Enemy or Ally? – Fasting as an Essential Regulator of Immune Responses

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ABSTRACT

Nutrition is essential for supplying an organism with sufficient energy to maintain its bodily functions. Apart from serving as an energy supply, the immunomodulatory effects of diet are emerging as a central aspect of human health. The latest evidence suggests that dietary restriction may play an important regulatory role by influencing the activation and effector functions of immune cells. However, depending on the context, nutrient restriction may have both pathogenic and beneficial effects. Here, we discuss the diverse roles of fasting programs, including ketogenesis in infection and chronic inflammation, aiming to clarify their detrimental and/or beneficial effects. Understanding these differences may help identify conditions under which dietary interventions might serve as putative effective approaches to treat various diseases.

Keywords: ketogenic diet, ketone bodies, infection-induced anorexia, caloric restriction, immune response

Diet as an immune regulator

The acquisition of external nutrients is key to providing the energy required for the homeostatic maintenance of all organisms. In addition, it ensures the supply of crucial molecules, such as vitamins, that cannot be synthesized internally but are necessary for fundamental biological processes [1, 2]. However, beyond being an immediate supply of energy and micro- and macronutrients, diet is being increasingly recognized as a key direct modulator of immune functions [3]. In particular, the crucial effect of micronutrients, such as vitamins A, C, and D, zinc or iron, on the immune system have been studied for years and are discussed in detail elsewhere [4-8]. During the past few decades, changes in nutritional habits in the Western World have been correlated with an increased incidence of immunopathological conditions, such as asthma, type 1 diabetes, multiple sclerosis, and **inflammatory bowel disease** (**IBD**) [2]. In light of the idea that immune activation is an energetically costly process, reduced nutrient availability and malnutrition are known to have a severe impact on immune functions. Since our ancestors experienced periods of unstable food intake and starvation, evolutionary immune responses may have developed in the context of a general sparseness of nutrients. Thus, one may hypothesize that the development of chronic inflammation, driven by unrestrained immune activation, might be the consequence of an overall increased availability of nutrients and a general lack of fasting. Indeed, a plethora of data supports the notion that reduced nutrient uptake is one of the most effective measures for increasing lifespan and healthspan [9-11]. Accumulating evidence suggests that even in the context of dietary restriction, immunity towards infection is maintained, and that refraining from nutrient intake for a defined period of time, rather than acting as a general immunosuppressant, can enhance specific host-defense programs, including protection against parasites or recurrent viral infections [12-15]. Furthermore, dietary restriction can improve conditions of chronic inflammation [16, 17] and can also boost antitumor immunity (reviewed in detail in [18-21]). These findings suggest that refraining from nutrient intake (i.e. fasting) may represent an underappreciated host-metabolic program that can modulate both protective and pathogenic immune functions. Herein, we discuss the impact of different nutrient restriction scenarios on mammalian host immune responses and survival. In addition, we address the potential of fasting programs to be used as potential modulators of immune responses and dietary interventions that might serve as candidate therapeutic strategies against chronic inflammation.

Fasting as a crucial immunomodulatory program

While severe dietary restriction, resulting in malnutrition, has a profound impact on the functionality of the immune response [13, 22], the consequences for the immune system caused by refraining from dietary intake for a defined period of time are less well understood. In this regard, the latest research in mice suggests that dietary and metabolic adaptations, activated in the context of infection, may increase tolerance and thus survival of the host [23-28]. Thus, a distinction between prolonged fasting, resulting in depletion of essential nutrients and malnutrition, versus a transient state of nutrient deprivation or caloric restriction, where essential nutrients are reduced but not exhausted, may be important.

Infection-induced anorexia

In general, infection induces a variety of behavioral changes, generally referred to as **sickness-behaviors**. Among the physiological adaptations to infections, such as an increase in body temperature and iron sequestration, which are believed to serve the purpose of microbial inhibition, **infection-induced anorexia** is also commonly observed [29-32].

