Nutrition and Dietary Supplements Dovepress

Open Access Full Text Article REVIEW

Immune Dysregulation Orchestrated by High-Salt Diet: Mechanistic Insights into Disease Pathogenesis

Li Chen[1,2], Xi-Le Peng[1,2], Zhi-Xuan Chen[1,2], Lu-Ming Qi[1,2], Ting-Ting Deng[2,3], Li-Na Xia[1,2]

[1]School of Health Preservation and Rehabilitation, Chengdu University of TCM, Chengdu, Sichuan, People's Republic of China; [2]Key Laboratory of Traditional Chinese Medicine Regimen and Health Industry Development, State Administration of TCM, Chengdu, Sichuan, People's Republic of China; [3]School of Nursing, Chengdu University of TCM, Chengdu, Sichuan, People's Republic of China

Correspondence: Li-Na Xia, School of Health Preservation and Rehabilitation, Chengdu University of TCM, Chengdu, Sichuan, People's Republic of China, Email xialina@cdutcm.edu.cn

Background: Excessive salt consumption has been associated with detrimental health consequences, including hypertension, colitis, and autoimmune disorders. However, recent studies have proposed that high salt diet (HSD) can both stimulate the immune system, affecting the differentiation of immune cells, promoting or inhibiting cytokine secretion to fight cancer or elicit a more potent autoimmune response, and exerting an immunosuppressive effect to influence disease development, providing mechanistic insights into the direction of immune regulation in which HSD affects disease.

Objective: This paper reviews the immunomodulatory effects of HSD on various innate immune and adaptive cells, especially macrophages, dendritic cells, and T cells, in relation to disease development.

Methods: We identified papers by electronically searching the Web of Science (WOS) database from inception through March 2023.

Results: A growing number of animal experiments and in vitro cell culture studies have shown that HSD can regulate the differentiation and activation of a variety of immune cells, and promote or inhibit different cytokines to mediate the development of a variety of diseases, including nephropathy, hypertension, cancer, inflammatory bowel disease, and a number of autoimmune diseases. These findings provide a new mechanism for pathological changes in the direction of immune regulation and suggest that HSD is a predisposing factor for a variety of diseases, providing new mechanistic insights into dietary health modification.

Conclusion: HSD mediates the development of multiple diseases by regulating the differentiation and activation of a variety of immune cells, and the underlying mechanisms may be related to gut microbes and their metabolites.

Keywords: HSD, immune dysregulation, disease pathogenesis, mechanistic insights, review

Introduction

Table salt is an essential component and an important ingredient in food. Salt can enhance the taste of food and increase its palatability. In Western countries, salt is often added to food and consumed in larger amounts than recommended. Numerous studies have shown that high salt intake is inversely correlated with human health,[1] leading to various conditions such as hypertension,[2] osteoporosis,[3] colitis,[4] kidney disease,[5] gastric cancer,[6] dementia,[7] obesity,[8] and more. High salt intake is a significant risk factor for numerous diseases and should be of great concern.

The immune system is a complex network of organs, cells, and proteins that protect the body from infection. This defense system is carried out by identifying and handling foreign objects. The network consists of the lymphatic system, complement system, spleen, thymus, bone marrow, and cells (white blood cells, B cells, T cells). Immune cells have a protective and preventive effect against pathogens that invade the host. The state of the immune environment is influenced by dietary factors. HSD has been shown to adversely affect autoimmune diseases by shifting immune cell balance to a pro-inflammatory state.[9,10] In addition to affecting effector T cells (Teff) responses, such as Th17 cells.[11,12] It has also been shown that HSD can also affect the function of regulatory T cells (Tregs).[13–17] Increased salt concentration favors the

Received: 6 August 2024
Accepted: 4 October 2024
Published: 11 October 2024

differentiation of CD4+T cells to pathogenic Th17 cells, which predispose to a variety of inflammatory diseases by regulating the immune environment.[18] In addition, high salt interferes with the mitochondrial respiration of Tregs, leading to the dysfunction of Tregs, and the "downtime" of Tregs increases the risk of many diseases.[19] Therefore, immune imbalance due to excessive salt intake is a key factor in triggering diseases. Thus, immune imbalance plays a key role in HSD-induced disease development. There is a need to further summarize the data linking HSD, the immune environment, and disease.

To date, many reviews have focused on the role of sodium in modulating immune cell function. Examine studies by Nicola Wilck et al[20] that have demonstrated a role for high extracellular salt in modulating the differentiation and function of innate and adaptive immune cell populations. Western diets are rich in salt. However, there is still a lack of discussion of recent studies on the intestinal immune imbalance induced by HSD in disease and its corresponding mechanisms. Therefore, this paper aims to systematically summarize the characteristics of HSD-induced immune imbalance in disease and reveal the potential mechanisms of interaction in the HSD model. The following sections systematically illustrate the effects of HSD-mediated immune imbalance with various diseases such as hypertension, nephropathy, cancer, and IBD and their corresponding mechanisms.

Material and Methods

All data related to high salt in the immune field reported in this paper were found using the advanced search function of the WOS core collection in March 2023, and the language is limited to "English". All data were analyzed using the local function of WOS. The potential search keywords are the following: TS = ((immune or immunity or inflammation) AND "high salt").

Results

HSD-induced immunity is closely associated with kidney disease, hypertension, cancer, inflammatory bowel disease, and autoimmune diseases. Animal experiments and in vitro cell culture studies provided evidence that HSD mediates diseases development by affecting immune cells and their secreted cytokines (Figure 1).

Influences of HSD on Immunity Toward Kidney Disease

Renal damage in Dahl salt-sensitive (Dahl SS) hypertension is attributed to oxidative stress and inflammation within the kidneys.[21,22] Infiltration of immune cells in the kidneys plays a crucial role in the pathogenesis of hypertension and renal

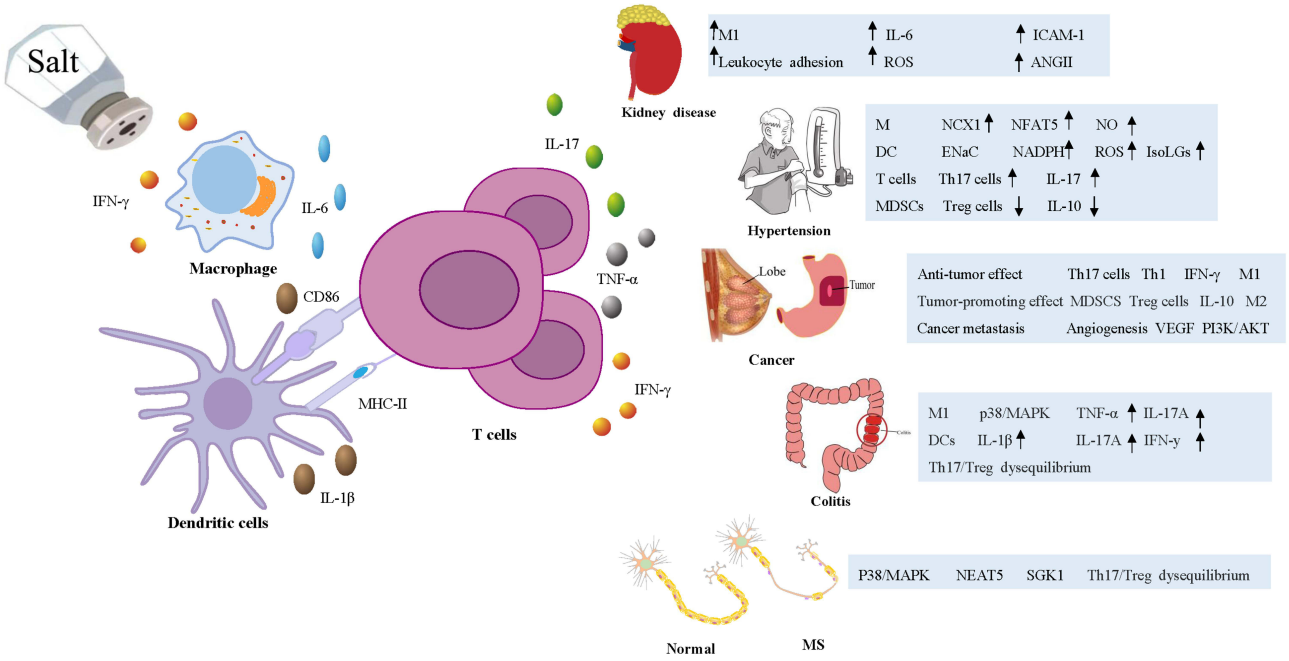

Figure 1 HSD-induced immunity is closely associated with kidney disease, hypertension, cancer, inflammatory bowel disease, and autoimmune diseases.

injury in Dahl SS rats.[23] Compared to Dahl SS rats on a low-salt diet, rats fed an HSD exhibit increased numbers of macrophages, T cells, and B cells in the kidneys, with the severity of hypertension and renal damage correlating with the presence of these immune cells.[24–27] High salt intake-induced T cell infiltration into the kidneys is significantly attenuated in RAG1-deficient rats, and the average arterial blood pressure and urinary albumin excretion rate are significantly lower in RAG1-null mutants than in SS rats. Furthermore, the glomerular and tubular damage in the kidneys of SS rats fed an HSD is also reduced in RAG1 mutants.[28] Experimental evidence demonstrates that treatment with immunosuppressive agents during high NaCl intake prevents T-cell infiltration in the kidneys and alleviates SS hypertension and renal injury in Dahl SS rats.[25,26,29,30] The current study suggests that T lymphocytes that infiltrate the kidney can participate in the development of SS hypertension and kidney disease in Dahl SS rats by increasing levels of free radicals in the kidney,[29] and oxygen radical scavengers can mitigate the progression of salt-induced hypertension and related kidney damage.[31] In kidney tissue from Dahl SS rats fed HSD, there was an association between increased T-cell infiltration, increased oxidative stress, and increased expression of NADPH oxidase.[29] Dahl SS rats (SSP 67 Phox) inhibited NADPH oxidase by p 67 Phox mutation, improving salt-induced hypertension, kidney damage, and kidney immune cell infiltration.[32] Long-term administration of immunosuppressants during periods of high salt intake reduces T lymphocyte infiltration, reduces the oxidative status and kidney expression of the NADPH oxidase subunit P67 Phox, and improves hypertension and kidney disease.[29] In addition, Antioxidant therapy administered to rats with Dahl SS resulted in a reduction of kidney inflammatory cytokines and chemokines, kidney immune cells, NF-kB, as well as arterial pressure, and improved kidney function and damage.[33]

Macrophage accumulation plays a key role in kidney injury.[34–36] In Liu's study, 5/6 NX rats receiving HSD exhibited strongly enhanced macrophage infiltration and activation in kidney tissue, accompanied by worsening kidney inflammation.[37] Emerging evidence indicates that high salt intake can independently stimulate the immune activation of macrophages via STAT1 and exacerbate renal inflammation, leading to kidney damage.[37] In the Dahl SS model, the addition of dietary salt has been shown to promote the conversion of kidney macrophages to the pro-inflammatory phenotype M1,[27] increase the production of pro-inflammatory cytokines (IL-6, TNF-α, IL-β), and the expression of chemokines (MCP-1, CXCL1, and CCR2).[37] Research has demonstrated that administering anti-IL-6 antibodies to Dahl SS rats attenuates the development of salt-sensitive hypertension and ensuing kidney damage,[38] indicating that an HSD potentially induces hypertension and associated renal damage by eliciting the release of the pro-inflammatory cytokine IL-6 from macrophages. In addition, IL-6 can produce intercellular adhesion molecule-1 (ICAM-1) by activating vascular endothelial cells, however, Takahashi's research shows that HSD rapidly increases leukocyte adhesion through overexpression of the ICAM-1.[39] Prostacyclin and nitric oxide are potent inhibitors of white blood cells, and levels of vasodilators such as prostacyclin and nitric oxide have been reported to be reduced, and levels of vasoconstrictors are elevated in Dahl SS rats. Increased leukocyte adhesion in prehypertensive prehypertension is responsible for subsequent kidney injury in rats with Dahl SS. In addition, an imbalance between endothelial cell adhesion, vasodilation, and vasoconstrictor substances may be responsible for early angiotensin-II-independent leukocyte adhesion.[40–43] It has been reported that Dahl SS rats are susceptible to angiotensin-induced kidney damage. Thus, the rapid increase in leukocyte adhesion caused by HSD may be associated with the high sensitivity of the renin-angiotensin system in Dahl SS rats.[44]

Neutrophils are the main immune effector against pyelonephritis.[45] The innate immune defense of urinary tract infections (UTIs) relies on neutrophils, which clear Urinary tract pathogenic E. coli (UPEC) through phagocytosis, as well as mononuclear phagocytes, such as macrophages or dendritic cells, which attract and activate neutrophils by chemokines and cytokines.[46–48] It has been shown that HSD suppresses intrarenal neutrophil NFAT5 by altering the local microenvironment (osmotic gradient of urea) and systemic glucocorticoid-mediated immunity. However, HSD does not enhance the response of neutrophils; rather, it systematically damages the antibacterial activity of neutrophils by changing hormones and metabolism.[45]

Influences of HSD on Immunity Toward Hypertension

Antigen-presenting cells (APCs), mainly including dendritic cells (DCs), monocytes (macrophages), and T cells, are the first responders to hypertension stimulation and drive T cell proliferation through antigen-MHC receptor interactions.[49]

High salt, as a strong stimulus of inflammatory activation and oxidative stress, can activate APCs,[50–53] and indirectly activate T cells, leading to hypertension by damaging blood vessel and kidney function.

