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Cruciferous vegetables: prototypic anti-inflammatory food components

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Abstract

There is increasing evidence that food components contribute to the pathogenesis of various disorders such as inflammatory bowel diseases, atherosclerosis, cancer or type 2 diabetes. Dietary factors especially enriched in Western diet cause and promote inflammatory processes throughout the organism involving various pathways but mainly the induction of pro-inflammatory cytokines. In contrast, there is increasing evidence that certain food components such as present in cruciferous vegetables have important anti-inflammatory properties. Cruciferous vegetables contain large amounts of various indole derivatives and are able via these components to activate aryl hydrocarbon receptors (AhR). Activation of these intracellular receptors results in potent intestinal immune modulation including regulation and maintenance of intestinal intraepithelial lymphocytes and innate lymphoid cells, induction of the key barrier cytokine interleukin-22 and manipulation of the intestinal microbiota. Lack of AhR is associated with an impaired barrier function and increased intestinal vulnerability suggesting that the continuous presence of dietary AhR ligands may be of importance throughout life. Sulforaphane, an isothiocyanate compound of cruciferous vegetables, also exerts mainly anti-inflammatory properties on immune processes. Therefore, evidence is accumulating that certain food components are healthy by targeting intestinal immune responses and reshaping the microbiota.

Keywords: Anti-inflammatory; Carbazoles; Cruciferous plants; Isothiocyanates; Healthy food

Introduction

Diet is a well established risk factor for many disorders ranging from inflammatory bowel diseases (IBD), type 2 diabetes, atherosclerosis and various cancers [1]. The marked increase of many of these disorders has been paralleled in the last decades by changing habits regarding food consumption and overall industrialization. Epidemiological studies have revealed that many inflammatory conditions are associated with increased consumption of a Western diet enriched in saturated fatty acids, carbohydrates, refined grains, processed red meat and a low content of vegetables, fruits and fish. This diet is increasingly consumed worldwide and it is assumed that the spread of such dietary behaviors has contributed significantly to changing disease patterns as e.g. observed for IBD. Diets enriched in vegetables and fruits such as the Mediterranean diet have been proposed to provide health benefits [2]. Therefore, dietary components overall might have a major impact on disease pathogenesis and manifestation.

It is increasingly understood that dietary components interact with the host mainly by affecting and shaping the intestinal microbiota and immunity [3]. The interaction between food components and the gastrointestinal tract involves several components of the immune system including intestinal intraepithelial lymphocytes, innate lymphoid cells, immune mediators, epithelial cells and a heterogeneous group of immune cells including dendritic cells [1]. Molecular pathways used by both pathogens and dietary components such as the aryl hydrocarbon receptor (AhR) could be an example for understanding how diet affects and drives intestinal immunity [4–6]. The microbiota is the key factor determining development and maintenance of the intestinal and systemic immune response [7, 8]. The diet controls the dynamics and composition of the microbiota, and the relationship diet – microbiota – immunity is essential for human development and health. The contributions of the intestinal microbiota to development of immunity

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and respective effects of dietary components on its composition are complex and beyond the scope of this review. The adage "You are what you eat" is increasingly supported by scientific evidence. This article will briefly summarize aspects of pro-and anti-inflammatory food components focusing on healthy aspects of cruciferous vegetables.