Detrimental effects of anorexia in infection

External nutrients supplied via oral gavage were able to rescue animals from an otherwise lethal influenza virus (IAV) infection [23].In line with the idea that nutrient starvation is detrimental during infection, it was reported that food restriction of mice infected orally with ***Salmonella*** **Typhimurium** drastically reduced survival in contrast to mice fed ad libitum [27]. Inhibition of anorexic behavior was mediated by the effector protein *Salmonella* leucine rich repeat protein (SlrP), which prevented inflammasome activation and thus the maturation of IL-1β, increasing host survival. In contrast, mice infected with ***Salmonella*** **Typhimurium** deficient for SlrP, produced IL-1β, which caused anorexia decreasing their survival [27]. This suggested that there must be important trade-off mechanisms between the host and pathogen. Following this, mice that were able to increase the supply of intestinal glucose were found to be more likely to survive a gastrointestinal bacterial infection with the invasive bacteria ***Citrobacter rodentium*** [26]. Here, the animals that survived a lethal dose of IC_{50} -- the dose that kills 50% of the infected animals-- responded with increasing systemic insulin resistance and reduced intestinal glucose absorption relative to non-surviving animals; this in turn, augmented the intestinal glucose availability and glucose supply to ***C rodentium*** resulting in attenuated pathogenicity [26]. Accordingly, an external supply of orally administered glucose was able to rescue mice

from an otherwise lethal infection with ***C rodentium*** [26]. This suggested that such metabolic trade-offs might reduce nutrient competition between the host and pathogen, leading to an overall reduction in pathogenicity. This notion is nicely exemplified by the finding that invasive bacteria, such as ***C rodentium***, can shut down their pathogenicity factors and become commensal bacteria if transferred into germ-free (GF) mice, in an environment lacking any competing bacterial communities [33]. In general, GF animals represent a threat-free environment for bacteria, displaying reduced pressure from the immune system and neighboring harmful microbes, which might also contribute to explain the observed reduction in pathogenicity of ***C rodentium***. However, a body of literature suggests that pathogenicity is predominately a result of nutrient stress, as glucose and other rapidly metabolizable carbon sources can inhibit the production of toxins and virulence factors in bacteria [34-36]. Thus, bacteria can employ the production of toxins in response to nutrient sparseness as a potential survival strategy to invade new niches and escape limited nutrient supply, with potentially damaging capacity for a nutrient-deprived host, as observed for nutrient restricted mice infected with ***Salmonella*** **Typhimurium** [27].

Beneficial effects of anorexia in infection

In contrast, other studies support the concept of infection-controlled anorexia as a possible protective metabolic survival program, thus allowing disease tolerance. Specifically, apart from increasing survival in systemic bacterial infections with ***Listeria monocytogenes*** [23, 37], the inhibition of glycolysis by application of the pharmacological inhibitor, 2-deoxyglucose (2DG), prevented the development of cerebral malaria in mice infected with ***Plasmodium bergei*** [24]. How the integration of both nutritional stress and inflammatory stimuli occurred remained elusive, until recently. Growth and differentiation factor 15 (GDF15**),** signaling through GDNF family receptor alpha like (GFRAL) [38-41] is a previously recognized host sensor of exercise and nutritional stress [42], induced by the **unfolded protein response** and **ER stress** [43]. Notably, GDF-15 was found to be highly induced in the context of sepsis in human patients or in experimental models of bacterial and viral inflammation in mice induced by injection of **lipopolysaccharide** (**LPS**) or **polyinosinic:polycytidylic acid** (**Poly (I:C)**), respectively [25]. In the context of inflammation, GDF-15 served the important function to stimulate hepatic triglycerides (TG) export, increasing the amounts of TG in circulation, which mediated cardio protection [25]. As a consequence, mice injected with LPS to induce sepsis or infected with IAV displayed decreased survival when treated with neutralizing GDF-15 antibodies to block the function of GDF-15. In contrast, another study demonstrated that GDF15-deficient mice are better

protected against abdominal sepsis caused by cecal ligation and puncture (CLP). TLR2 activation by translocating bacteria resulted in the production of GDF15 from macrophages and increased the recruitment of neutrophils through the chemokine CXC ligand 5 (CXCL5), thus enhancing pathogen control and clearance [44]. The discrepancy between these two studies might be potentially and partially explained by the use of different disease models (LPS treatment versus cecal ligation) and the employment of antibody blocking experiments compared to a genetic deletion of GDF15, respectively. Although these studies underscore the importance of understanding host metabolic adaptation for survival, it is evident that further robust experimental studies are required to understand, whether sickness-induced anorexia is beneficial or detrimental for the host **(Table 1)** and to paint a coherent picture.

