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Nutrition and the Immune System

Authors
Stephanie Blum, Sami Damak, Sophie Nutten, Jalil Benyacoub, Jennifer Dean, Annick Mercenier, Peter van Bladeren & Johannes le Coutre

Nestlé Research Center,
1000 Lausanne 26, SWITZERLAND

The immune system is a fascinatingly complex and dynamic system protecting the body against challenges such as pathogens, foreign substances and tissue damage. It must be able to distinguish pathogens from innocuous self or food antigens, to maintain homeostasis and optimal health. The immune response comprises two complementary components: innate and adaptive immunity. At the innate level, the immune response to invading pathogens or toxin is immediate, but non-specific. The complementary adaptive immune system provides a more targeted and specific reaction to pathogens- and antigens for protection which is more robust and long lasting.

The 2011 Nobel Prize in Physiology or Medicine was awarded to Bruce Beutler, Jules Hofmann and Ralph Steinman for their pioneering characterization of innate immune cells (dendritic cells), pathways (Toll-like receptor signalling) and mechanisms that instruct adaptive immunity. Their findings acknowledge the integral role of innate immunity in the onset, course and control of adaptive immune responses.

Chronic inflammatory disorders

Inflammation is the culmination of physiological responses by the immune system acting to protect the body from infections, irritants and tissue injury. In normal conditions, the interplay of innate and adaptive immune responses leads to the cessation of inflammation, a return to homeostasis and initiation of tissue repair (Fig 1).

If environmental factors and/or genetic susceptibilities impair control of inflammation, it may become chronic and lead to disease conditions. Persistent inflammation of which the cause is ill defined, and does not result from infection or tissue damage, is implicated in a variety of diseases such as: inflammatory bowel disease (IBD), allergy, obesity, diabetes, cardiovascular disease and a variety of autoimmune disorders which predominantly affect people in developed countries[1]. The prevalence of such chronic diseases has rapidly increased in the past decades, linked with the adoption of a sedentary lifestyle and Western diet[2-3]. Although the phenotype of these chronic diseases may be diverse, there are

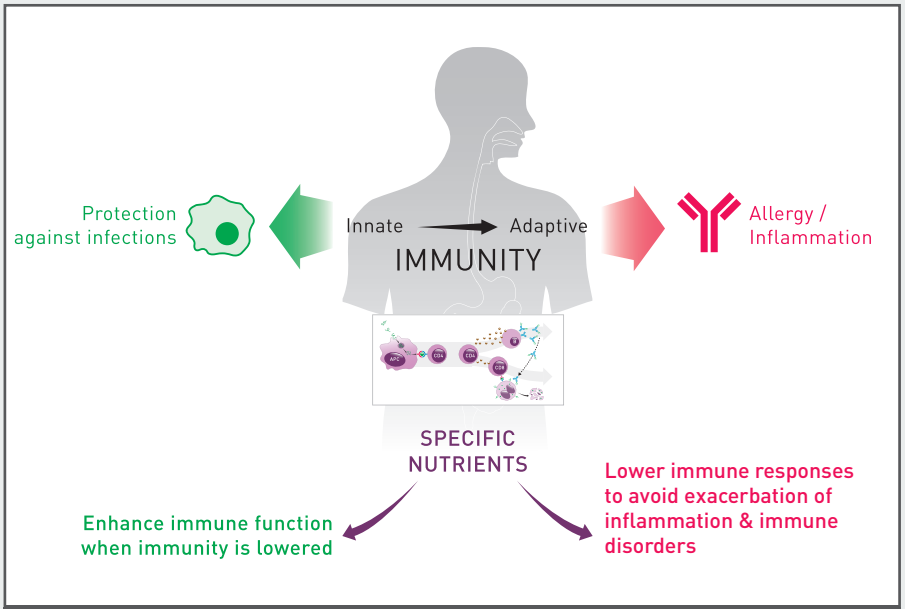

Figure 1 | Potential influence of nutrition to enhance immunity and reduce the risk of chronic inflammation.