Review

Inflammatory diets: potential mode of actions

The incidence of many chronic inflammatory disorders has changed dramatically in the last three to four decades. Many of those disorders such as IBD, rheumatoid arthritis, metabolic syndrome, and atherosclerosis, are characterized by continuous low-grade systemic inflammation. In most of those diseases environmental factors such as diet seem to play a major role as genetic factors can only explain the minority of cases. Western diets may promote inflammatory processes through various mechanisms. Fatty acids support inflammation through various mechanisms, including direct actions on immune cells, toll-like receptors (TLRs), and cytokine signaling, as well by affecting intestinal permeability [9, 10]. In healthy subjects, a high-fat Western diet results in endotoxemia and may thereby lead to low-grade systemic inflammation [11, 12]. A high fat diet (HFD) induces intestinal inflammation and the expression of tumor necrosis factor-alpha (TNF-α) in the ileum in obesity, and this effect is only observed in conventionally raised specific-pathogen free mice, but not in germ-free mice [13]. As a Western diet is enriched in polyunsaturated fatty acids (PUFA), this mechanism has also been shown to contribute to intestinal inflammation especially in older mice, as demonstrated by increased influx of neutrophils and macrophages [14]. Importantly, Western diet is especially enriched in n-6 PUFA and deficient in n-3 PUFA and it is assumed that the ratio of n-6 to n-3 PUFA in Western diet is an issue but not PUFA in general. Overall it can be concluded that Western diets affect immunity, promote inflammation, and these effects importantly also include major effects on the microbiota and metabolome via many pathways. All these effects may negatively influence human health and contribute to the disease burden which is caused by consumption of an imbalanced and rather "pro-inflammatory" Western diet. A more extensive discussion of these "pro-inflammatory" aspects of diet is beyond the focus of this article.

Anti-inflammatory diets: Cruciferous vegetables as prototypic proponents

Diet-derived indole derivatives as major activators of aryl hydrocarbon receptors (AhR)

A main question remains what happens in humans when they consume higher amounts of cruciferous vegetables. Jiang and colleagues [15] have studied the effects of vegetable intake in 1005 middle-aged Chinese women. Indeed, an increased intake of cruciferous vegetables was associated with decreased serum levels of the pro-inflammatory cytokines IL-1β, TNFα and IL-6 supporting the concept of many *in vitro* studies that this type of diet may have anti-inflammatory properties. As nutrition contributes substantially to disease development, it remains crucial and mandatory to better understand how diets enriched in vegetables and fruits might constitute anti-inflammatory effects. Aryl hydrocarbon receptor, a transcription factor expressed by immune cells, epithelial cells, and some tumor cells, has been identified as fundamental receptor for certain dietary components. Indeed, in the last years many exogenous and endogenous AhR ligands have been characterized—some derived from foods such as broccoli, other include phytochemicals, natural chemicals, and bacterial metabolites. Ligand binding activates the AhR, resulting in its translocation into the nucleus, where it dimerizes with the AhR nuclear translocator. This heterodimer regulates many genes that control immunity and inflammation, such as the important barrier cytokine IL-22, which has many beneficial metabolic functions [16].

Several studies published in the last few years have highlighted how dietary-derived AhR ligands affect local/systemic immunity. Specific components of certain vegetables of the family Brassicaceae (for example, broccoli, Brussel's sprouts or cabbage) are physiologic ligands of the AhR. Li et al. [5] observed that AhR signaling maintains numbers and functions of intraepithelial lymphocytes and innate lymphoid cells, and that AhR-deficiency increased epithelial vulnerability and immune activation in mice. AhR-deficiency furthermore affected the microbiota, and decreased intestinal production of granzymes A and B, C-type lectins, and matrix metalloproteinase-7, accompanied by a 4-fold increase in the proportion of *Bacteroidetes*. Interestingly, absence of AhR ligands increased severity of colitis in mice; when animals were fed with diet enriched in AhR ligands, observed alterations were reversed. Kiss et al. [6] showed that activation of AhR by dietary ligands is essential for post-natal expansion of certain innate lymphoid cells and the development of intestinal lymphoid follicles. Mice deficient in AhR exhibited an impaired intestinal immunity and were highly susceptible to infection with *Citrobacter rodentium*. AhR ligands increased numbers of IL-22-producing RORγt$^+$ intestinal lymphoid cells. These cells contribute in a major fashion to gastrointestinal innate immune functions such as the production of antimicrobial peptides and mucus and maintenance of epithelial integrity. Also other studies have shown that AhR is required for the production of IL-22, supporting the importance of this relationship [17]. The studies of Li et al.