Chronic infection and cachexia

When distinguishing transient and chronic nutrient deprivation, it is reasonable to hypothesize that prolonged periods of fasting will lead to malnutrition and exhaustion of essential micronutrients, amino and fatty acids, and have clearly detrimental effects for the host. Thus, the beneficial effects of fasting, caloric restriction, and malnutrition may be limited to situations of transient or mild nutrient deficiencies, which might be compensated for by the body for a period of time. As a consequence, whether the effects of infection-induced weight loss are protective or detrimental may crucially depend on the availability of stored (essential) nutrients, and the outcome might be largely dependent on how much fasting depletes these stores and thus exhausts the nutritional reserves of the organism. This mechanism may be particularly important when considering that in infection, nutrients may be re-allocated from maintaining homeostasis to fueling the energetic demand of immune responses [45-47]. Accordingly, another important aspect that may help determine if fasting is protective or pathogenic is whether acute or chronic infections are considered. Here, a recent study revealed that IAV infection and systemic chronic viral infections with **lymphocytic choriomeningitis virus (LCMV)** (Clone 13) in mice differ in terms of the weight loss induced by each infection [48]. Specifically, Pair-feeding, a technique in which the amount of food provided to a control group of mice is matched to that consumed by the experimental group, was used to assess if the weight loss of infected mice was solely caused by refraining from dietary intake. Indeed, in the context of an acute IAV infection, pair-fed animals lost the same amount of weight as infected animals [48]. However, weight loss in mice chronically infected with LCMV could not exclusively be attributed to anorexic behavior, since pair-fed animals lost significantly less weight than the mice chronically infected with LCMV [48]. Although not explored

in the context of chronic LCMV infection, it is generally assumed that **cachexia** (the proteolysis of muscle tissue leading to an exhaustion of amino acid supplies) contributes to the pathology of disease [49]. Yet, mice gavaged daily with a total amount of 1 kcal of chow-like control diet, glucose, olive oil, or casein recovered at a slower rate than the untreated animals. [48]. Although of general interest, the comparison of two different viruses (IAV versus LCMV Clone 13) and infection sites (systemic versus pulmonary infection) may limit some of the conclusions drawn from this study. Nonetheless, these data suggested that even in chronic infections, anorexic behavior might in some cases, have a beneficial effect for the host, although this remains to be further investigated. Of note, the delayed recovery from infection observed in food-supplemented mice might suggest that infection-induced anorexia might constitute an important host-metabolic program that supports biological processes that include the resolution of inflammation and host recovery after infection, although these possibilities remain to be rigorously tested. It is conceivable that by refraining from food intake for a limited period of time during viral infection, and that via some unknown mechanism this enables tissue repair and healing, anorexia might represent a long-term benefit for surviving individuals. Nevertheless, this possibility remains hypothetical and contentious, and will require substantial experimental testing.

Application of fasting and CR in chronic inflammation

When considering the effects of non-infection-related nutrient restriction, early studies of **caloric restriction (CR)** or **intermittent fasting** in mice and rats demonstrated an amelioration of **experimental autoimmune encephalomyelitis (EAE)** (rodent model of multiple sclerosis) relative to healthy controls [16, 50-52]. Specifically, CR equivalent to a 66% restriction of food, prior to the onset of disease, resulted in a complete lack of a clinical disease score, concomitant with a decrease in splenic, lymph node, and thymic $CD4^+$ T cell numbers and their production of IFN-γ relative to ad libitum fed rats [50]. Accordingly, subjecting mice to 24 h cycles of intermittent fasting drastically reduced monocyte infiltration into the spinal cord and ameliorated EAE compared with controls [53]. Moreover, Fasting activated the low-energy sensor **5′-AMP-activated protein kinase** (**AMPK**) in hepatocytes, which triggered the downstream target **peroxisome proliferator-activator receptor alpha** (**PPARα**); This sequence of events impaired the systemic production of chemokine CCL2 and resulted in a reduced mobilization of monocytes from the bone marrow and migration into the spinal cord, thus suppressing neuro-inflammation. However, protective immunity against infection with ***Listeria monocytogenes*** or wound repair remained unaffected [53].