The effects of DCs and hypertension are bidirectional, DCs not only aggravate hypertension, but hypertension enhances the activity and activation of DCs. Neoantigens produced by mechanical trauma of hypertension can activate DCs,[54,55] which are presented by DCs to T cells, and induce the production of pro-inflammatory cytokines and ROS,[54–57] further aggravating hypertension. Isolevuglandins (IsoLGs) are highly active products of lipid oxidation that form covalent bonds with lysine residues, resulting in post-translational modification of protein.[58] Related studies have shown that IsoLGs play an important role in promoting the activation of T cells and hypertension.[59] Transfer of isoketal-activated DCs into wild-type mice was shown to increase blood pressure,[59] and removal of IsoLGs reduces T-cell activation and prevents hypertension and end-organ damage.[59] It was demonstrated that in a murine model, elevated Na+ is a potent stimulus for the formation of IsoLGs adducts in DCs.[60] High salt intake increases the epithelial sodium channel (ENaC)-mediated sodium entry into DCs and exchanges with calcium (Ca2+) via Na+/Ca2+ exchangers. Ca2+ enters the activating protein kinase C (PKC), which in turn phosphorylates the NADPH oxidase subunit P47 phox.[60] This leads to NADPH oxidase activation, increased superoxide, and derived ROS.[60] The production of ROS leads to the formation of IsoLGs, the presentation of costimulatory factor CD86, and the secretion of pro-inflammatory factors IL-6, IL-1β, and IL-23.[61] Activated DCs promote T cell activation by accumulating IsoLGs and presenting them to T cells via MHC-II cell surface receptors, stimulating the production of IFN-γ and TNF-α (from CD8+ and CD4+Th1) and IL-17A (from γδ-T cells and CD4+Th17), resulting in vascular and renal dysfunction and salt-sensitive hypertension.[59,60] Van Bethescom et al demonstrated that salt can activate DCs through serum glucocorticoid kinase 1 (SGK1) and that the loss of SGK1 in DCs reduces salt-sensitive hypertension.[62] Mice lacking SGK1 expression in T cells are protected from ANGII infusion and DOCA salt-induced hypertension and eliminate hypertension-induced renal and vascular inflammation and end-organ damage.[63] IL-17 is a marker of inflammation produced by Th 17 cells. Studies have found that IL-17 acts on endothelial cells and leads to eNOS Thr 495 phosphorylation, which is mediated by RhoA/Rho kinases and leads to reduced NO production and reduced NO-mediated vasodilation,[64] leading to hypertension. Deletion of SGK1 in T cells eliminates an increase in the frequency of spleen Th 17 cells in response to ANGII infusion.[63] In addition, studies have shown that HSD can induce the production of Th 17 cells by reducing lactobacilli, resulting in hypertension in mice and humans.[65]

High-salt-activated monocytes/macrophages have a dual role in regulating vascular function and blood pressure. High sodium concentrations are recognized by macrophages as chemotactic stimuli in a dose-dependent manner.[66] Macrophages can sense high sodium concentrations via the sodium-calcium exchanger 1 (NCX 1), leading to macrophage activation followed by activation of the osmoprotective transcription factor nuclear factor of T cell 5 (NFAT5).[67] NFAT5 leads to increased NO production by nitric oxide synthase (NOS)-2 and the production of pro-inflammatory cytokines such as IL-1β, IL6, and TNF-α, which are released in high-salt reactions.[50] In addition, NFAT 5 triggers the secretion of vascular endothelial growth factor (VEGF)-C.[67,68] VEGF-C signaling, in turn, leads to VEGF receptor (VEGFR)3-dependent hyperplasia of the lymphatic capillary network, which enhances interstitial sodium clearance by improving drainage of interstitial fluid and electrolytes into the vascular ventricle. VEGF-C also stimulates the expression of endothelial nitric oxide synthase (eNOS) via VEGFR2 receptors, increases NO production, and acts as a direct compensatory vasodilation mechanism to buffer blood pressure increases due to excess extracellular volume.[68] In addition, disturbances in macrophage infiltration or VEGF-C signaling can increase blood pressure in rats on HSD.[68] Macrophages cause vascular dysfunction and hypertension by releasing ROS and pro-inflammatory cytokines in different tissues, including the vasculature, kidneys, and brain[69] In addition, Mahnik et al observed that high-salt treated rats acquired a pro-inflammatory macrophage(M1) response and also exhibited fluid retention, leading to hypertension.[70] Figure 2 shows the mechanism of HSD-induced immune disorders in kidney disease and Hypertension.

Myeloid-derived suppressor cells (MDSCs) are a group of immature myeloid cells that inhibit T cell activation as well as Th17 and Th1 cells,[71,72] MDSCs by inhibiting inducible nitric oxide synthase (iNOS), ROS, and peroxynitrite inhibit T cells function.[71] In addition, MDSC cells can induce the differentiation of Tregs by producing IL-10.[72]

The impact of the immune system on cardiovascular health includes not only hypertension, but macrophages have been shown to play a key role in the pathogenesis of atherosclerosis, acute myocardial infarction, and heart failure, highlighting the importance of myeloid cells for cardiovascular disease.[73] In addition, DCs are also involved in

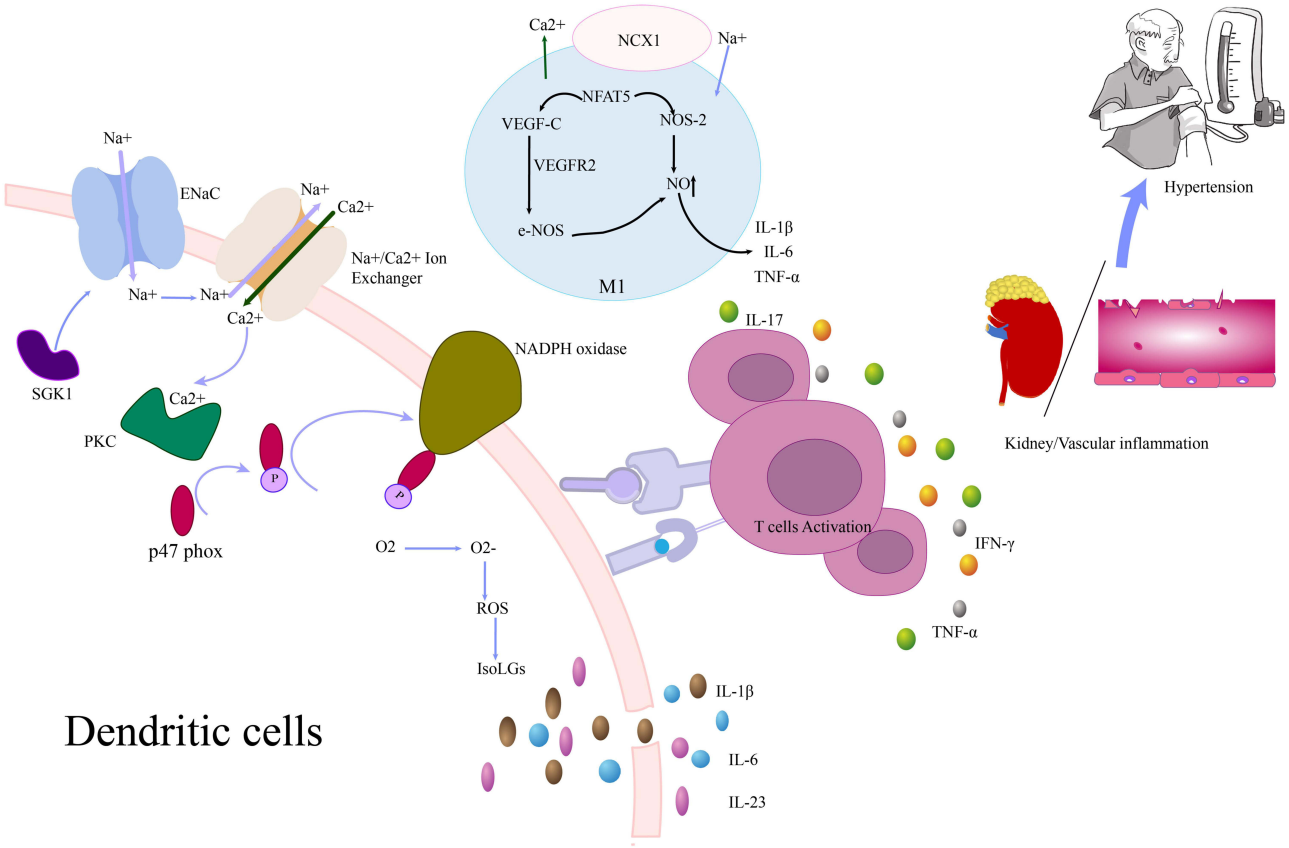

Figure 2 Influences of HSD on immunity toward hypertension and kidney disease: High salt intake increases sodium entry into dendritic cells through ENaC-mediated transport and exchanges with Ca^{2+} via the Na^{+}/Ca^{2+} exchanger. This leads to NADPH oxidase activation, increased O2- production, and generation of ROS, ultimately promoting the secretion of pro-inflammatory cytokines. Activated dendritic cells accumulate IsoLGs and present them to T cells via MHC-II cell surface receptors, thereby facilitating T cell activation and stimulating the production of IFN-γ, TNF-α, and IL-17A, resulting in vascular and renal dysfunction, as well as salt-sensitive hypertension. Furthermore, high levels of sodium activate macrophages through NCX1, subsequently activating NFAT5. NFAT5 triggers the secretion of VEGF-C and NOS-2, increasing the production of NO as a compensatory vasodilatory mechanism to mitigate the resulting increase in blood pressure.

cardiovascular remodeling,[74] and the elimination of DCs prevents the development of cardiac hypertrophy and perivascular fibrosis. Neutrophil gelatinase-associated lipocalin (NGAL) produced by DCs may play a key role in adaptive immune activation, leading to cardiovascular fibrosis caused by excessive mineralocorticoid hormone.