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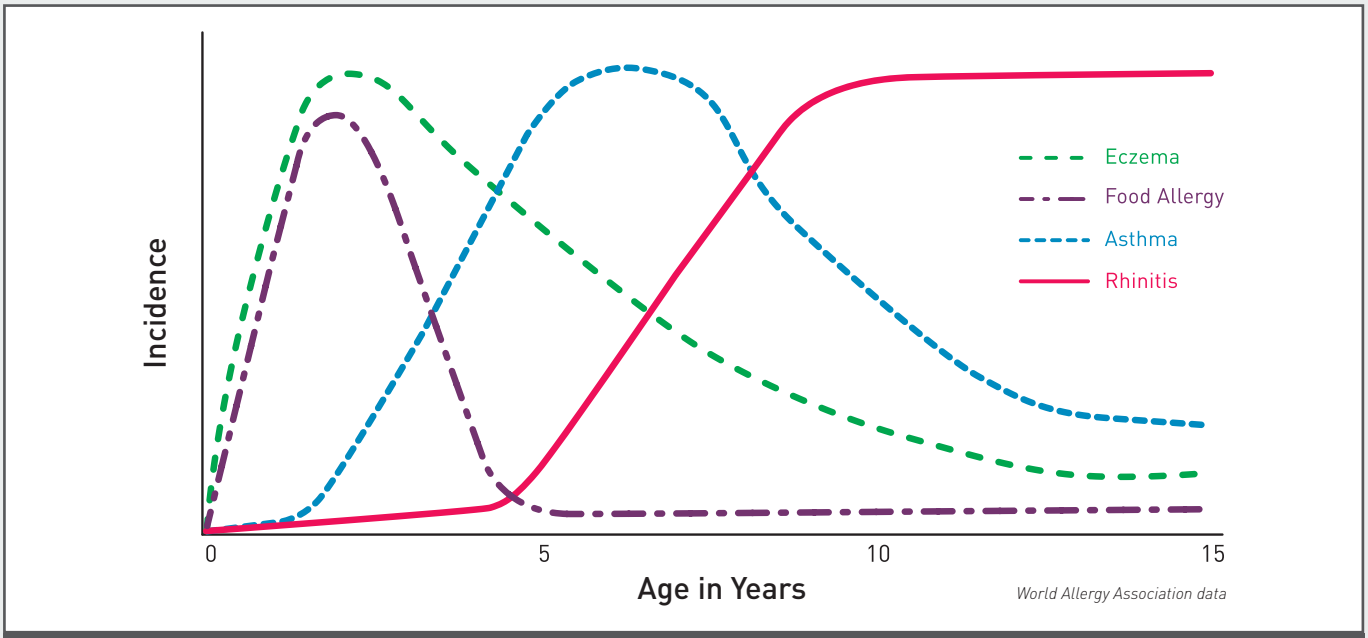

Figure 2 | The atopic march.

similarities at the molecular and cellular levels. Because nutrition may influence various mechanisms of inflammation, specific food components and nutrients have therapeutic potential to ameliorate some conditions of chronic inflammation.

Inflammatory bowel disease is manifested in the two main forms of Crohn's disease and Ulcerative Colitis, which are deemed acute and chronic inflammatory diseases. IBD is characterized by an aberrant immune response to normal bacteria in the gut microbiota in individuals with a weakened epithelial barrier. Though the etiology is not fully known, research indicates that IBD involves numerous factors such as: genetics and environment, microbial influences, reduced barrier function and a loss of mucosal homeostasis, and metabolic stress[1].