From another angle, chronic inflammatory conditions, such as asthma caused by exposure to allergens, have been blunted by dietary intervention in mice and humans, mainly by modulating the **Type 2 immune responses** [54-57]. In a pilot human study, registered in ClinicalTrials.gov (NCT02471300), the effect of 24-h fasting on immune responses was tested in mild asthmatics. In this cohort of 18 patients, fasting resulted in inhibition of the **NOD-, LRR- and pyrin domain- containing protein 3** (**NLRP3**) **inflammasome**, and reduced the production of disease mediating cytokines, such as thymic stromal lymphopoietin (TSLP), in airway epithelial cells and IL-4 from **Type 2 T helper (Th2)** cells [57]. Thus, although pending further studies, it is possible that CR or transient fasting might counterbalance certain mechanisms promoting chronic inflammation, without impairing protective immunity to infection. Presumably, dietary restriction might even enhance protective immune responses against viruses and tumors, by inducing homing of memory T cells to the bone marrow [12]. In fact, placing mice on a 50% restriction of daily caloric intake, induces the homing of memory CD8+ T cells to the bone marrow. An effect associated with protection in both a ***Yersinia pseudotuberculosis*** infection model and a melanoma model in mice. However, in some cases, fasting might also abolish protective immunity. For example, temporal fasting appears to also diminish the number of germinal centers and oral antigen-specific IgA^+ B cells in the Peyer's patches thus reducing oral tolerance to the model antigen ovalbumin and causing an exacerbation of food-antigen-induced diarrhea in mice [58]. We posit that with exceptions, a scenario is emerging in which nutrient restriction may be beneficial for energy preservation and acute survival, but potentially also regulate immune over-activation, which might contribute to chronic inflammation in certain contexts (**Figure 1**). Of note, in most laboratory settings, mice have unlimited access to food--an environment that closely resembles the prevalent eating conditions in the western world. As a consequence, dietary restriction in laboratory mice might actually prevent overeating and thus restore a more "physiological" state experienced in the wild. Evidently, these hypotheses need to be carefully tested and validated.

Ketogenic diet as a putative treatment for chronic inflammation

An important step in the analysis of the fasting response through a defined dietary intervention was the development of the **ketogenic diet** (**KD**): a diet with reduced carbohydrate and protein contents but increased fat (Box 1) [59-61].

The Ketogenic diet can prevent Th1 and Th17 cell-associated EAE and MS chronic inflammation

As described above, several early studies investigated the beneficial effects of dietary restriction in the form of CR, intermittent fasting, and KD for the prevention of EAE by reducing inflammation and enhancing neuroprotection when administered prior to the onset of disease in rodents [16, 51, 62, 63] (Figure 1). Recently the efficacy of the KD was also therapeutically tested. Feeding mice either a KD or a fasting mimicking diet (FMD) (consisting of three cycles of very low calorie and low protein intake for three days every seven days) after the onset of EAE disease increased the concentration of corticosterone in the circulation relative to mice fed a control diet [17]. As a consequence, the number of **T regulatory cells** (Treg) was increased in the spleen and the draining lymph nodes of EAE mice, which efficiently suppressed the generation of pro-inflammatory **type 1 T helper (Th1) cells and type 17 T helper (Th17) cells**. This correlated with reduced cellular infiltration in the spinal cord and ameliorated established EAE, evident by delayed disease onset and reduced severity scores [17]. Of clinical relevance, these animal studies were confirmed by a three-armed parallel grouped, single center, controlled and randomized clinical pilot human trial (registered in ClinicalTrials.gov – NCT01538355) that reported safe administration of KD for relapsing-remitting MS (RRMS) patients with positive effects [17]. 60 patients suffering from RRMS were randomly assigned to a control diet (n=20), KD for 6 months (n=20), and a single cycle of an FMD diet for 7 days (n=20). Both diet cohorts displayed an improvement in overall heath and quality of life relative to baseline. During the study period, fewer cases of relapse were observed in the KD cohort, accompanied by increased concentrations of βOHB in plasma and reduced lymphocyte and white blood cell counts. Nevertheless, it will be important for more detailed and well-controlled clinical trials to be performed, to support this first promising clinical assessment of the KD in the treatment of MS, in terms of efficacy and potential adverse effects [17].