Influences of HSD on Immunity Toward Cancer

Chronic inflammation is a key hallmark of cancer development and progression.[75] The microenvironment of chronic inflammation can be induced by reactive oxygen/nitrogen species (ROS/RNS),[76] paracrine factors, or tumor-infiltrating cells, leading to sustained cell proliferation, DNA damage, or cancer transformation.[77] Inflammatory cytokines[78,79] and chemokines[80–82]provide beneficial signals that promote cancer cell proliferation[78,83] and tumor angiogenesis.[84] High salt intake serves as an effective inducer of pro-inflammatory states. In a high-salt environment, the immune balance between Th17 cells and Treg cells is disrupted. High salt intake induces the differentiation of Th17 cells and the production of inflammatory cytokines such as IL-1, IL-6, and IL-23, as well as inflammatory mediators including prostaglandins, leukotrienes, transforming growth factor (TGF), and iNOS.[85] iNOS is a recognized inflammatory marker and its upregulation has been associated with various cancers, including breast cancer.[86] Existing research suggests that IL-17 has both tumor-suppressive and tumor-promoting effects.[87] High salt intake has been shown to accelerate breast cancer growth, promote lung metastasis, and increase the levels of Th17 cells.[88] The elevated levels of Th17 cells, potentially through the secretion of IL-17F, can activate the MAPK signaling pathway in breast cancer cells, thereby promoting breast cancer growth.[88]

HSD can disrupt the balance of immune cells, promoting the induction of pro-inflammatory cells (such as helper Th17 cells and M1-like macrophages), while impairing the function of anti-inflammatory cells (such as M2-like macrophages and Tregs).[6,50,65] Current research indicates that high salt intake activates a pro-inflammatory Th17 phenotype in CD4+ T cells and polarizes anti-inflammatory CD4+FOXP3+Tregs towards an inflammatory Th1 phenotype.[13,89] This polarization is accompanied by the secretion of pro-inflammatory cytokine IFN-γ,[13,90,91] induction of M1,[92] and exertion of anti-tumor effects. Figure 3(a) shows an anti-tumor effect of HSD in the early stages of tumors. Myeloid-derived suppressor cells (MDSCs) play a pivotal role in tumor-induced immune tolerance.[93,94] Upon entering the tumor environment, M-MDSCs rapidly differentiate into tumor-associated macrophages (TAMs), leading to increased IL-10 secretion and impaired T-cell responses.[95,96] HSD may inhibit the production of Treg cells through the function of MDSC, thus activating anti-tumor immune surveillance and inhibiting tumor growth in mice.[97]

The effect of high salt on tumors may change with different stages of tumor growth. Salt exerts anti-tumor effects by activating the immune system leading to tumor elimination in the early stages, and then antagonizes these effects and has pro-tumor effects through immune exhaustion in the later stages.[98] During the initial stages of tumor growth, salt promotes tumor elimination through immune surveillance, whereas continued high-salt treatment can lead to the failure of CD4+ T cells.[99] Long-term in vitro treatment of human monocytes with high salt has resulted in M2 macrophage phenotypic switching, which is both anti-inflammatory and pro-tumor.[100] Long-term HSD may inhibit the formation of MDSCs in the tumor microenvironment, and when MDSCs are depleted, HSD plays a pro-tumor role.[101]

Tumor neo-angiogenesis is essential for tumor metastasis. VEGF induces tumor angiogenesis through activation of cancer-specific PI3K/Akt signaling mechanisms.[102] Inflammation-induced cellular stress induces the release of several growth factors, which induce neointima formation in tumors. Cancer cells metastasize to various parts of the body through these newly- formed blood vessels.[84] It has been shown that high salt induces an anti-inflammatory M2 phenotype in the tumor microenvironment,[100] M2 phenotype secretes pro-tumor IL-10 and VEGF.[84] In addition, high salt synergistically induces cancer cell proliferation, and RNS/ROS release and promotes angiogenic VEGF secretion with IL-17,[103,104] enhancing cancer cell metastasis.[105] Figure 3(b) shows the pro-tumor effects of HSD-induced immunomodulation in the tumor microenvironment.

Influences of HSD on Immunity Toward Inflammatory Bowel Diseases

IBD is a chronic, recurrent disorder that typically presents with ulcerative colitis (UC) and Crohn's disease (CD).[106] IBD is a high-risk factor for colorectal cancer and a serious threat to human health worldwide. Although its etiology is currently unknown, the findings of available studies suggest that IBD is a complex process involving genetics, environment, and immunity.[107–110] The results showed that HSD could exacerbate DSS and TNBS-induced colitis, leading to increased mortality in mice.[111,112]

Innate and adaptive immune cells play different roles in the pathogenesis of IBD. A large number of studies have shown that Th17, Th1, Tregs, and macrophages play an important role in the pathogenesis of IBD. For example, the number of Th17 cells in the lamina propria (LP) of the mucosa in colitis patients is significantly increased, resulting in IL-17, which causes mucosal damage and enhances disease activity.[113,114] Th1 polarization is associated with colon inflammation by inducing the production of IFN-γ and TNF-α, while different tendencies to develop colitis are associated with an inherent tendency of the immune system to produce Th1 or Th17/Treg responses.[115] Tregs are very important Tregs, highly expressing IL-10 in IBD and inhibiting inflammation.[116] In colitis patients, macrophages in the intestinal mucosa secrete cytokines TNF-α, IL-1, and IL-6.[117] Intestinal macrophages are the main population of APCS in the intestinal mucosa, and they determine the type of response of T cells to luminal antigens.[118] Excess salt leads to monocyte- and T-cell-driven inflammation, as well as parallel loss of immunoregulatory mechanisms involving the Th17 axis, M2 macrophages, and Tregs.[119]

Sodium chloride mediates the inflammatory effects of immune cells, which is very important for IBD. In one study, high salt content induced pro-inflammatory factor production by enhancing the signaling pathways of LPS-induced macrophage activation p38 and ERK1.[53] High NaCl pro-inflammatory factors in LPS and IFN-γ-activated laminar propria monocytes (LPMCs) rely on upregulation of the p38 mitogen-activated protein kinase (p38/MAPK) axis, and inhibition of p38/MAPK can effectively inhibit the production of inflammatory mediators.[120] HSD activates Th17 cells

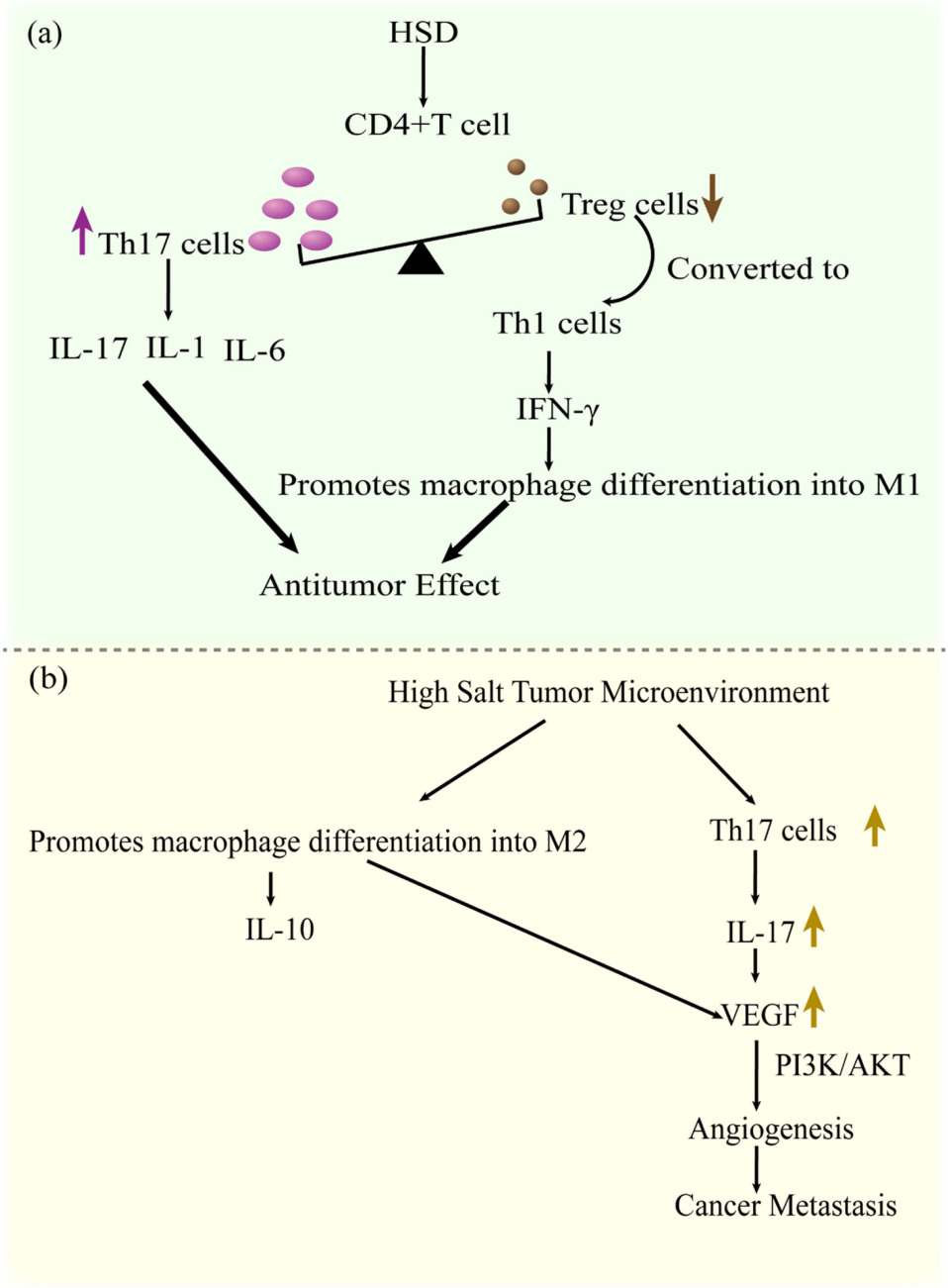

Figure 3 Influences of HSD on immunity toward cancer. (**a**) HSD exerts anti-tumor effects in the early stages of tumors: In the early stages of tumors, HSD activates CD4+ T cells to promote the pro-inflammatory Th17 phenotype and leads to the polarization of anti-inflammatory Tregs into an inflammatory Th1 phenotype. This results in the secretion of inflammatory cytokines such as IFN-γ, inducing the expression of pro-inflammatory M1 macrophages, and exerting an anti-tumor effect; (**b**) Protumor effects of HSD-mediated immunomodulation in the tumor microenvironment: In the later stages of tumor progression, HSD promotes the differentiation of macrophages into the M2 phenotype and induces the pro-inflammatory Th17 phenotype. This leads to increased secretion of pro-angiogenic VEGF, resulting in enhanced tumorigenicity and metastasis.

in vitro and in vivo by activating the p38/MAPK/NFAT 5 pathway and the SGK1 pathway of T cells.[12] In one study, exposing human LPMCs to high concentrations of NaCl enhanced TNF-α and IL17A release in a p38-dependent manner, and feeding mice a salt-rich diet exacerbated experimental colitis.[121] In addition, high NaCl enhances the expression of M1 proinflammatory gene in LPS-activated peritoneal macrophages, and colitis caused by high NaCl level may be the result of polarization of M1 macrophages. Therefore, HSD may enhance LPS and IFN-γ through activation, enhance M1 macrophage polarization, upregulate the p38/MAPK axis, and induce the production of pro-inflammatory factors, thereby

aggravating colitis. In addition, in mouse DCs, excess sodium increases IL-1β production, which promotes the production of pro-inflammatory cytokines such as IL-17A and IFN-γ by T cells.[119] Therefore, HSD-induced colitis is associated with the promotion of NaCl-promoting M1 macrophage polarization and IL-1β production in DCs, which in turn promotes Th17 polarization and the production of pro-inflammatory factors. Figure 4 shows the mechanism by which HSD mediates inflammation in IBD by inducing immune disorders.

Empirical evidence supports the notion that the consumption of HSD exerts a stimulatory effect on the Th17 immune response via the activation of caspase-1 in macrophages.[112,122] Th17 cells are present in the entire LP of the intestine,[123] and emerging evidence suggests that Th17 cells and related molecules play a critical role in the pathogenesis of IBD.[114,124,125] Existing research indicates that HSD promotes the activation of Th17 cells in the LP and exacerbates experimental colitis in mice.[112,121] The upregulation of IL-17A and IL-17F has been implicated in the development of IBD.[112,114,121,124,125] In animal models, knockout of the IL-17 receptor gene in mice prevents the development of IBD.[124] The orphan nuclear receptor (RORγt) is a key transcription factor that drives the development of CD4+ T cells to Th17 cells,[123,126] and we found that HSD significantly increased the expression of RORγt in SILP CD4+TCRβ+ cells. RORγt has been reported to control the production of IL-17A and IL-17F, thereby regulating the pathogenicity of mouse models of IBD.[112,114] As immunosuppressive cells, Tregs secrete a variety of cytokines, including anti-inflammatory factors represented by TGF-β and IL-10, which are crucial in maintaining intestinal homeostasis.[127] Studies have shown that HSD significantly inhibits IL-10 secretion and inhibitory function of Treg cells.[68,112] In β7-deficient mice treated with DSS, colonic Tregs are depleted, and the upregulation of ICAM-1 between colonic epithelial cells leads to excessive infiltration of macrophages in the colon, which promotes the expression of pro-inflammatory cytokines and aggravates DSS-induced colitis.[128] Disruption of balance may allow T cells to proliferate in an increased manner, thereby contributing to the development of chronic intestinal inflammation,[129] and HSD may increase the risk of IBD by impairing the intestinal Th17/Treg balance.