Obesity is characterized by the storage of triglycerides in adipose tissue, but frequently also in skeletal muscle and the liver. This brings metabolic changes and insulin resistance, which may promote inflammation. Hotamisligil et al first illustrated the link between obesity and inflammation through the positive correlation of adipose tissue and expression of TNFα[1,2]. It was further established that the adipocyte has an impact on the inflammatory response through the release of a cocktail of inflammatory mediators and signalling molecules. It is speculated that obesity is a state of low-grade inflammation which is stimulated by adipocytes[1,4].

A major cause of cardiovascular disease is atherosclerosis, or the hardening of the arteries. The incremental adhesion and accumulation of atherosclerotic plaque is complex, and its evolution is marked by the inflammatory response of monocyte/macrophage and T-lymphocyte permeation[1].

Allergy – like other chronic inflammatory diseases – has been on the rise in Western countries over the past decades. Statistics show that the recent incidence of allergic reactions is higher than reported cardiovascular diseases and diabetes. Figures from 2008 provided by the National Center for Health Statistics in the U.S. indicate that four out of every 100 US children have a food allergy. And it is predicted that the incidence of allergic rhinitis will continue to increase. Similar to inflammatory bowel disease, allergy is a multifactorial disease which can stem from genetic, environmental and immune factors. Other contributors can include diet and living conditions, family size, contact with pets and farm animals, exposure to airborne allergens and pollution, and characteristics of the host itself including the gut microbiota[3].

Allergic reaction is the heightened response of the immune system (often in predisposed individuals) to ordinarily harmless antigens. Food (*e.g.* milk, egg, peanuts/nuts, soy, wheat/cereals, fish, shellfish), airborne (*e.g.* pollen, dust mites, pet dander) and contact allergens (*e.g.* Nickel) can all cause sensitization in the sufferer, which upon re-exposure to the allergen will lead to different symptoms at the level of the gastrointestinal tract, the respiratory tract or the skin. With the exception of anaphylactic shock, allergic diseases are not life threatening but can drastically reduce quality of life. Atopic eczema (dermatitis) affects 10-20% of young children and 1-3% of adults, while diagnosed food allergies occur in 5-6% of young children and 2-4% of adults. Globally, the prevalence of respiratory allergies is much higher, exceeding 30% in some countries[3].

Treatment for food allergy typically means avoiding foods which contain the offending allergen(s)[5]. When patients are allergic to wheat or egg, it may be difficult to find appropriate foods that do not exacerbate the allergy. Children who do not spontaneously outgrow their food allergy are at a much higher risk (a three-fold increase) of subsequently developing allergic rhinitis. This predisposition to allergy development, known as the "atopic march," (Fig 2) therefore reinforces the importance of developing preventive strategies.

New insights in the development of inflammatory disease

There has been recent focus on new features of the physiopathology of inflammation including: microbiota dysbiosis, defects in T cell homeostasis and differentiation, authophagy and endoplasmic reticulum stress.

Endoplasmic reticulum (ER) stress response

Multiple cellular stress responses are involved in chronic disease. Different exogenous, but also endogenous insults can lead to cellular stress (Fig 3). Beyond its initial role for membrane protein synthesis, folding and transport, the ER also serves as a cellular stress integrating site[6]. Accumulation of misfolded proteins during protein synthesis leads to so-called 'ER stress.' In antagonistic response to this ER stress, eukaryotic cells develop a tightly controlled mechanism, the unfolded-protein response (UPR), enabling elimination of un- and misfolded proteins.

ER stress and inflammatory pathways were shown to intersect at several stages and in experiments, has been shown as a potential mechanism implicated in IBD. Moreover, genetic polymorphism studies reported that UPR molecules are associated with IBD in human patients[7].

Increasing evidence suggests that energy metabolism and the UPR are connected, and the ER acts as a sensor for cellular lipid status and exposure[6,7]. It therefore presents an exciting avenue to explore the possible use of nutrition to modulate ER stress response, and further links to chronic inflammatory diseases.