The Ketogenic diet can prevent chronic airway inflammation

Besides the prevention of Th1- and Th17-driven autoimmune inflammation, KD can also protect mice from pathogenic type 2 immune responses in allergen-driven airway inflammation, induced by the protease-allergen papain [64]. Pathogenic activation of **group 2 innate lymphoid cells** (**ILC2**), important drivers of airway inflammation, leads to a distinct change in the metabolic profile of these cells, with increased uptake of glucose and extracellular FA [64]. Although, externally acquired lipids are important as they are used as building blocks for membranes in highly proliferating cells, they need to be transiently stored as lipid droplets

to prevent **lipotoxicity** [65]. This process is controlled by the availability and sensing of glucose through **mammalian target of rapamycin (mTOR)** signaling[64]. As a consequence, feeding wild type mice a KD and thus restricting glucose availability, impaired mTOR signaling and lipid metabolism in lung ILC2, which strongly alleviated airway inflammation in this model, relative to mice fed a control diet [64]. In support of the notion that KD might be used as a specific treatment for chronic inflammation, it was notable that ILC2 remained unaffected in non-inflamed tissues, such as the intestine or adipose tissue [64]. The decrease in pathogenic ILC2 by KD appeared to be independent of the microbiota, because antibiotic treatment did not alter the suppressive capacity of KD [64]. In contrast, other beneficial effects of KD such as a known anti-seizure effect [66], or decreased induction of intestinal Th17 cells were tested, hypothesizing that these might be mediated through changes in the microbiota [67]. Thus, KD selectively inhibited the growth of intestinal ***Bifidobacterium*** in wild type mice and healthy humans, which resulted in an overall lower induction of intestinal pro-inflammatory Th17 cells compared with mice or humans fed a control diet [67]. It was suggested that this effect might be directly mediated by βOHB, given that *Bifidobacterium* cultured with βOHB *in vitro* selectively inhibited bacterial growth. However, whether there was a direct effect of βOHB on Th17 cell differentiation was not explored [67]. Since the induction of EAE in mice is critically linked to the expression of IL-17A and differentiation of Th17 cells in the intestine, the anti-inflammatory effect of KD in autoimmune diseases could be directly linked to the suppression of intestinal Th17 cells [68]. Overall, this highlights the therapeutic potential of KD to modulate the activation of pro-inflammatory immune cells to suppress chronic inflammation such as asthma or MS.

Ketogenic diet can protect from certain viral infections

Despite some conflicting results suggesting that the following a KD may reduce survival in IAV-infected animals [23], recent studies support a protective function for KD in viral infection. Feeding Mx1 mice (carrying functional alleles of *Mx1*) a KD for one week provided protection from IAV infection by increasing the survival of the mice along with reducing the viral load in the lungs and **bronchoalveolar lavage** (**BAL**) fluid relative to mice fed a normal chow diet. This protection correlated with a concomitant increase in **γδ T cells** in the lungs, a tissue-resident cell type mediating protective immune responses against viruses [69] [70]. However, even in mice lacking γδ T cells (Tcrd$^{-/-}$), which display an impaired recovery from IVA infection, a KD was still able to increase the overall survival time in contrast to mice fed a normal chow diet, which suggested that some of the beneficial effects of KD might be independent of γδ T cells. The authors also compared KD with

a **high-fat diet** (**HFD**) fed to Mx1 mice to address whether the protective effects of a KD were simply due to an increase in FA uptake and availability. However, by increasing the FA content alone, an HFD showed no effect, suggesting that FA increase might need to be combined with a simultaneous decrease in glucose and protein to achieve a beneficial effect on IAV infection. The protective effects of KD were probably not directly mediated by ketone bodies because feeding mice 1,3-butanediol, a precursor of ketone bodies, neither improved the outcome of an IAV infection nor led to the expansion of γδ T cells in the lungs [69]. Taken together, KD not only prevents harmful immune responses in chronic inflammation, but also appears to support protective immunity in infection.