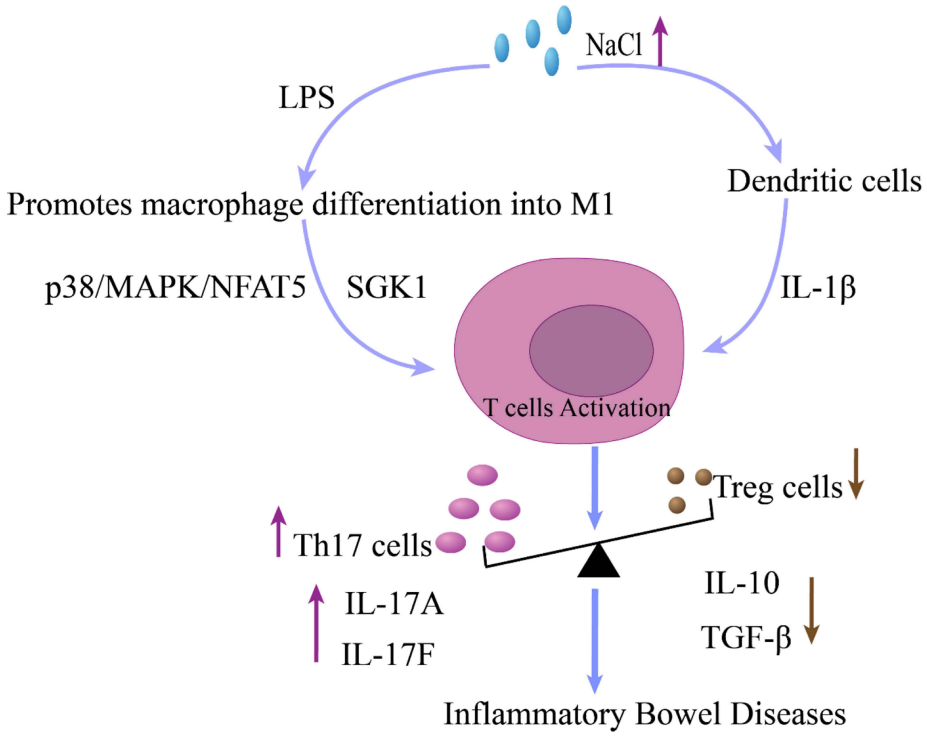

Figure 4 Influences of HSD on immunity toward IBD: HSD promotes the polarization of macrophages into the M1 phenotype and induces the production of IL-1β in DCs, thereby promoting the polarization of Th17 cells and the secretion of pro-inflammatory cytokines IL-17A and IL-17F, leading to the development of IBD.

In a cross-sectional study examining dietary intake patterns among 67 patients with remission-ending CD, it was observed that salt intake exceeded recommended levels in all study cohorts. Notably, both male and female individuals with Crohn's disease exhibited higher salt consumption compared to their respective control groups.[130] However, in a comprehensive women's health study investigating dietary habits and lifestyles, there was no clear evidence supporting a causal link between dietary salt intake and the occurrence of CD events.[131] Consequently, further human-based research endeavors are imperative to gain a more comprehensive understanding of the potential role of HSD in IBD.

Influences of HSD on Immunity Toward Autoimmune Disease

Autoimmune diseases, such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and IBD, showcase a strong association with HSD-induced immune dysregulation. In our earlier discussion, we elucidated the intricate mechanisms linking HSD-mediated immune disturbances with the pathogenesis of IBD. Moving forward, we aim to delve into the precise mechanisms through which HSD influences immunity in the context of multiple sclerosis, SLE, and RA.

MS is a chronic, inflammatory, autoimmune disease of the central nervous system (CNS)[132] characterized by the destruction of myelin sheath by autoreactive T cells and axons crossing the blood-brain barrier (BBB).[133,134] It is a disease that currently has no cure and causes motor, sensory, and cognitive deficits. In genetically predisposed individuals, environmental factors play an important role in the pathogenesis of MS.[135] High intake of sodium chloride is currently considered a potentially important factor in the onset of MS. EAE is one of the most commonly used animal models for MS, and it can be induced by active immunity of myelin peptides or passive transfer of myelin-responsive T cells.[136] More recently, in experimental autoimmune myelitis models (EAEs), increased NaCl intake has been shown to promote the development of Th 17 cells via the MAPK/P38 pathway[12] or by altering MAPK signaling in macrophages, promoting pro-inflammatory macrophage polarization, and exacerbating CNS autoimmunity.[137] In mouse studies, HSD altered the development of different cytokine-producing T-helper cell types, and HSD-aggravated EAE mice showed enhanced peripheral-induced pathogenic Th17 cell infiltration in CNS.[12,35] Sodium intake enhances the polarization of naive Th17 cells to pathogenic Th 17 cells lymphocytes by activating the p38/MAPK and SGK1 signaling pathways and drives the development of multiple sclerosis-like pathologies.[35,138] Studies have shown that excessive dietary sodium intake can induce an increase in the frequency of pro-inflammatory Th17 and Th1, as well as impaired function of Treg cells to affect autoimmunity.[139] It is generally believed that the autoimmune basis of MS stems from an imbalance between pro-inflammatory Th 1 and Th 17 cells and anti-inflammatory Tregs.[140] The role of the gut microbiota in this process was highlighted in one study, supplementing Lactobacillus murine to blunt salt-induced pathogenic Th17 cells and improving EAE deterioration.[65] DCs are specialized APCS that present antigens to T cells and initiate adaptive immunity.[141,142] However, in autoimmune neuroinflammation, evidence suggests that the effects of high salt on T cells are applied directly, rather than mediated by DCs.[143] This suggests that different immune cell subtypes respond differently to NaCl and that the production of a salt-induced pro-inflammatory environment involves a specific effect on immune cells rather than nonspecific activation of all lymphocytes and APCs.

Data from humans suggest that the effects of high salt on MS are controversial. One cohort study reported that high salt intake was associated with increased disease activity in MS.[144] Conversely, four other human studies found no association between HSD and MS progression.[145–147] In a randomized cross-intervention study on the effect of altering salt intake with human cytokines, high salt intake (or dietary changes) did not induce significant changes in any characteristic cytokines that controlled Th1, Th2, or Th17 polarization, nor were several other pro-inflammatory interleukins, chemokines, and growth factors affected by high salt intake, suggesting that clinically relevant changes in salt intake in humans do not reflect systemic concentrations of pro-inflammatory cytokines in the body.[148] In addition, a case-control study of MSin children and salt intake showed no strong association between dietary salt intake and the risk of developing MS in children, and salt intake may not play a significant role in susceptibility to MS among children.[146] Reasons for inconsistencies in clinical studies and studies using mouse models may include true species-specific differences in electrolyte metabolism and immune cell activation. In addition, the salt load used in mouse models and human HSDs is also significantly different, requiring high salt concentrations and exogenous Th-polarizing cytokines when human lymphocytes are polarized to the Th17 direction in a salt-absorbable manner in vitro.[13]

SLE is an autoimmune connective tissue disease characterized by increased production of various autoantibodies against autoantigens, mainly affecting women of childbearing age,[149–151] involving multiple systems. Lupus nephritis is one of the most

serious organ manifestations of SLE. The data showed that HSD accelerated lupus progression and increased mortality in MRL/LPR mice (mouse models of SLE).[152,153] The proportion of Th17/Treg is significantly increased in MRL/LPR mice fed HSD,[153] and a higher proportion of Tfh cells is observed in the spleen. High NaCl promotes autoimmunity through Tet2-induced DNA demethylation and differentiation of Tfh (follicular T helper cell) cells, thereby accelerating the development of SLE in experimental MRL/LPR mouse models[152] and demonstrating the key role of Tfh cells in autoantibody production and lupus pathogenesis.[154–158] In the lupus model, excess salt did not increase the number of DCs but significantly promoted the activation and maturation of DCs, increased antigen presentation of DCs, and the production of pro-inflammatory cytokines.[159] This enhancement of differentiation of various Th cell subsets, including Tfh cells, is subsequently achieved by modified DCs.[159] Furthermore, cells cultivated in high salt concentrations exhibited higher expression levels of the p38 gene.[12] The downstream target of the p38 gene is the nuclear factor that activates T cells, which triggers the production of IL-17.[160] IL-17 further enhances the production of pro-inflammatory mediators. According to studies, the intake of HSD speeds up the development of SLE by promoting immune activation in DCs via the p38/MAPK-STAT1 signaling pathway.[159]

RA is a chronic inflammatory joint disease that can lead to cartilage, bone damage, and disability.[161] Collagen-induced arthritis (CIA) and K/BxN serotransfer-induced arthritis (STIA) are mouse models of RA. CIA relies on both adaptive and innate immunity, while STIA mainly mimics the innate effector phase.[162] CIA mice fed HSD showed more severe arthritis, a higher proportion of Th17 cells in spleen cells, and increased IL-17 expression in the synovial membrane and intestine.[163] A study recruiting patients with RA and SLE showed that limiting dietary salt intake suppressed the pro-inflammatory response in patients with autoimmune diseases.[164] Figure 5 shows the mechanism by which HSD induces immune disorders to produce autoimmune diseases.

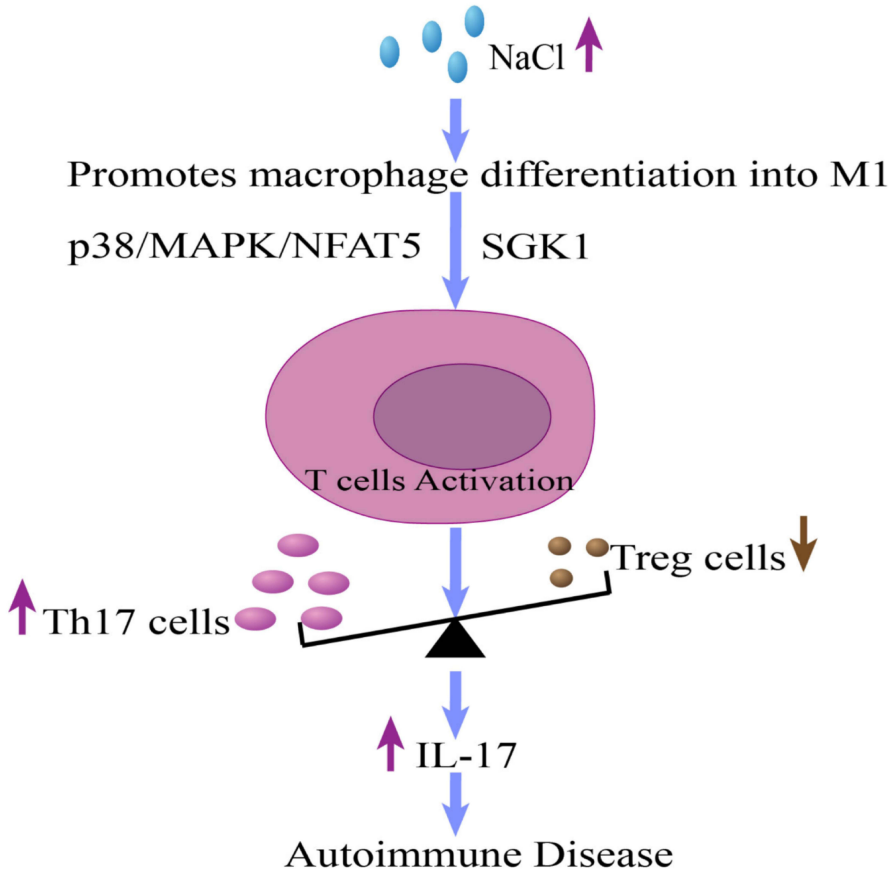

Figure 5 Influences of HSD on immunity toward autoimmune diseases: HSD promotes the polarization of macrophages into the M1 phenotype and enhances the polarization of naive T helper cells towards pathogenic Th17 cells through the activation of the p38/MAPK/NFAT5 and SGK1 signaling pathways. This results in the production of pro-inflammatory cytokine IL-17, leading to the development of autoimmune diseases.