Th17 cells – new players in the initiation of inflammation

Besides the differentiation of naïve CD4+ T cells into Th1 and Th2 helper cells, a new T helper subpopulation, Th17 cells, has been implicated in the onset and cause of antigen-specific

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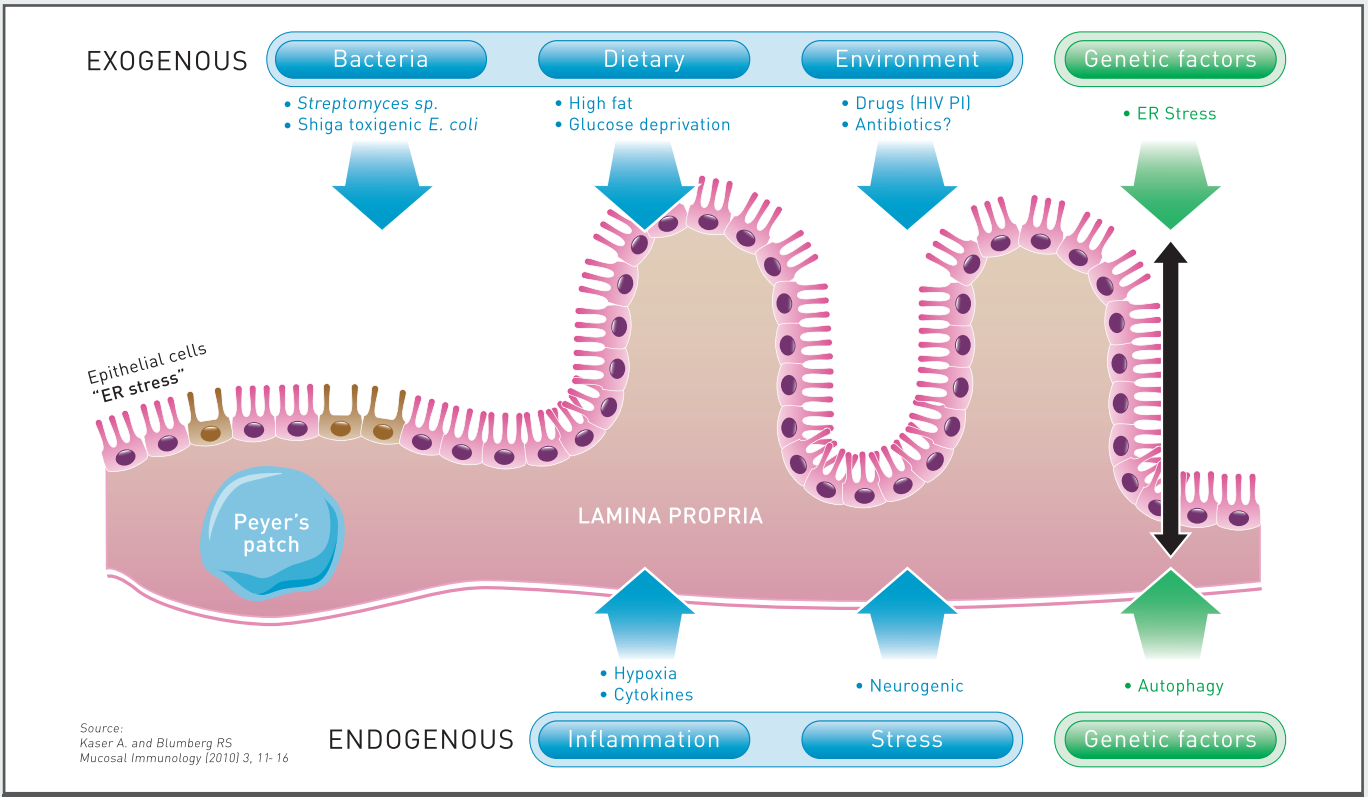

Figure 3 | Genetic and environmental factors drive ER stress in the intestinal epithelium.