[5] and Kiss [6] et al. provide evidence that some sort of "dietary pattern recognition receptors" might exist that link diet with intestinal immunity and the microbiota (Table 1).

The pathway between AhR ligands and IL-22 is highly relevant in the area of intestinal immunity and metabolism. Administration of IL-22 diminished metabolic defects and restored mucosal immunity to mice on HFDs, as well as in leptin receptor-deficient (*db/db*) mice [16]. Overall, dietary factors that activate the AhR have the capacity to affect expression of cytokines (particularly IL-22), synthesis of certain mucins, production of antimicrobial peptides, and consequently shape the intestinal barrier and furthermore the composition of the intestinal microbial community. Although findings of these two major studies are solely based on preclinical experimental data, they could have major clinical implications as (i) a continuous presence of beneficial dietary antigens might be needed in the intestinal tract to maintain functionality of the immune system including tolerance throughout life and (ii) if oral supplementation of such beneficial food components is interrupted such as observed in intensive care patients undergoing long-term parenteral nutrition this could severely impair local immunity, barrier function and at the end contribute to disease burden as observed in such patients.

Further beneficial examples for indole derivatives

Concentrations of carbazoles may be increased by other dietary compounds such as quercetin, resveratrol, and curcumin as demonstrated recently [18]. These compounds induce cytochrome P4501A1 in an indirect manner by inhibiting the metabolism of indole derivatives. Indole-3 carbinole (I3C) and its derivatives may also have beneficial effects on bone metabolism. An acid-condensation product of I3C, 3,3′-diindolymethane (DIM), prevents ovariectomized-induced bone loss by suppressing osteoclastic bone resorption [19]. Although not studied, it can be speculated that interference with the pro-inflammatory cytokine milieu in the bone as observed in osteoporosis might be one of those protective mechanisms. Administration of DIM also suppressed the nuclear factor kappaB (NF-κB) signaling pathway in microglia and protected cortical neurons from inflammatory toxicity [20]. When tested in mice, DIM attenuated LPS-induced brain inflammation in mouse hippocampus. Interestingly, in this model I3C did not show protective effects. When male C57BL/6 mice received a HFD and were treated intraperitoneally with I3C for 12 weeks, this resulted in a profound improvement of metabolic inflammation in adipose tissue by the substantial decrease of macrophage infiltration and their cytokine production [21].

Tryptophan: a dietary anti-inflammatory amino acid

The essential amino acid tryptophan is another nutrient also found in cruciferous vegetables which shows anti-inflammatory activities. Tryptophan is metabolized by the microbiota, e.g. *Lactobacilli,* to indole-3-aldehyde, another AhR agonist. This interaction is accompanied by induction of IL-22, which affected the microbiota, providing resistance to colonization by *Candida albicans* and protecting the mucosa against inflammation. This study therefore nicely highlights how another beneficial nutrient might results in gastrointestinal health again involving the microbiota and various immune pathways [22]. Tryptophan might exert anti-inflammatory effects via additional pathways such, as after conversion to kynurenine by indoleamine 2,3-dioxygenase (IDO). Both kynurenine and IDO have immunomodulatory functions that include promotion of regulatory T cells and

Table 1 Effects of anti-inflammatory diets on immunity

Anti-inflammatory	Foods	Microbiota-dependent	Potential pathways	Effects on Immunity	References
	cruciferous vegetables (carbazoles)	+ [a]	AhR ligands Suppression of NFκB	IL-22 ↑, maintenance of intraepithelial lymphocytes and innate lymphoid cells, suppression of inflammation	[5, 6]
	Cruciferous vegetables and fish (tryptophan)	+ [b]	AhR ligands GPCRs	IL-22 ↑, mucosal protection from inflammation	[5, 6, 17]
	cruciferous vegetables (sulfarophane)	?	Suppression of NFκB	Suppression of inflammation, induction of apoptosis, activation of phagocytosis	[23, 24]
	mediterrenian diet (enriched in ω-3 fatty acids)	?	Gpr120	pro-inflammatory cytokines ↓	[43]