Influences of HSD on Immunity Toward Other Diseases

HSD disrupts immune homeostasis, provoking a pro-inflammatory milieu that underlies the pathogenesis of multiple diseases. In murine models, HSD not only facilitates the expansion of bone-derived Th17 cells but also impedes the development of anti-bone-derived Treg cells. These perturbations in the host immune system perturb the delicate equilibrium between Treg and Th17 cell populations, consequently exacerbating bone loss and compromising bone microstructure integrity,[91] amplifying the risk of osteoporosis. In addition, HSD has been shown to inhibit the production of cerebral endothelial NO by inducing the synthesis of IL-17, the primary effector cytokine secreted by intestinal Th 17 cells. This effect results in cerebral hypoperfusion, neurovascular imbalance, and cognitive impairment in mice.[165] Furthermore, HSD can exacerbate ischemic stroke by reducing the expression of phagocytosis molecules expressed on triggering receptor expressed on myeloid cells 2a (TREM2) and inducing a pro-inflammatory phenotype in macrophages, leading to the delayed recovery of stroke lesions.[166] Additionally, HSD can worsen liver fibrosis by activating enterococcus-dependent macrophages, which can impair intestinal barrier function.[167] Studies have also shown that HSD can exacerbate food allergy in mice[168] and may be involved in the progression of atopic dermatitis by regulating the Th 2 response through sodium.[169] Therefore, it is crucial to further investigate the effects of HSD on various diseases and their underlying mechanisms to develop effective prevention and treatment strategies.

Discussion

This article highlights the potential role of HSD in triggering immune disorders that lead to various chronic diseases. The regulation of immune cell differentiation, activation, and function, induced by HSD, can ultimately contribute to the development of immune-mediated diseases like IBD, kidney disease, hypertension, cancer, and autoimmune diseases. This comprehensive review explores the intricate mechanisms underlying the impact of HSD on innate immune cells. It highlights the pivotal role of HSD in promoting macrophage differentiation and dendritic cell activation, enhancing their functionality as APCS. Furthermore, HSD exerts profound effects on T cells, driving their proliferation through antigen-MHC receptor interactions and influencing their differentiation towards Th17 cells. Concomitantly, HSD compromises the regulatory function of Treg cells, destabilizing immune homeostasis. This dysregulation is further accentuated by the upregulation of pro-inflammatory factors, including IL-17, and the concomitant decrease in anti-inflammatory factors such as IL-10. These intricate cellular and molecular processes collectively contribute to the altered disease development observed in response to HSD. Figures 2–5 elucidates the intricate interplay between HSD-mediated regulation of SGK1, NFAT5/TONEBP, and p38/MAPK signaling pathways, their impact on T cell differentiation, the delicate balance between Th17 and Treg cells, as well as the consequential release of pro-inflammatory and anti-inflammatory factors. The elucidated relationships provide valuable insights into the mechanistic underpinnings that drive the development and progression of various diseases.

Recent studies have highlighted the crucial role of the gut and gut microbiota in the adverse effects of high-salt conditions on immune cells.[170] Further investigation into the microbiome's involvement in salt-induced colitis exacerbation in a mouse model of IBD has revealed a decline in lactobacilli and butyrate, a potent anti-inflammatory agent, and an aggravation of colitis in mice fed an HSD.[4] Interestingly, this effect was absent in germ-free mice,[4] indicating the involvement of gut microbiota in the exacerbation of colitis. Additionally, HSD-induced reduction in lactobacilli has been shown to induce the production of Th 17 cells, leading to hypertension in mice and humans.[65] Therefore, future research should focus on exploring the mechanisms underlying the gut microbiota's response to high-salt conditions and its impact on immune function and disease pathogenesis. Such studies are essential in developing novel therapeutic strategies aimed at modulating the gut microbiota to prevent or treat salt-induced immune dysfunction and associated diseases.

While animal experiments suggest that HSD can lead to immune-mediated diseases, it is important to note that the impact of salt on immune cells may not always be pathogenic.[171] The effects of HSD on humans are complex and variable, depending on the cellular environment in local tissues and the types and stages of diseases. Salt has an anti-tumor effect by activating the immune system in the initial stage of tumors, while it exerts antagonistic and pro-tumor effects through immune exhaustion in the later stages.[98] Moreover, increased mesenchymal salt concentrations at the site of skin infection have been shown to enhance the bactericidal response of macrophages through NFAT5-dependent mechanisms, thereby promoting host defenses.[50] Thus, it is crucial to call for further high-quality research to investigate

the effects of HSD on immune cells and to determine the full range of its impact on human health. Future studies may focus on exploring the molecular pathways underlying the effects of HSD on gut microbes and their metabolites and investigating the development of effective interventions to prevent or treat immune-mediated diseases caused by HSD.

Conclusion

A high-salt diet is an environmental trigger for immune-mediated diseases that can increase tissue sodium concentrations, affect immune responses in the microenvironment, regulate the differentiation, activation and function of a wide range of immune cells, and thus influence the development of immune-regulatory disorders, including kidney disease, hypertension, cancer, inflammatory bowel disease, and some autoimmune diseases. The underlying mechanism may be related to gut microbes and their metabolites.

Abbreviations

HSD, high-salt diet; WOS, Web of Science; IBD, inflammatory bowel disease; Teff, effector T cells; Tregs, regulatory T cells; Dahl SS, Dahl salt-sensitive; ROS, reactive oxygen species; UTIs, urinary tract infections; UPEC, Urinary tract pathogenic E. coli; APCs, Antigen-presenting cells; DCs, dendritic cells; IsoLGs, Isolevuglandins; ENaC, epithelial sodium channel; PKC, protein kinase C; SGK1, serum glucocorticoid kinase 1; NCX 1, sodium-calcium exchanger 1; NFAT5, nuclear factor of T cell 5; NOS, nitric oxide synthase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; eNOS, endothelial nitric oxide synthase; M1, pro-inflammatory macrophage; iNOS, inducible nitric oxide synthase; NGAL, Neutrophil gelatinase-associated lipocalin; RNS, reactive nitrogen species; TGF, transforming growth factor; MDSCs, Myeloid-derived suppressor cells; IMCs, immature myeloid cells; M-MDSCs, monocyte-like bone marrow stromal cells; PMN-MDSCs, polymorphonuclear-like bone marrow stromal cells; TAMs, tumor-associated macrophages; UC, ulcerative colitis; CD, Crohn's disease; LP, lamina propria; DSS, dextran sodium sulfate; LPMCs, laminar propria monocytes; p38/MAPK, p38 mitogen-activated protein kinase; RORγt, orphan nuclear receptor; MS, multiple sclerosis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; CNS, central nervous system; BBB, blood-brain barrier; CIA, Collagen-induced arthritis; STIA, serotransfer-induced arthritis; TREM2, triggering receptor expressed on myeloid cells 2a.

Ethics Approval and Consent to Participate

This study did not involve the use of any animal or human data or tissue. It's not applicable.

Acknowledgments

This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-3450521/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (82274384) and Sichuan Science and Technology Program (20220302211605083).

Disclosure

The authors report no conflicts of interest in this work.

References

1. EFSA Panel on Nutrition NF, Allergens F, Turck D, Castenmiller J. et al. Dietary reference values for sodium. *EFSA j*. 2019;17(9):e05778. doi:10.2903/j.efsa.2019.5778.
2. Dahl LK. Effects of chronic excess salt feeding: induction of self-sustaining hypertension in rats. *J Exp Med*. 1961;114(2):231–236. doi:10.1084/jem.114.2.231
3. Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr*. 1995;62(4):740–745. doi:10.1093/ajcn/62.4.740
4. Miranda PM, De Palma G, Serkis V, et al. High salt diet exacerbates colitis in mice by decreasing Lactobacillus levels and butyrate production. *Microbiome*. 2018;6(1):1–17. doi:10.1186/s40168-018-0433-4
5. Ritz E, Koleganova N, Piecha G. Role of sodium intake in the progression of chronic kidney disease. *J Ren Nutr*. 2009;19(1):61–62. doi:10.1053/j.jrn.2008.10.007
6. D'Elia L, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P. Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clin Nutr*. 2012;31(4):489–498. doi:10.1016/j.clnu.2012.01.003
7. Hu L, Zhu S, Peng X, et al. High salt elicits brain inflammation and cognitive dysfunction, accompanied by alternations in the gut microbiota and decreased SCFA production. *J Alzheimers Dis*. 2020;77(2):629–640. doi:10.3233/JAD-200035
8. He FJ, Marrero NM, MacGregor GA. Salt intake is related to soft drink consumption in children and adolescents: a link to obesity? *Hypertension*. 2008;51(3):629–634. doi:10.1161/HYPERTENSIONAHA.107.100990
9. Müller DN, Wilck N, Haase S, Kleinewietfeld M, Linker RA. Sodium in the microenvironment regulates immune responses and tissue homeostasis. *Nat Rev Immunol*. 2019;19(4):243–254. doi:10.1038/s41577-018-0113-4
10. Manzel A, Muller DN, Hafler DA, Erdman SE, Linker RA, Kleinewietfeld M. Role of "Western diet" in inflammatory autoimmune diseases. *Curr Allergy Asthma Rep*. 2014;14(1):404. doi:10.1007/s11882-013-0404-6
11. Chuan W, Nir Y, Theresa T, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature*. 2013;496(7446):513–517. doi:10.1038/nature11984
12. Kleinewietfeld M, Manzel A, Titze J, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*. 2013;496(7446):518–522. doi:10.1038/nature11868
13. Hernandez AL, Kitz A, Wu C, et al. Sodium chloride inhibits the suppressive function of FOXP3+ regulatory T cells. *J Clin Invest*. 2015;125 (11):4212. doi:10.1172/JCI81151
14. Sumida T, Lincoln MR, Ukeje CM, et al. Activated β-catenin in Foxp3+ regulatory T cells links inflammatory environments to autoimmunity. *Nat Immunol*. 2018;19(12):1391–1402. doi:10.1038/s41590-018-0236-6
15. Safa K, Ohori S, Borges TJ, et al. Salt accelerates allograft rejection through serum-and glucocorticoid-regulated Kinase-1–dependent inhibition of regulatory T cells. *J Am Soc Nephrol*. 2015;26(10):2341–2347. doi:10.1681/ASN.2014090914
16. Yang YH, Istomine R, Alvarez F, et al. Salt sensing by serum/glucocorticoid-regulated kinase 1 promotes Th17-like inflammatory adaptation of Foxp3+ regulatory T cells. *Cell Rep*. 2020;30(5):1515–29.e4. doi:10.1016/j.celrep.2020.01.002
17. Luo Y, Xue Y, Wang J, et al. Negligible Effect of Sodium Chloride on the Development and Function of TGF-β-Induced CD4+ Foxp3+ Regulatory T Cells. *Cell Rep*. 2019;26(7):1869–79.e3. doi:10.1016/j.celrep.2019.01.066
18. Balan Y, Packirisamy RM, Mohanraj PS. High dietary salt intake activates inflammatory cascades via Th17 immune cells: impact on health and diseases. *Arch Med Sci*. 2022;18(1):459.
19. Côrte-Real BF, Hamad I, Hornero RA, et al. Sodium perturbs mitochondrial respiration and induces dysfunctional Tregs. *Cell Metab*. 2023;35 (2):299–315.e8. doi:10.1016/j.cmet.2023.01.009
20. Wilck N, Balogh A, Markó L, Bartolomaeus H, Müller DN. The role of sodium in modulating immune cell function. *Nat Rev Nephrol*. 2019;15 (9):546–558. doi:10.1038/s41581-019-0167-y
21. Lin L, Phillips WE, Manning Jr RD. Intrarenal angiotensin II is associated with inflammation, renal damage, and dysfunction in dahl salt-sensitive hypertension. *J Am Soc Hypertens*. 2009;3(5):306–314. doi:10.1016/j.jash.2009.08.002
22. Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. *Kidney Int*. 2003;63(5):1791–1800. doi:10.1046/j.1523-1755.2003.00929.x
23. Pechman KR, Basile DP, Lund H, Mattson DL. Immune suppression blocks sodium-sensitive hypertension following recovery from ischemic acute renal failure. *Am J Physiol Regul Integr Comp Physiol*. 2008;294(4):R1234–R9. doi:10.1152/ajpregu.00821.2007
24. Mattson DL. Infiltrating immune cells in the kidney in salt-sensitive hypertension and renal injury. *Am J Physiol Renal Physiol*. 2014;307(5): F499–F508. doi:10.1152/ajprenal.00258.2014
25. De Miguel C, Das S, Lund H, Mattson DL. T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. *Am J Physiol Regul Integr Comp Physiol*. 2010;298(4):R1136–R42. doi:10.1152/ajpregu.00298.2009
26. Mattson DL, James L, Berdan EA, Meister CJ. Immune suppression attenuates hypertension and renal disease in the Dahl salt-sensitive rat. *Hypertension*. 2006;48(1):149–156. doi:10.1161/01.HYP.0000228320.23697.29
27. Fehrenbach DJ, Abais-Battad JM, Dasinger JH, Lund H, Mattson DL. Salt-sensitive increase in macrophages in the kidneys of Dahl SS rats. *Am J Physiol Renal Physiol*. 2019;317(2):F361–F74. doi:10.1152/ajprenal.00096.2019
28. Mattson DL, Lund H, Guo C, Rudemiller N, Geurts AM, Jacob H. Genetic mutation of recombination activating gene 1 in Dahl salt-sensitive rats attenuates hypertension and renal damage. *Am J Physiol Regul Integr Comp Physiol*. 2013;304(6):R407–R14. doi:10.1152/ajpregu.00304.2012
29. Miguel CD, Guo C, Lund H, Feng D, Mattson DL. Infiltrating T lymphocytes in the kidney increase oxidative stress and participate in the development of hypertension and renal disease. *Am J Physiol Renal Physiol*. 2011;300(3):F734–F42. doi:10.1152/ajprenal.00454.2010
30. De Miguel C, Lund H, Mattson DL. High dietary protein exacerbates hypertension and renal damage in Dahl SS rats by increasing infiltrating immune cells in the kidney. *Hypertension*. 2011;57(2):269–274. doi:10.1161/HYPERTENSIONAHA.110.154302
31. Yoshio U, Yukari K, Nobuhito H, et al. Possible radical scavenging properties of cicletanine and renal protection in Dahl salt sensitive rats. *Am J Hypertens*. 1993;6(6_Pt_1):463–472. doi:10.1093/ajh/6.6.463
32. Abais-Battad JM, Lund H, Dasinger JH, Fehrenbach DJ, Mattson DL. NOX2-derived reactive oxygen species in immune cells exacerbates salt-sensitive hypertension. *Free Radic Biol Med*. 2019;146(333–339). doi:10.1016/j.freeradbiomed.2019.11.014