auto-immunity and tissue inflammation. Activated Th17 cells produce inflammatory cytokines, with a primary role of clearing pathogens. In line with this protective function, Th17 cells are potent inducers of inflammation in a variety of tissues. The molecular mechanism by which an adaptive immune response is skewed towards Th17 seems to rely, at least partially, on the specific pathogen sensed by innate cells. The role of Th17 pathogenicity has been highlighted in the context of several chronic inflammatory disorders including Crohn's disease, rheumatoid arthritis and multiple sclerosis[8,9]. Better understanding of Th17 cell differentiation determinants could open new possibilities for therapeutic and nutritional intervention strategies. Both ER stress response and T cell homeostasis are new aspects under investigation in Nestlé research programmes on inflammation and metabolic diseases.

Interactions of the gut microbiota and the host immune system

The gastrointestinal tract is a multifaceted system integral in educating the early immune system and modulating host responses. It is populated by diverse microorganisms (>1,000 bacterial species) who vary in number and type along the intestine according to local biochemical conditions and nutrient availability. This complex microbiota interacts with the host, impacting its metabolic and immune functions, and is also able to send signals to the gut and enteric nervous system. Numerous studies have demonstrated the importance of the microbiota in mucosa barrier function, immune modulation and metabolism[1,10-11].

A specific characteristic of the gut-associated immune system is to mount a protective inflammatory response against invading pathogens while developing homeostatic/immune tolerance towards commensal bacteria. Most commensal bacteria are coated with secretory IgA antibodies (SIgA). The SIgA interaction is not exclusively antigen specific, but can be glycan-mediated, suggesting an important role for polyreactive SIgA in controlling microbiota composition. SIgA, as well as its primary role in immune exclusion and prevention of pathogen translocation, has the capacity to selectively retro-transport bound bacteria into Peyer's patches and initiate an immune response without harmful inflammatory reaction. This process is thought to be important in developing tolerance to endogenous microbiota[12].

Dysbiosis of the microbiota is a perturbation in the microbiota composition, resulting in changes in host metabolic and immune activity. Evidence suggests that dysbiosis may be associated with chronic diseases such as IBD, allergy, obesity and type 2 diabetes[10-11]. For example, it has been observed that allergic patients have an altered gut microbiota, as well as IBD patients; however, it has not been established whether changes in the gut microbial composition are a cause or a consequence of the aberrant immune response[11].

Nestlé's interest in the role of nutrition and inflammation

Although persistent inflammation and related tissue damage occurs in an organ-specific manner (gut, joints, skin, adipose tissues, etc), they share similarities at the molecular and cellular levels. This presents a variety of possibilities for nutrition interventions common across inflammatory pathologies. In addition, due to the significant role of the gut and associated immune system, certain foods and ingredients may help ameliorate or prevent chronic inflammation and related disorders. Potential nutrients that may have anti-inflammatory benefits include; omega-3 fatty acids, polyphenols, antioxidants, vitamins and pre-and probiotics[1,2].

Nestlé researchers are working to further understand the complexity of the gut ecosystem and its implications for health and disease prevention – in addition to exploring potential nutrients that may exert beneficial effects. Using an integrative, multidisciplinary approach and modern molecular technologies, Nestlé is investigating the link between genetic and metabolic signatures of the host, as well as the impact of environmental factors, to gain deeper insight into the pathophysiology of chronic inflammatory disorders.

These studies are accompanied by analyses of the fecal microbiota and in-depth study of how the microbiota can be influenced by diet and functional food ingredients. The future challenge will be to decipher the role and impact of diet or single nutrients to prevent or delay the onset of disease, to alleviate symptoms or to prevent related mortality.

Polyphenol antioxidants are keenly relevant for Nestlé, due to their presence in many foods and beverages and the possible benefits for health. Polyphenols are being investigated by Nestlé for their anti-inflammatory profile, especially for their possible impact on allergic manifestations and the ageing process.