Functions of ketone bodies in immunity

Accumulating evidence suggests that some of the effects of a KD might be mediated through ketone bodies, such as AcAc and βOHB, exerting direct effects on immune cells (**Figure 2**) [71]. In this context, hepatocytes might influence the function of macrophages in the liver directly through the production of AcAc [72]. For example, after AcAc is secreted from liver cells, it is further metabolized to acetyl CoA by succinyl-CoA:3-ketoacid CoA transferase (SCOT), which is expressed in macrophages. In addition, macrophages preferentially metabolize AcAc over glucose. Macrophage specific deletion of SCOT, using *Oxct1*$^{flox/flox}$ mice crossed to LysM-Cre mice impairs macrophage function and results in increased collagen deposition and HFD-induced liver fibrosis, suggesting that ketone bodies might be essential for the maintenance of hepatocyte–macrophage crosstalk to maintain liver homeostasis in this model [72]. The direct function of ketone bodies as modulators of pathogenic immune functions is further emphasized by the finding that βOHB, but not AcAc, inhibits activation of the ATP-induced NLRP3 inflammasome in human and murine macrophages [73]. Treatment of macrophages with βOHB resulted in decreased potassium efflux and prevented **apoptosis-associated speck-like protein (ASC) oligomerization**, and the secretion of caspase-1 activated IL-1β and IL-18 [73]. Additionally, exogenous administration of βOHB or feeding mice a KD, improved the NLRP3-driven auto-inflammatory disease, **Muckle-Wells syndrome**, by inhibiting constant NLPR3 activation preventing neutrophilia [73]. βOHB administration can also suppress NLRP3 inflammasome activation and IL-1β secretion from neutrophils, and feeding mice with a KD ameliorated the autoinflammatory disorder, urate-crystal-induced gout, as evidenced by a decrease in knee swelling and IL-1β serum levels compared to mice fed a normal chow diet [74]. In line with these previously outlined studies,

since administration of βOHB did not impair protective immunity against ***Staphylococcus aureus*** infection in mice, KD appears to target chronic inflammation without increasing the risk of infection [74], although this will require further validation. And, to our knowledge, whether signaling of AcAc and βOHB through specific receptors represents an important pathway in immune cells remains unknown. Human and murine macrophages express both the G-protein-coupled receptor GPR43 (also called free fatty acid receptor 2 (FFAR2)) and the hydroxy-carboxylic acid receptor 2 (HCA_2, GPR109a), which have been recently identified as specific receptors for AcAc and βOHB, respectively [75-77]. Yet, the specific function of GPR109a on monocytes and macrophages has to our knowledge, only been investigated in the context of stimulation with the GPR109a-specific ligand nicotinic acid [76]. Future research will hopefully address this particular aspect of ketone-body biology in immune cells.

βOHB can promotes immune memory

Besides regulating the effector function of immune cells, the ketone body βOHB can also drive the development of $CD8^+$ **T memory cells** in both mice and humans, as demonstrated in a recent report [78]. β-hydroxybutyrylation of histones was recently discovered as a novel form of histone modification [79], in addition to the previously reported histone deacetylase inhibitor activity of βOHB [80]. Feeding mice with KD or intraperitoneal administration of βOHB resulted in β-hydroxybutyrylation of histones in the promoter region of the transcription factors forkhead box protein O1 (*FoxO1*) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1a*) [78]. This epigenetic modification caused an upregulation of both of these genes and simultaneously increased the expression of their target gene phosphoenolpyruvate carboxykinase 1(*PCK1*), promoting carbon flux towards gluconeogenesis and the **pentose phosphate pathway [81]**. NADPH produced in the pentose phosphate pathway is needed as a reducing equivalent for the regeneration of glutathione (GSH) and thus is involved in protecting against the toxicity of **reactive oxygen species** (**ROS**). This process was shown to be crucial for the survival and maintenance of $CD8^+$ T memory cells as insufficient levels of NADPH failed to balance ROS leading to cell death [81] (**Figure 2**). Consequently, elevated concentrations of βOHB in mice and humans, presumably exerted a beneficial effect on the development and survival of memory $CD8^+$ T cells; in addition in an OVA-B16 melanoma tumor model in mice, the efficiency of T cell immunotherapy against tumors was enhanced in mice injected intraperitoneally with βOHB relative to control mice treated with saline, as evidenced from reduced tumor size