Abbrevations
AhR aryl hydrocarbon receptor
GPCRs G-protein coupled receptors
NFκB Nuclear factor kappaB
Gpr G-protein receptor
SCFA short chain fatty acids
TH t helper cell
[a]Diet results in an altered microbiota
[b]Tryptophan metabolized by microbiota (e.g. lactobacilli) to indole-3 aldehyde and kynurenine (both AhR ligands)

regulation of immune tolerance. The tryptophan metabolite kynurenine is an additional tryptophan-derived ligand of the AhR. Beside indole derivates, several other plant products, such as flavonoids and polyphenols, also bind to the AhR — however with lower affinity. The AhR therefore can be viewed as a major anti-inflammatory factor that integrates dietary ("dietary pattern recognition receptors"), microbial, metabolic, and endogenous signals to alter the composition of the microbiota and elicit protective immune reactions (Table 1).

Other anti-inflammatory components of cruciferous vegetables

Sulforaphane (SFN), an isothiocyanate compound of cruciferous vegetables, protects from oxidative stress, inflammation and radiation injury. It inhibits LPS-induced monocyte adhesion via suppression of intercellular adhesion molecule-1 (ICAM-1) [23]. Furthermore, SCN also suppresses NF-κB activity in LPS-stimulated endothelial cells and these anti-inflammatory activities were dependent on intracellular glutathione levels. Such an inhibitory effect could also be observed in mouse peritoneal macrophages [24]. Interestingly, this anti-inflammatory effect was dependent on nuclear factor erythroid-2-related factor 2 (Nrf2) as it was not observed in Nrf2 (−/−) primary peritoneal macrophages. Nrf2 activates the transcription of more than 500 genes, most of which are protective and anti-inflammatory. Therefore, regulation of Nrf2 by isothiocyanates can be considered as an important aspect of its anti-inflammatory capacities. Nrf2 has been discussed to extend both healthspan and lifespan. Cruciferous vegetables can therefore be considered a diet with Nrf2-raising and therefore highly beneficial properties.

SFN is able to inhibit TNF-α-induced NF-κB activation through the inhibition of IκBα phosphorylation, IkBα degradation and p65 nuclear translocation [25]. This effect was paralleled by induction of apoptosis through activation of reactive oxygen species (ROS)-dependent caspase-3. Importantly, and this supports a relevant anti-inflammatory role for SFN, it also suppresses vascular cell adhesion molecule (VCAM)-1 in LPS-stimulated endothelial cells [26]. In these experiments, SFN decreased the phosphorylation of extra-cellular signal-regulated kinase (ERK), JUN N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK), all important inflammatory signaling cascades. In addition, SFN also affected TLR4 expression and suppressed MyD88, a key member of the signaling machinery of TLRs and the IL-1 pathway. Isothiocyanate suppresses LPS-induced synthesis of interferon-inducible protein-10 (IP-10) and phosphorylation of interferon regulatory factor 3 (IRF3) in RAW 264.7 cells [27]. Therefore, beneficial and anti-inflammatory effects of SFN might be mediated by various pathways including modulation of Toll-interleukin-1 receptor domain-containing adapter inducing interferon-beta (TRIF) signaling pathway of TLRs. SFN also shows anti-atherosclerotic activities as it inhibits endothelial lipase (EL) activity in endothelial cells [28]. Endothelial lipase is a member of the triacylglycerol lipase family released during inflammation and has the capacity to decrease high-density lipoprotein levels. Therefore, suppression of EL by SCF could contribute to an important systemic anti-inflammatory profile exerted by cruciferous vegetables (Table 1).