Cocoa is also being studied by Nestlé researchers for its associated health benefits, some of which could indirectly impact inflammation including lipid lowering, endothelial function, antioxidant activity, suppression of platelet activation, etc[2]. More recent studies are targeting the direct effects of cocoa on inflammatory markers.

Another key area of interest for Nestlé Research is the role of lipids to modulate inflammatory disorders. Essential fatty acids, specifically fish oils rich in long-chain polyunsaturated fatty acids (LC-PUFA), have been extensively studied. Dietary intervention with omega-3 (N-3) fatty acids such as eicosapentataenoic acid (EPA) and docosahexaenoic acid (DHA) proved both experimentally and clinically to promote brain development and to reduce the risk of cardiovascular disease. It is thought that EPA and DHA interfere with pro-inflammatory pathways such as cyclooxigenases (COX) and lipoxygenases (LOX), activating the formation of anti-inflammatory metabolites[1].

Modulation of microbiota composition and metabolic activity

Given the vital role of the microbiota in inflammatory and metabolic diseases, nutritional strategies to maintain and/or restore microbial balance are of great interest. Prebiotics, non-digestible carbohydrates that promote the growth and/or metabolic activity of selected colonic bacteria, have been thoroughly investigated[10]. Several studies have reported their positive impact on microbiota composition, particularly in the case of inulin-type fructans and galactooligosaccharides, for promoting immune defence and reducing infection in infants and the elderly. An improvement in clinical outcomes was reported for inulin-type fructans when consumed by IBD patients[1].

Another approach to balance the microbiota and influence its metabolic activity is through the use of probiotics – live microorganisms which improve health when consumed in sufficient quantities. Interest in probiotics among nutrition and health researchers has intensified in recent years. Myriad studies have examined the effects of various probiotic strains in ameliorating symptoms of diarrhea, constipation, chronic intestinal inflammation, irritable bowel syndrome, atopic dermatitis and allergy[1,5,10-11]. The anti-inflammatory actions of certain probiotic strains, including lactobacilli and bifidobacteria is said be a result of their ability to interact directly with intestinal epithelial cells and the gut-associated immune system[10-11]. For probiotics to be effective in disease treatment, finding the correct strain for the right outcome is necessary[10].

Nestlé is extremely active in the field of probiotics research, aiming to gain deeper knowledge about the effects of probiotics on inflammation and allergy. In the context of inflammatory conditions such as IBD, some specific strains of probiotics were experimentally shown to activate the innate immune system, support maintenance of mucosal homeostasis and interfere with inflammatory reactions, typically by promoting maturation of regulatory dendritic cells, induction of regulatory T cells, and by producing immune modulatory molecules such as TGF-β and altering the NF-Kb cascade[1,10-11]. More research is needed to fully elucidate the benefits of probiotics and their impact on chronic inflammation.

Nestlé's nutrition strategies to mitigate food allergies

Food can be a valuable intervention in the management of allergy. Nestlé has broadened its interest in food allergies to skin and respiratory manifestations of allergy. Current research covers two main approaches to mitigate the development of food allergy:

Reducing ingredient allergenicity

Lowering the allergenic potential of raw materials can be achieved through different processes, including a combination of heat treatment and hydrolysis, as pursued by Nestlé. These processes break down allergenic proteins into less-allergenic components, such as peptides. For example, extensively hydrolyzed infant formula contain mostly very small peptides of cow's milk proteins (CMP) and thus offer a safe alternative for infants with established cow's milk allergy. When hydrolysis of CMP is partial, the reduced allergenicity of the formula is accompanied by a capacity to induce oral immune tolerance to allergens[5,13]. This concept of less allergenic, tolerogenic foods has been extended beyond milk to wheat and egg (typically consumed by children at weaning), as proven by preclinical data presently consolidated in small pilot human trials.