33. MRS TN, Braddy S, A RR, W GJ, D HM, Manning Jr RD. Interactions between oxidative stress and inflammation in salt-sensitive hypertension. *Am J Physiol Heart Circ Physiol*. 2007;293(6):H3388–H95. doi:10.1152/ajpheart.00981.2007
34. Eddy AA, Neilson EG. Chronic kidney disease progression. *J Am Soc Nephrol*. 2006;17(11):2964–2966. doi:10.1681/ASN.2006070704
35. Wu C, Yosef N, Thalhamer T, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature*. 2013;496 (7446):513–517.
36. Vernon MA, Mylonas KJ, Hughes J. Macrophages and renal fibrosis. *Semin Nephrol*. 2010;30(3):302–317. doi:10.1016/j.semnephrol.2010.03.004
37. Liu Y, Dai X, Yang S, Peng Y, Hou F, Zhou Q. High salt aggravates renal inflammation via promoting pro-inflammatory macrophage in 5/6-nephrectomized rat. *Life Sci*. 2021;274:119109. doi:10.1016/j.lfs.2021.119109
38. Hashmat S, Rudemiller N, Lund H, Abais-Battad JM, Van Why S, Mattson DL. Interleukin-6 inhibition attenuates hypertension and associated renal damage in Dahl salt-sensitive rats. *Am J Physiol Renal Physiol*. 2016;311(3):F555–F61. doi:10.1152/ajprenal.00594.2015
39. Takahashi H, Nakagawa S, Wu Y, et al. A high-salt diet enhances leukocyte adhesion in association with kidney injury in young Dahl salt-sensitive rats. *Hypertens Res*. 2017;40(11):912–920. doi:10.1038/hr.2017.31
40. Barton M, Vos I, Shaw S, et al. Dysfunctional renal nitric oxide synthase as a determinant of salt-sensitive hypertension: mechanisms of renal artery endothelial dysfunction and role of endothelin for vascular hypertrophy and glomerulosclerosis. *J Am Soc Nephrol*. 2000;11(5):835–845. doi:10.1681/ASN.V115835
41. Lindemann S, Gierer C, Darius H. Prostacyclin inhibits adhesion of polymorphonuclear leukocytes to human vascular endothelial cells due to adhesion molecule independent regulatory mechanisms. *Basic Res Cardiol*. 2003;98(1):8–15. doi:10.1007/s00395-003-0383-1
42. Kubes P, Suzuki M, Granger D. Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci*. 1991;88(11):4651–4655. doi:10.1073/pnas.88.11.4651
43. Moazzam F, DeLano FA, Zweifach BW, Schmid-Schönbein GW. The leukocyte response to fluid stress. *Proc Natl Acad Sci*. 1997;94 (10):5338–5343. doi:10.1073/pnas.94.10.5338
44. Asagami T, Reaven GM, Tsao PS. Enhanced monocyte adherence to thoracic aortae from rats with two forms of experimental hypertension. *Am J Hypertens*. 1999;12(9 Pt 1):890–893. doi:10.1016/S0895-7061(99)00072-2
45. Jobin K, Stumpf NE, Schwab S, et al. A high-salt diet compromises antibacterial neutrophil responses through hormonal perturbation. *Sci Transl Med*. 2020;12(536):eaay3850. doi:10.1126/scitranslmed.aay3850
46. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13(5):269. doi:10.1038/nrmicro3432
47. WC SM, Franken L, Gutweiler S, Dixit A, Meyer-Schwesinger C, Engel DR. Crosstalk between sentinel and helper macrophages permits neutrophil migration into infected uroepithelium. *Cell*. 2014;156(3):456–468. doi:10.1016/j.cell.2014.01.006
48. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol*. 2013;13(3):159–175. doi:10.1038/nri3399
49. Kambayashi T, Laufer TM. Atypical MHC class II-expressing antigen-presenting cells: can anything replace a dendritic cell? *Nat Rev Immunol*. 2014;14(11):719–730. doi:10.1038/nri3754
50. Jantsch JJ, Schatz V, Friedrich D, Schröder A, Kopp C, Siegert I. Cutaneous Na+ storage strengthens the antimicrobial barrier function of the skin and boosts macrophage-driven host defense. *Cell Metab*. 2015;21(3):493–501. doi:10.1016/j.cmet.2015.02.003
51. Mcmaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, Immunity, and Hypertensive End-Organ Damage. *Circ Res*. 2015;116 (6):1022–1033. doi:10.1161/CIRCRESAHA.116.303697
52. Buqing Y, Jens T, Marina R, et al. Effects of dietary salt levels on monocytic cells and immune responses in healthy human subjects: a longitudinal study. *Transl Res*. 2015;166(1):103–110. doi:10.1016/j.trsl.2014.11.007
53. Zhang WC, Zheng XJ, Du LJ, et al. High salt primes a specific activation state of macrophages, M(Na). *Cell Res*. 2015;25(008):893–910. doi:10.1038/cr.2015.87
54. Titze J, Shakibaei M, Schafflhuber M, Schulze-Tanzil G, Hilgers KF. Glycosaminoglycan polymerization may enable osmotically inactive Na+ storage in the skin. *Am J Physiol Heart Circ Physiol*. 2004;287(1):H203–8. doi:10.1152/ajpheart.01237.2003
55. Schafflhuber M, Volpi N, Dahlmann A, Hilgers KF, Titze J. Mobilization of osmotically inactive Na+ by growth and by dietary salt restriction in rats. *Am J Physiol Renal Physiol*. 2007;292(5):F1490–500. doi:10.1152/ajprenal.00300.2006
56. Shapiro L, Dinarello CA. Osmotic regulation of cytokine synthesis in vitro. *Proc Natl Acad Sci*. 1995;92(26):12230–12234. doi:10.1073/pnas.92.26.12230
57. Shapiro L, Dinarello CA. Hyperosmotic stress as a stimulant for proinflammatory cytokine production. *Exp Cell Res*. 1997;231(2):354–362. doi:10.1006/excr.1997.3476
58. Iyer RS, Ghosh S, Salomon RG. Levuglandin E2 crosslinks proteins. *Prostaglandins*. 1989;37(4):471–480. doi:10.1016/0090-6980(89)90096-8
59. Kirabo A, Fontana V, De Faria AP, et al. DC isoketal-modified proteins activate T cells and promote hypertension. *J Clin Invest*. 2014;124 (10):4642–4656. doi:10.1172/JCI74084
60. Barbaro NR, Foss JD, Kryshtal DO, et al. Dendritic cell amiloride-sensitive channels mediate sodium-induced inflammation and hypertension. *Cell Rep*. 2017;21(4):1009–1020. doi:10.1016/j.celrep.2017.10.002
61. Elijovich F, Laffer CL, Sahinoz M, Pitzer A, Ferguson JF, Kirabo A. The gut microbiome, inflammation, and salt-sensitive hypertension. *Curr Hypertens Rep*. 2020;22(10):1–5. doi:10.1007/s11906-020-01091-9
62. van Beusecum JPB, Natalia R, McDowell Z, et al. High Salt Activates CD11c(+) Antigen-Presenting Cells via SGK (Serum Glucocorticoid Kinase) 1 to Promote Renal Inflammation and Salt-Sensitive Hypertension. *Hypertension*. 2019;74(3):555–563. doi:10.1161/HYPERTENSIONAHA.119.12761
63. Norlander AE, Saleh MA, Pandey AK, Itani HA, Madhur MS. A salt-sensing kinase in T lymphocytes, SGK1, drives hypertension and hypertensive end-organ damage. *JCI Insight*. 2017;2(13):e92801. doi:10.1172/jci.insight.92801
64. Nguyen H, Chiasson VL, Chatterjee P, Kopriva SE, Young KJ, Mitchell BM. Interleukin-17 causes Rho-kinase-mediated endothelial dysfunction and hypertension. *Cardiovasc Res*. 2013;97(4):696. doi:10.1093/cvr/cvs422
65. Wilck MN, Kearney MG, Olesen SM, Forslund SW. Salt-responsive gut commensal modulates TH17 axis and disease Link. *Nature*. 2017;551 (7682):585–589. doi:10.1038/nature24628

