chain fatty acids [SCFAs]) [3].

Elucidating the mechanisms by which the diet may affect the immune system remains challenging. The available data are of limited relevance, for several reasons: in vitro findings may not

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Box 1: The immune system and gut barrier

The gut-associated lymphoid tissue (GALT) includes intraepithelial lymphocytes (IELs) and lymphocytes located within the lamina propria. A population of IELs known as natural or innate-like IELs predominates in all epithelial barriers before birth [4]. Natural IELs express a type αβ or γδ T-cell receptor and produce an abundance of interferon-γ, but are unable to produce interleukin-17. They are the first line of defense after the initial encounter with microorganisms [5]. After birth, they are replaced by memory T-cells called inducible IELs, which produce a lasting antigen-specific response [6]. In animal models, exposure to vitamin A in utero is indispensable for IEL homing to the epithelium and for subsequent GALT development. In humans, vitamin A deficiency during pregnancy increases the risk of neonatal infection and blunts the neonate's response to vaccines. Immune tolerance of antigens found in the diet and gut microbiota is ensured by effects of dendritic cells (DCs) on lymphocyte subsets. In the lamina propria of the small bowel, the predominant DC subset is $CD103^{+}CD11b^{+}$. This subset presents gut bacterial antigens captured by the cell dendrites and induces CD4+ T-cells to differentiate into $FoxP3^{+}$ regulatory T-cells via the production of TGF-β and retinoic acid [7]. The $CX3CR1^{+}$ DC subset recognizes bacterial metabolites via toll-like receptors, produces IL-10, and regulates gut barrier integrity by inducing the production of IL-22 by IELs [4]. The lamina propria constitutionally contains large numbers of CD4+ T-cells of the Th17 type [4]. These Th17 cells play a key role in protecting the integrity of the gut barrier, a fact that may explain the adverse effects of IL-17 antagonist drugs on chronic inflammatory bowel disease (CIBD) [8]. The antigens in the microbiota and the micronutrients at the surface of the gut epithelium stimulate the adaptive responses of Th17 cells. Dietary salt activates Th17 cells via activation of the salt-sensitive kinase pathway serum/glucocorticoid-regulated kinase-1 (SGK-1), which increases the expression of the IL-23 membrane receptor [9]. Data from animal models suggest that certain bacteria such as flavobacteria and bacteroides may be required for the T-cells in the lamina propria to differentiate into Th17 cells, and elimination of these bacteria by antibiotics may induce FoxP3 transcription and differentiation to regulatory cells [10].

The arhylhydrocarbone (AhR) receptor is a nuclear receptor that belongs to the same family as hypoxia-inducible factor-α. This family of proteins translates environmental stimuli into cellular responses [11]. AhR binds to dioxin and other industrial pollutants. It can also bind to micronutrients and bacterial metabolic products such as indole-3-carbinol (I3C), which is found in green vegetables [12]. AhR is strongly expressed in IELs and in lamina propria Th17 cells. It induces the production of IL-22 [13]. Studies of AhR knockout animals have confirmed the crucial contribution of this receptor to GALT integrity. Mice fed a synthetic diet that was high in vitamins but contained no plant products had a marked decrease in gut IEL counts contrasting with normal epidermal IEL counts. I3C supplementation corrected this abnormality.

The role for AhR in humans remains somewhat unclear. AhR may be involved in GALT maturation and in maintaining gut barrier integrity via IL-22. It may be one of the mechanisms by which the intake of fruit and vegetables may influence immune responses and the gut microbiota in a way that decreases the risk of inflammatory diseases, particularly those affecting the bowel. CIBD is associated with the western diet and with a lower intake of plant foods [14], and AhR expression in the gut is decreased in patients with Crohn's disease [15].

Box 2: The gut microbiota

A comprehensive description of the role for the microbiota in inflammatory rheumatic diseases would be beyond the scope of this work. Nevertheless, the diet has a major influence on microbiota diversity. A varied diet induces a diversified and resilient microbiota, whereas a meager microbiota is associated with disease. Chronic stimulation of the epithelium by bacterial products enhances the epithelial repair response and induces an eicosanoid and cytokine environment conducive to immune tolerance. Any imbalance in these factors may induce intestinal and systemic immune responses. Recently, differences in the gut microbiota were found between patients with RA and healthy controls [16] and proved reversible in the event of a response to methotrexate [16]. No proof exists to date that manipulating the microbiota (by dietary changes or other means) improves inflammatory rheumatic diseases. Data suggest, however, that control of RA activity by a period of fasting followed by a vegetarian diet (i.e., a high fiber intake) [17] may act by increasing the production of short-chain fatty acids (SCFAs, see Box 3) by the gut microbiota.

be applicable to complex systems, no relevant animal models are available, confounding factors exist, observational studies cannot provide proof of causality, and the interventional studies conducted to date are biased and of limited duration. Nevertheless, insights into the interactions between cell metabolism and immune responses have been provided by new techniques such as multicolor flow cytometry to examine cell populations and studies of the gut microbiota. Recently introduced high-throughput DNA sequencing techniques can supply information on the microbial populations in the gut without prior culturing. The results demonstrate a link between the diversity of the diet and the diversity of the gut microbiota. Metagenomic studies can detect associations (e.g., between a disease and specific microbial populations) but cannot prove causality. Nevertheless, these advances have shed light on the role for nutrition in inflammatory diseases.

The diet is widely recognized as capable of modulating susceptibility to chronic inflammatory disease (i.e., of exerting pathogenic effects) and of providing therapeutic benefits. The variables involved are the intestinal immune system and the barrier function of the intestinal mucosa (Box 1), the gut microbiota (Box 2), and the ingestion of dietary substances (which may or may not be metabolized by the gut microbiota) that exert immunomodulating effects (Boxes 3 and 4).

2. Nutrition and risk of developing inflammatory rheumatic disease (IRD)

2.1. Links between nutrition and incidence of IRDs

Epidemiological studies of links between nutrition and IRDs have largely focused on rheumatoid arthritis (RA). Most of them used a nested case-control design (based on incident cases arising within a cohort) to identify risk factors for the development of the disease. Nutrition was analyzed in terms of food groups (alcohol, fruit and vegetables, fish) or nutrients (omega-3 fatty acids [ω3FAs], vitamins, and antioxidants). Research into RA has been developed based on data from vast cohort studies such as the US Nurses' Health Study (NHS) of 121,701 women followed-up from 1980 and 2000 and the Iowa Women's Health Study (IWHS) of 31,336 women aged 55 to 69 years and followed-up from 1986 to 1997 [25] and the Danish Diet Cancer and Health Study (DDCHS) [26].

A limitation inherent in the IWHS and DDCHS is the small number of validated cases: in the IWHS, only 152 incident cases of RA were validated and in the DDCHS 69 cases were validated among