Preventing or reducing symptoms of allergic manifestations

Functional ingredients may help prevent the development of allergies in susceptible consumers through modulation of their immune system towards a non-allergic state, thereby minimizing digestive, respiratory or skin allergy symptoms. Probiotics are at the forefront of investigation as health-preserving and/or health promoting food ingredients. Monitoring of allergy management with probiotics has shown encouraging results worldwide. Nestlé has identified and selected a proprietary probiotic strain (*Lactobacillus paracasei*) to alleviate allergic rhinitis symptoms in adults[14]. Other probiotic strains are currently being studied for their potential in preventing or reducing symptoms of skin and food allergies. In addition to probiotics, specific food ingredients are being tested *in vitro*, *in vivo* and in clinical trials for their efficacy in prevention of allergy and/or symptom reduction. It was recently shown by Nestlé researchers that a polyphenol-enriched apple extract can attenuate food allergy symptoms in experimental models[15].

More research is needed to elucidate the mechanisms of action of these candidates and significantly, the optimal window of intervention should be adapted to the respective type of allergic manifestation (skin, respiratory, digestive) and the targeted effect, i.e. prevention or symptom alleviation.

Taste 'interventions' against inflammation

Certain inflammatory signal transduction mechanisms seem to interfere with the chemical senses of smell and taste, which have notable implications for nutrition. Among groups such as the elderly or cancer patients undergoing chemotherapy, in which low grade inflammation is common, maintaining adequate nutrition can be difficult due to reduced appetite. Various studies with Crohn's disease patients showed increased taste thresholds for all tastes, or only for salt or sweet compounds[16]. Subjective taste disorders is a common complaint in cancer patients, though changes in taste thresholds are minimal, which may actually be related to decreased or modified olfactory function[17]. Taste disturbances have also been described in people with rheumatoid arthritis; however, data is not sufficient to confirm this as a direct consequence of inflammation.

Nestlé Research considers the interaction between taste and inflammation as important in understanding the nature of changes which may occur during inflammation at both sensory and molecular levels. This knowledge will guide the development of foods and nutritional supplements to be adapted to the specific sensory profiles of patients – palatable food which provides optimal nutrition.

Work by Nestlé Research to decipher the interaction between molecular signal transduction pathways of taste and inflammation was rewarded through the discovery of intestinal "taste cells." It was observed that populations of solitary cells throughout the gastrointestinal tract express taste receptors and taste signalling elements such as umami and sweet receptors T1rs, the G-protein gustducin, and the cation channel Trpm5[18]. Interestingly, those cells also express inflammatory markers, including COX-1, COX-2, cytokines and chemokines, suggesting an interaction between inflammation and taste signalling. Preliminary data suggests that mice lacking Trpm5 have lower expression of inflammatory markers in the colon. Similar cells are found in the nasal epithelium and express bitter taste receptors (T2rs), gustducin and Trpm5. Recently, it was shown that stimulation of these bitter taste receptors with denatonium benzoate induces leakage of plasma albumin into the nasal epithelium and activates dendritic cells, therefore inducing an inflammatory and immune response in the nasal cavity. This effect disappears in mice lacking Trpm5 or gustducin[19].

Taste tissue expresses several inflammatory molecules and receptors such as Toll-like receptors, interleukins, and interferon receptors. Using a rodent model, Wang et al showed that inflammation activates the interferon signalling pathways in taste tissue, shortening the lifespan of taste bud cells[20]. Work by Nestlé researchers discovered that CCR6, the receptor for the cytokine CCL20 is expressed in type II taste cells, the subset of cells involved in the transduction of sweet, bitter and umami tastes and Nestlé is continuing the investigation of its physiological significance.

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Future Considerations

Much remains to be discovered about the intricacies of the immune system, especially pertaining to chronic inflammation, disease development and the effect of nutrition on these conditions. Nestlé is committed to the pursuit of scientific knowledge and technological advancements to leverage the benefits of food and nutrition for health, wellness and improved quality of life for people at all ages and stages of life.

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