66. Hemmersbach R, Quast T, Klotz L, Schroeder A, Gerzer R. Salt-dependent chemotaxis of macrophages. *PLoS One*. 2013;8(9):e73439. doi:10.1371/journal.pone.0073439
67. Neubert P, Homann A, Wendelborn D, et al. NCX1 represents an ionic Na+ sensing mechanism in macrophages. *PLoS Biol*. 2020;18(6): e3000722. doi:10.1371/journal.pbio.3000722
68. Machnik A, Neuhofer W, Jantsch J, et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med*. 2009;15(5):545. doi:10.1038/nm.1960
69. Rucker AJ, Rudemiller NP, Crowley SD. Salt, Hypertension, and Immunity. *Annu Rev Physiol*. 2018;80(1):283–307. doi:10.1146/annurev-physiol-021317-121134
70. Machnik A, Dahlmann A, Kopp C, et al. Mononuclear Phagocyte System Depletion Blocks Interstitial Tonicity-Responsive Enhancer Binding Protein/Vascular Endothelial Growth Factor C Expression and Induces Salt-Sensitive Hypertension in Rats. *Hypertension*. 2010;55(3):755–761. doi:10.1161/HYPERTENSIONAHA.109.143339
71. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol*. 2009;9(3):162. doi:10.1038/nri2506
72. Park MJ, Lee SH, Kim EK, et al. Interleukin-10 produced by myeloid-derived suppressor cells is critical for the induction of Tregs and attenuation of rheumatoid inflammation in mice. *Sci Rep*. 2018;8(1):3753. doi:10.1038/s41598-018-21856-2
73. Nahrendorf M. Myeloid cell contributions to cardiovascular health and disease. *Nat Med*. 2018;24(6):711–720. doi:10.1038/s41591-018-0064-0
74. Araos P, Lozano C, Figueroa M, et al. Dendritic cells are crucial for cardiovascular remodeling and modulate neutrophil gelatinase-associated lipocalin expression upon mineralocorticoid receptor activation. *J Hypertens*. 2019;37(7):1482–1492. doi:10.1097/HJH.0000000000002067
75. Gabriele M, Michael M, Jürgen R. Chronic Inflammation in Cancer Development. *Front Immunol*. 2011;2:98. doi:10.3389/fimmu.2011.00098
76. Colotta F, Allavena P, Sica A, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis*. 2009;30(7):1073–1081. doi:10.1093/carcin/bgp127
77. Tait BD, Hudson F, Cantwell L, Brewin G, Jose M. Review article: luminex technology for HLA antibody detection in organ transplantation. *Nephrology*. 2008;14(2):247–254. doi:10.1111/j.1440-1797.2008.01074.x
78. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer*. 2004;4(1):11–22. doi:10.1038/nrc1252
79. Svetkey LP, Chen YT, Mckeown SP, Preis L, Wilson AF. Preliminary Evidence of Linkage of Salt Sensitivity in Black Americans at the 2-Adrenergic Receptor Locus. *Hypertension*. 1997;29(4):918–922. doi:10.1161/01.HYP.29.4.918
80. Niedzwiecki A. Modulation of MMP-2 and MMP-9 by cytokines, mitogens and inhibitors in lung cancer and malignant mesothelioma cell lines. *Oncol Rep*. 2009;22(06):1283–1291. doi:10.3892/or_00000566
81. Vindrieux D, Escobar P, Lazennec G. Emerging roles of chemokines in prostate cancer. *Endocr Relat Cancer*. 2009;16(3):663. doi:10.1677/ERC-09-0109
82. Tiriveedhi V, Takenaka M, Ramachandran S, et al. T regulatory cells play a significant role in modulating MHC class I antibody-induced obliterative airway disease. *Am J Transplant*. 2012;12(10):2663–2674. doi:10.1111/j.1600-6143.2012.04191.x
83. Chulpanova DS, Kitaeva KV, Green AR, Rizvanov AA, Solovyeva VV. Molecular Aspects and Future Perspectives of Cytokine-Based Anti-cancer Immunotherapy. *Front Cell Dev Biol*. 2020;8:8. doi:10.3389/fcell.2020.00008
84. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646. doi:10.1016/j.cell.2011.02.013
85. Puebla C-V, Assis F, Araújo LF, et al. iNOS Activity Modulates Inflammation, Angiogenesis, and Tissue Fibrosis in Polyether-Polyurethane Synthetic Implants. *Mediators Inflamm*. 2015;2015(1):138461. doi:10.1155/2015/138461
86. Lechner M, Lirk P, Rieder J. Inducible nitric oxide synthase (iNOS) in tumor biology: the two sides of the same coin. *Semin Cancer Biol*. 2005;15(4):277–289. doi:10.1016/j.semcancer.2005.04.004
87. Bailey SR, Nelson MH, Himes RA, Li Z, Mehrotra S, Paulos CM. Th17 cells in cancer: the ultimate identity crisis. *Front Immunol*. 2014;5 (5):276. doi:10.3389/fimmu.2014.00276
88. Chen J, Liu X, Hongyan H, Fangfang Z, Yongjun L, Hai H. High salt diet may promote progression of breast tumor through eliciting immune response. *Int Immunopharmacol*. 2020;87(1):106816. doi:10.1016/j.intimp.2020.106816
89. Luo T, Ji WJ, Yuan F, Guo ZZ, Li YM. Th17/Treg Imbalance Induced by Dietary Salt Variation Indicates Inflammation of Target Organs in Humans. *Sci Rep*. 2016;6(1):26767. doi:10.1038/srep26767
90. Ma P, Zha S, Shen X, Zhao Y, Liu W. NFAT5 mediates hypertonic stress-induced atherosclerosis via activating NLRP3 inflammasome in endothelium. *Cell Commun Signal*. 2019;17(1):102. doi:10.1186/s12964-019-0406-7
91. Dar HY, Singh A, Shukla P, et al. High dietary salt intake correlates with modulated Th17-Treg cell balance resulting in enhanced bone loss and impaired bone-microarchitecture in male mice. *Sci Rep*. 2018;8(1):2503. doi:10.1038/s41598-018-20896-y
92. Lewis CE, Pollard JW. Distinct Role of Macrophages in Different Tumor Microenvironments. *Cancer Res*. 2006;66(2):605–612. doi:10.1158/0008-5472.CAN-05-4005
93. Ouzounova M, Lee E, Piranlioglu R, et al. Monocytic and granulocytic myeloid derived suppressor cells differentially regulate spatiotemporal tumour plasticity during metastatic cascade. *Nat Commun*. 2017;8(1):14979. doi:10.1038/ncomms14979
94. Bauer R, Udonta F, Wroblewski M, et al. Blockade of myeloid-derived suppressor cell expansion with all-trans retinoic acid increases the efficacy of anti-angiogenic therapy. *Cancer Res*. 2018;78(12):3220–3232. doi:10.1158/0008-5472.CAN-17-3415
95. Yang L, Laura M, DeBusk K, et al. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. *Cancer Cell*. 2004;6(4):409–421. doi:10.1016/j.ccr.2004.08.031
96. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol*. 2012;12(4):253–268. doi:10.1038/nri3175
97. He W, Xu J, Mu R, Li Q, Dong L. High-salt diet inhibits tumour growth in mice via regulating myeloid-derived suppressor cell differentiation. *Nat Commun*. 2020;11(1):1732.
98. Allu AS, Tiriveedhi V. Cancer salt nostalgia. *Cells*. 2021;10(6):1285. doi:10.3390/cells10061285
99. Tiriveedhi V, Ivy MT, Myles EL, Zent R, Titze J. Ex Vivo High Salt Activated Tumor-Primed CD4+T Lymphocytes Exert a Potent Anti-Cancer Response. *Cancers*. 2021;13(7):1690. doi:10.3390/cancers13071690
100. Amara S, Whalen M, Tiriveedhi V. High salt induces anti-inflammatory MΦ2-like phenotype in peripheral macrophages. *Biochem Biophys Rep*. 2016;7:1–9. doi:10.1016/j.bbrep.2016.05.009

101. Hamad I, Willebrand R, Van Z, et al. High Salt Inhibits Tumor Growth by Enhancing Anti-tumor Immunity. *Front Immunol*. 2019;49:693.
102. Pidgeon GP, Barr MP, Harmey JH, Foley DA, Bouchier-Hayes DJ. Vascular endothelial growth factor (VEGF) upregulates BCL-2 and inhibits apoptosis in human and murine mammary adenocarcinoma cells. *Br J Cancer*. 2001;85(2):273–278. doi:10.1054/bjoc.2001.1876
103. Myles E, Amara L, Suneetha T, et al. Sodium channel gamma ENaC mediates IL-17 synergized high salt induced inflammatory stress in breast cancer cells. *Cell Immunol*. 2016;302:1–10. doi:10.1016/j.cellimm.2015.12.007
104. Amara S, Alotaibi D, Tiriveedhi V. NFAT5/STAT3 interaction mediates synergism of high salt with IL-17 towards induction of VEGF-A expression in breast cancer cells. *Oncol Lett*. 2016;12(2):933–943. doi:10.3892/ol.2016.4713
105. Wu X, Yang T, Liu X, Guo JN, Yang H. IL-17 promotes tumor angiogenesis through Stat3 pathway mediated upregulation of VEGF in gastric cancer. *Tumour Biol*. 2016;37(4):5493–5501. doi:10.1007/s13277-015-4372-4
106. Astó E, Méndez I, Audivert S, Farran-Codina A, Espadaler J. The Efficacy of Probiotics, Prebiotic Inulin-Type Fructans, and Synbiotics in Human Ulcerative Colitis: a Systematic Review and Meta-Analysis. *Nutrients*. 2019;11(2):293. doi:10.3390/nu11020293
107. Boedeker EC. Gut microbes, the innate immune system and inflammatory bowel disease: location, location, location. *Curr Opin Gastroenterol*. 2007;23(1):1–3. doi:10.1097/MOG.0b013e328011b837
108. Van Limbergen J, Russell RK, Nimmo ER, et al. Genetics of the innate immune response in inflammatory bowel disease. *Inflamm Bowel Dis*. 2007;13(3):338–355. doi:10.1002/ibd.20096
109. Ianiro G, Bibbo S, Scaldaferri F, Gasbarrini A, Cammarota G. Fecal Microbiota Transplantation in Inflammatory Bowel Disease: beyond the Excitement. *Medicine*. 2014;93(19):e97. doi:10.1097/MD.0000000000000097
110. Dutta AK. Influence of environmental factors on the onset and course of inflammatory bowel disease. *World J Gastroenterol*. 2016;22(3):1088–1100. doi:10.3748/wjg.v22.i3.1088
111. Tubbs AL, Liu B, Rogers TD, Sartor RB, Mia EA. Dietary Salt Exacerbates Experimental Colitis. *J Immunol*. 2017;199(3):1051–1059. doi:10.4049/jimmunol.1700356
112. Wei Y, Lu C, Chen J, Cui G, Diao H. High salt diet stimulates gut Th17 response and exacerbates TNBS-induced colitis in mice. *Oncotarget*. 2016;8(1):70–82. doi:10.18632/oncotarget.13783
113. Jiang W, Su J, Zhang X, Cheng X, Zhang H. Elevated levels of Th17 cells and Th17-related cytokines are associated with disease activity in patients with inflammatory bowel disease. *Inflamm Res*. 2014;63(11):943–950. doi:10.1007/s00011-014-0768-7
114. Gheorghe H, Neurath MF, Jonas M. Functional relevance of T helper 17 (Th17) cells and the IL-17 cytokine family in inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(1):180–186. doi:10.1002/ibd.21677
115. Fangli Y, Danan W, Yan L, et al. Th1/Th2 Balance and Th17/Treg-Mediated Immunity in relation to Murine Resistance to Dextran Sulfate-Induced Colitis. *J Immunol Res*. 2017;2017:1–11.
116. Groux H, O'Garra A, Bigler M, et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature*. 1997;389(6652):737–742. doi:10.1038/39614
117. Nobuhiko K, Tadakazu H, Susumu O, et al. Unique CD14+ intestinal macrophages contribute to the pathogenesis of Crohn disease via IL-23/IFN-γ axis. *J Clin Invest*. 2008;118(6):2269–2280. doi:10.1172/JCI34610
118. Mahida Y. The key role of macrophages in the immunopathogenesis of inflammatory bowel disease. *Inflamm Bowel Dis*. 2000;6(1):21–33. doi:10.1097/00054725-200002000-00004
119. Rebecca K, SJD O, RDADR C, Filippos K, Binion DG. Is Salt at Fault? Dietary Salt Consumption and Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2023;29(1):140–150. doi:10.1093/ibd/izac058
120. Feng YJ, Yong Yu LI. The role of p38 mitogen-activated protein kinase in the pathogenesis of inflammatory bowel disease. *J Dig Dis*. 2011;12(5):327–332. doi:10.1111/j.1751-2980.2011.00525.x
121. Monteleone I, Marafini I, Vincenzo D, et al. Sodium chloride-enriched Diet Enhanced Inflammatory Cytokine Production and Exacerbated Experimental Colitis in Mice. *J Crohns Colitis*. 2017;11(2):237–245. doi:10.1093/ecco-jcc/jjw139
122. WKE I, Medzhitov R. Macrophages monitor tissue osmolarity and induce inflammatory response through NLRP3 and NLRC4 inflammasome activation. *Nat Commun*. 2015;6(1):6931. doi:10.1038/ncomms7931
123. II I, BS M, Zhou L, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*. 2006;126(6):1121–1133. doi:10.1016/j.cell.2006.07.035
124. Zili Z, Mingquan Z, Julie B, Paul S, Kolls JK. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. *Inflamm Bowel Dis*. 2006;12(5):382–388. doi:10.1097/01.MIB.0000218764.06959.91
125. Julia S, Ira E, Julia D, et al. Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD. *Inflamm Bowel Dis*. 2010;14(4):437–445.
126. Thomas Korn EB, Oukka M, Vijay KK. IL-17 and Th17 cells. *Annu Rev Immunol*. 2009;27(1):485–517. doi:10.1146/annurev.immunol.021908.132710
127. Geng X, Xue J. Expression of Treg/Th17 cells as well as related cytokines in patients with inflammatory bowel disease. *Pak J Med Sci*. 2016;32(5):1164–1168. doi:10.12669/pjms.325.10902
128. Zheng YJ, Zhang HL, Yuan MY, et al. Regulatory T-cell depletion in the gut caused by integrin beta(7) deficiency exacerbates DSS colitis by evoking aberrant innate immunity. *Mucosal Immunol*. 2016;9(2):391–400. doi:10.1038/mi.2015.68
129. David G, Elizabeth R, Glen D. Keeping the bowel regular: the emerging role of Treg as a therapeutic target in inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19(12):2716–2724. doi:10.1097/MIB.0b013e31829ed7df
130. Lorian T, Abdulelah A, Nusrat S, et al. Cross-Sectional Analysis of Overall Dietary Intake and Mediterranean Dietary Pattern in Patients with Crohn's Disease. *Nutrients*. 2018;10(11):1761.
131. Hamed K, Sakshi M, Ananthakrishnan AN, et al. Identification and Characterization of a Novel Association between Dietary Potassium and Risk of Crohn's Disease and Ulcerative Colitis. *Front Immunol*. 2016;7:554. doi:10.3389/fimmu.2016.00554
132. Moghadasi ANPS, Sharifian M, Minagar A, Sahraian MA. Behavioral Neurology of Multiple Sclerosis and Autoimmune Encephalopathies. *Neurol Clin*. 2016;34(1):17–31. doi:10.1016/j.ncl.2015.08.002
133. Farez MF, Mascanfroni ID, Méndez-Huergo SP, et al. Melatonin contributes to the seasonality of multiple sclerosis relapses. *Cell*. 2015;162(6):1338–1352. doi:10.1016/j.cell.2015.08.025