Overall, these data suggest that SFN and above described mechanisms might contribute to anti-inflammatory properties of cruciferous vegetables. SFN also affects phagocytosis capacity of macrophages as it raises the phagocytic activity of RAW 264.7 murine macrophages [29]. Activation of phagocytosis remains an important mechanism to reduce and clear inflammatory insults. Recently it has also been shown that SFN inactivates macrophage migration inhibitory factor (MIF), an important inflammatory cytokine [30]. SFN is also protective in animal models of inflammation as it increases the survival of rats with hepatic failure as achieved after administration of *D-galactosamine* and LPS [31]. These effects were potentially achieved by its potent capability to suppress synthesis of pro-inflammatory cytokines such as TNF-α and Fas and ROS. SFN has also chemopreventive properties. An excessive expression of cyclooxygenase-2 (COX-2) links inflammation and cancer and SFN indeed suppresses COX-2 in human mammary epithelial cells after stimulation with 12-O-tetradecanoylphorbol-13-acetate (TPA) [32]. These effects were again mainly NF-κB- and ERK-mediated as demonstrated in earlier studies.

Berteroin (5-methylthiopentyl isothiocyanate) is another compound of cruciferous vegetables which is mainly present in cabbage, rucola salad leaves and mustard oil. Berteroin also decreases LPS-induced pro-inflammatory cytokines in RAW 264.7 macrophages. In the mouse ear, berteroin suppressed TPA-induced edema formation by down-regulating COX-2, NF-κB and ERK [33]. These authors suggested that this compound could be developed as local anti-inflammatory agent.

Potential toxicological aspects of cruciferous vegetables

Some earlier experimental studies have suggested that indole derivatives might exert detrimental effects including promotion of tumour development. High doses of I3C, probably never achieved after consumption in humans, exhibit a dose-dependent toxicity including a decrease in hepatic reduced glutathione and severe neurological toxicity in mice [34]. In another study, I3C after administration over 52 weeks showed a tendency for an increase of liver adenomas in rats after challenge with

diethylnitrosamine and thyroid gland tumour incidence was increased significantly [35]. Indole derivatives promoted at high dietary levels aflatoxin B1—initiated hepatocarcinogenesis in rainbow trouts, an effect which was explained by the authors by the observed increase in estrogenic activities and induction of P450 isoenzymes [36]. Another study showed that I3C-treated rats developed fewer mammary adenocarcinomas but with a greater average weight per tumour per rat suggesting again that I3C might negatively affect tumour growth [37]. I3C has also been shown to up-regulate genes associated with signaling pathways for cell growth and proliferation suggesting that at least in this model I3C might result in a toxigenomic profile [38].

Human clinical data are not supportive of above experimental findings, although clinical trials focusing on the intake on cruciferous vegetables are rare. A recent meta-analysis suggested that consumption of cruciferous vegetables may reduce the risk of ovarian cancer [39]. In a large European cohort study, consumption of vegetables but not fruit was associated with a lower incidence of hepatocellular carcinoma [40]. A pooled analysis of three Italian case–control studies has demonstrated that a mediterranian diet reduces endometrial cancer risk [41]. A very large study from UK demonstrated that a diet enriched in vegetables and fresh fruits reduced both incidence of cardiovascular disease and cancer [42]. All these studies are in support of beneficial effects of vegetable consumption on human health, although more studies specifically addressing the effects of indole derivatives are needed.

Conclusions

There exists a crucial and exciting relationship between food, immunity, and the microbiota. Many dietary components affect these interactions. Dietary components exert either dominantly pro-or anti-inflammatory effects on the host. A healthy diet might contain a balanced mixture of pro- and anti-inflammatory dietary components. Knowledge in this field has increased dramatically in the last years. Key dietary players and their potential mechanisms have been characterized and how they might act harmful or beneficial on the host. Interventional studies have also demonstrated that dietary factors have strong effects on the microbiota and thereby might exert many immunomodulatory effects. However, it will be important to perform respective clinical studies in the next years to gain deeper mechanistic insights. Such studies could lead to development of functional foods, with beneficial and even therapeutic effects on the immune system. Therefore, food could in the future be used in clinical medicine to prevent and treat various diseases.

Competing interests

The author declares that he has no competing interests.

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