and increased survival of animals [78]. This finding is in line with the previously reported function of βOHB as an important modulator of oxidative stress [80] and support the idea, that βOHB as host-derived metabolites could be used therapeutically to modulate cellular functions of immune cells. This approach could be beneficial to circumvent potential adverse effects accompanying the application of KD.

Concluding remarks

Immune responses that harm rather than benefit the host, are unlikely to have withstood the selective pressure of evolution. This leads us to the assumption that the mechanisms underlying chronic inflammation are a fundamental part of host protection, which ensured the survival of our species in the past. However, we hypothesize that such mechanisms might nowadays operate in a different way to cause immunopathology, and identifying such contextual changes might be the key to treating certain inflammatory diseases. The findings outlined in this review point towards a key role for fasting and fasting-induced ketogenesis in the host-metabolic program, which might contribute to preventing situations of immune over-activation and chronic inflammation. It is possible that the rise in pathogenic immune responses seen in the modern Western World may be fueled by a general lack of nutrient restraint, as one common aspect of a modern lifestyle is nutrient supplementation and excessive food intake. However, while clearly more experimental evidence is needed to further support or disprove such hypotheses (see **Outstanding Questions**), the continued investigation of dietary intervention as a possible and context-dependent immunomodulator offers interesting future avenues to better understand host responses to caloric restriction and diet in health and disease, and ideally treat any associated pathologies. Evidently, dietary interventions can have a number of advantages over traditional drug therapies, including expedited licensing, minimal costs to the health-care system, and simplified application and administration. As many diseases in different countries may be caused by a misbalance of an evolutionarily developed metabolic control of immune responses, identifying the aspects of this deregulation could offer a new perspective for the prevention and treatment of specific diseases.

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Figure Legends:

Figure 1: Dietary restriction can regulate immune responses in humans and mice: Schematic representation of the effects of a ketogenic diet and fasting on immune responses. Caloric restriction in the form of fasting, intermittent fasting, or application of a ketogenic diet leads to a decrease of available glucose but the liberation of free fatty acids (FFA). These liberated FFA are used in the liver for the production of the ketone bodies: acetoacetate (AcAc) and β-hydroxybutyrate (βOHB) [71]. Following their synthesis, ketone bodies enter the blood circulation to supply extra hepatic tissues with energy [71]. In addition, a ketogenic diet, caloric restriction, and fasting mediate a wide array of immune regulatory functions (CD8: CD8 T lymphocytes, Th1: T helper type 1 cells, Th2: T helper type 2 cells, Th17: T helper type 17 cells, γδ T cells: γδ T lymphocytes, ILC2: type 2 innate lymphoid cells, MΦs: macrophages, NΦs: neutrophils, CNS: central nervous system, BM: bone marrow, STOP: suppressive functions of a ketogenic diet, caloric restriction, and fasting, GO: promotional functions of a ketogenic diet, caloric restriction, and fasting).

Figure 2: Mechanistic overview of the function of ketone bodies on human and murine immune cells: Schematic representation of the immune regulatory functions of the ketone bodies, acetoacetate (AcAc) and β-hydroxybutyrate (βOHB). Consumption of a ketogenic diet or caloric restriction through fasting promotes lipolysis of adipose tissue with a subsequent liberation of free fatty acids (FFA). The liver utilizes these FFA through acetyl-CoA to produce the AcAc and βOHB. (**1**) Upon cellular uptake, AcAc is further metabolized to