134. Long T, Yang Y, Peng L, Li Z. Neuroprotective Effects of Melatonin on Experimental Allergic Encephalomyelitis Mice Via Anti-Oxidative Stress Activity. *J Mol Neurosci*. 2018;64(2):233–241. doi:10.1007/s12031-017-1022-x
135. Mandia D, Ferraro OE, Nosari G, Montomoli C, Zardini E, Bergamaschi R. Environmental factors and multiple sclerosis severity: a descriptive study. *Int J Environ Res Public Health*. 2014;11(6):6417–6432. doi:10.3390/ijerph110606417
136. Ralf G, Christopher L, Hans L. Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. *Brain*. 2006;129(Pt 8):1953–1971. doi:10.1093/brain/awl075
137. Hucke S, Eschborn M, Liebmann M, Herold M, Klotz L. Sodium chloride promotes pro-inflammatory macrophage polarization thereby aggravating CNS autoimmunity. *J Autoimmun*. 2016;67:90–101. doi:10.1016/j.jaut.2015.11.001
138. Krementsov DN, Case LK, Hickey WF, Teuscher C. Exacerbation of autoimmune neuroinflammation by dietary sodium is genetically controlled and sex specific. *FASEB J*. 2015;29(8):3446–3457. doi:10.1096/fj.15-272542
139. Friese MA, Fugger L, Dendrou CA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015;15(9):545–558. doi:10.1038/nri3871
140. Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of Functional Suppression by CD4CD25 Regulatory T Cells in Patients with Multiple Sclerosis. *J Exp Med*. 2004;199(7):971–979. doi:10.1084/jem.20031579
141. Andre S, Gunther W. Regulation of Dendritic Cell Function in Inflammation. *J Immunol Res*. 2015;2015(743169). doi:10.1155/2015/743169
142. Lan Q, Horwitz DA, Liu Z, et al. Polyclonal CD4+Foxp3+ Treg cells induce TGFβ-dependent tolerogenic dendritic cells that suppress the murine lupus-like syndrome. *J Mol Cell Biol*. 2012;4(006):409–419. doi:10.1093/jmcb/mjs040
143. Jrg S, Kissel J, Manzel A, Kleinewietfeld M, Linker RA. High salt drives Th17 responses in experimental autoimmune encephalomyelitis without impacting myeloid dendritic cells. *Exp Neurol*. 2016;279:212–222. doi:10.1016/j.expneurol.2016.03.010
144. Fitzgerald KC, Munger KL, Hartung HP, et al. Sodium intake and multiple sclerosis activity and progression in BENEFIT. *Ann Neurol*. 2017;82 (1):20–29. doi:10.1002/ana.24965
145. Cortese M, Yuan C, Chitnis T, Ascherio A, Munger KL. No association between dietary sodium intake and the risk of multiple sclerosis. *Neurology*. 2017;89(13):1322–1329. doi:10.1212/WNL.0000000000004417
146. Mcdonald J, Graves J, Waldman A, Lotze T, Waubant E. A case-control study of dietary salt intake in pediatric-onset multiple sclerosis. *Mult Scler Relat Disord*. 2016;6:87–92. doi:10.1016/j.msard.2016.02.011
147. Nourbakhsh B, Graves J, Casper TC, et al. Dietary salt intake and time to relapse in paediatric multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2016;87(12):1350–1353. doi:10.1136/jnnp-2016-313410
148. Niiranen T, Erlund I, Jalkanen S, Jula A, Salmi M. Effects of altered salt intake and diet on cytokines in humans: a 20-week randomized cross-over intervention study. *Eur J Immunol*. 2023;53(1):2250074. doi:10.1002/eji.202250074
149. Chang NH, Mckenzie T, Bonventi G, et al. Expanded Population of Activated Antigen-Engaged Cells within the Naive B Cell Compartment of Patients with Systemic Lupus Erythematosus. *J Immunol*. 2008;180(2):1276–1284. doi:10.4049/jimmunol.180.2.1276
150. Borchers AT, Leibushor N, Naguwa SM, Cheema GS, Shoenfeld Y, Gershwin ME. Lupus nephritis: a critical review. *Autoimmun Rev*. 2012;12 (2):174–194. doi:10.1016/j.autrev.2012.08.018
151. Rovin BH, Parikh SV. Lupus Nephritis: the Evolving Role of Novel Therapeutics. *Am J Kidney Dis*. 2014;63(4):677–690. doi:10.1053/j.ajkd.2013.11.023
152. Wu H, Huang X, Qiu H, et al. High salt promotes autoimmunity by TET2-induced DNA demethylation and driving the differentiation of Tfh cells. *Sci Rep*. 2016;6(1):28065. doi:10.1038/srep28065
153. Yang X, Yao G, Chen W, Tang X, Feng X, Sun L. Exacerbation of lupus nephritis by high sodium chloride related to activation of SGK1 pathway. *Int Immunopharmacol*. 2015;29(2):568–573. doi:10.1016/j.intimp.2015.09.027
154. Simpson N, Gatenby PA, Wilson A, Malik S, Cook MC. Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. *Arthritis Rheum*. 2014;62(1):234–244. doi:10.1002/art.25032
155. Yu D, Vinuesa CG. Multiple checkpoints keep follicular helper T cells under control to prevent autoimmunity. *Cell Mol Immunol*. 2010;7 (3):198–203. doi:10.1038/cmi.2010.18
156. Chen M, Guo Z, Ju W, Ryffel B, He X, Zheng SG. The development and function of follicular helper T cells in immune responses. *Cell Mol Immunol*. 2012;9(5):375–379. doi:10.1038/cmi.2012.18
157. Maogen C, Xiaohong L, Liu Y, et al. The function of BAFF on T helper cells in autoimmunity. *Cytokine Growth Factor Rev*. 2014;25 (3):301–305. doi:10.1016/j.cytogfr.2013.12.011
158. Maogen C, Xiaohong L, Cheukfai L, et al. Advances in T follicular helper and T follicular regulatory cells in transplantation immunity. *Transplant Rev*. 2018;32(4):187–193. doi:10.1016/j.trre.2018.07.002
159. Xiu Xiao XH Z, Zhang X, Chen Z, et al. High salt diet accelerates the progression of murine lupus through dendritic cells via the p38 MAPK and STAT1 signaling pathways. *Signal Transduct Target Ther*. 2020;5(1):34. doi:10.1038/s41392-020-0139-5
160. Lee JH, Kim M, Im YS, Choi W, Byeon SH, Lee HK. NFAT5 induction and its role in hyperosmolar stressed human limbal epithelial cells. *Invest Ophthalmol Vis Sci*. 2008;49(5):1827–1835. doi:10.1167/iovs.07-1142
161. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023–2038. doi:10.1016/S0140-6736(16)30173-8
162. Sehnert B, Pohle S, Heuberger C, et al. Low-Salt Diet Attenuates B-Cell- and Myeloid-Cell-Driven Experimental Arthritides by Affecting Innate as Well as Adaptive Immune Mechanisms. *Front Immunol*. 2021;12:765741. doi:10.3389/fimmu.2021.765741
163. Jung SM, Kim Y, Kim J, et al. Sodium chloride aggravates arthritis via Th17 polarization. *Yonsei Med J*. 2019;60(1):88–97. doi:10.3349/ymj.2019.60.1.88
164. Scrivo R, Massaro L, Barbati C, et al. The role of dietary sodium intake on the modulation of T helper 17 cells and regulatory T cells in patients with rheumatoid arthritis and systemic lupus erythematosus. *PLoS One*. 2017;12(9):e0184449. doi:10.1371/journal.pone.0184449
165. Faraco G, Brea D, Garcia-Bonilla L, et al. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response. *Nat Neurosci*. 2018;21(2):240. doi:10.1038/s41593-017-0059-z
166. Hu M, Lin Y, Men X, Wang S, Lu Z. High-salt diet downregulates TREM2 expression and blunts efferocytosis of macrophages after acute ischemic stroke. *J Neuroinflammation*. 2021;18(1):90. doi:10.1186/s12974-021-02144-9
167. Zhang X, Liang Y, Jiang J, et al. A High-Salt Diet Exacerbates Liver Fibrosis through Enterococcus-Dependent Macrophage Activation. *Microbiol Spectr*. 2023;11(2):e03403–22. doi:10.1128/spectrum.03403-22

168. Huang CF. A High-Sodium Diet Modulates the Immune Response of Food Allergy in a Murine Model. *Nutrients*. 2021;13(11):3684. doi:10.3390/nu13113684
169. Matthias J, Maul J, Noster R, et al. Sodium chloride is an ionic checkpoint for human TH2 cells and shapes the atopic skin microenvironment. *Sci Transl Med*. 2019;11(480):eaau0683. doi:10.1126/scitranslmed.aau0683
170. Haase S, Wilck N, Haghikia A, Gold R, Mueller DN, Linker RA. The role of the gut microbiota and microbial metabolites in neuroinflammation. *Eur J Immunol*. 2020;50:1863–1870.
171. Binger KJ, Gebhardt M, Heinig M, Rintisch C, Müller DN. High salt reduces the activation of IL-4- and IL-13-stimulated macrophages. *J Clin Invest*. 2015;125(11):4223. doi:10.1172/JCI80919