acetyl-CoA by the enzyme SCOT1. Malfunction of this enzyme impairs macrophages resulting in increased liver fibrosis induced by a high fat diet (HFD) [72]. (**2**) βOHB either enter the cells directly or bind to the receptors GPR43 or GPR109a and act through their signaling pathways to suppress the activation of the NLPR3 inflammasome impairing secretion of IL-1β and IL-18 from macrophages [74-77]. Additionally, **(3)** βOHB act through epigenetic modifications of gene expression either by inhibition of histone deacetylase (HDAC) activity or (**4**) by β-hydroxybutyrylation of histones facilitating increased expression of the genes forkhead box protein O1 (*FoxO1*) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1a*). In turn, the transcription factors FoxO1 and PGC-1α increase the expression of their target gene phosphoenolpyruvate carboxykinase 1 (*PCK1*), which accelerates carbon flux through the pentose phosphate pathway (PPP), generating NADPH and reducing glutathione (GSH). GSH is essential for quenching radical oxygen species (ROS) and facilitating the survival and maintenance of $CD8^+$ T memory cells [78-81].

Box 1. Fasting and the Ketogenic Diet.

During fasting the amount of available dietary carbohydrates is drastically decreased, forcing a switch in the nutrient supply [71]. As a result of fasting, ketogenesis is induced, in the liver and results in the production of ketone bodies, mainly acetone, acetoacetate (AcAc), and β-hydroxybutyrate (βOHB) from free fatty acids that are mobilized from adipose tissue [71]. Ketone bodies are secreted from hepatocytes into the circulation and act as an alternative fuel source in peripheral organs, such as brain, heart, and muscle, by replacing glucose as the major fuel [71]; This process can also be induced through a KD. The reduced supply of proteins and carbohydrates forces the organism to rely on free fatty acids as the predominant fuel source through the conversion of fat into ketone bodies, reflecting the central features of the starvation response [71]. This results in a radical change in host metabolism that mimics fasting but not starvation, because minimal amounts of carbohydrate and protein are still supplied to prevent depletion of essential nutrients and starvation [71]. This classic KD used in most human studies consists of a 4:1 ratio of fat to proteins and carbohydrates[59-61]. Although minor adverse effects, including nausea, diarrhea, and constipation, have been reported with long-term administration of a KD, these effects are mostly transient [82].

Glossary:

Apoptosis-associated speck-like protein (ASC) oligomerization: ASC protein consists of a pyrin domain (PYD) and a caspase recruitment domain (CARD). The oligomerization of ASC^{PYD} into filaments and the cross-linking of these filaments by ASC^{CARD} leads to the formation of ASC spec and inflammasome activation.

5′-AMP-activated protein kinase (AMPK): an energy sensor activated by increasing ratios of AMP/ATP and ADP/ATP that regulates catabolic metabolism to increase the generation of ATP.

Bifidobacterium: A group of bacteria, normally residing in the intestine and the stomach and associated with the production of a number of potentially health promoting metabolites including short chain fatty acids.

Bronchoalveolar lavage (BAL): a procedure for collecting respiratory secretions to analyze the cellular and non-cellular components.

Caloric restriction (CR): a dietary intervention where the caloric intake is reduced to a certain percentage of the *ad libitum* intake.

Cachexia: "wasting" syndrome characterized by exhaustion of nutrient stores, extreme weight loss, and muscle wasting.

Citrobacter rodentium: an extracellular enteric mouse-specific pathogen used to model infections with the human pathogenic *Escherichia coli*.

ER stress: cellular stress induced in response to an accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum, induced when the demand for protein folding exceeds the capacity of the ER for protein folding.

Experimental autoimmune encephalomyelitis (EAE): an experimental autoimmune condition that is commonly used to mimic aspects of multiple sclerosis, an autoimmune condition affecting the central nervous system.

Fasting: Refraining from food intake for a defined period of time.

γδ T cells: type of T cell expressing the gamma and one delta T cell receptor chain. γδ T cells are predominately located at barrier sites such as the gut, lung, skin, adipose tissue, and uterus.

High-fat diet (HFD): a diet containing increased fatty acid content, which is designed to induce obesity in animal models.

Inflammatory bowel disease (IBD): a disease characterized by chronic inflammation of the gastrointestinal tract. Subtypes of IBD include Crohn's disease and Ulcerative Colitis.

Infection-induced anorexia: a common behavioral change of the host upon infection. It is characterized by loss of appetite followed by decreased food consumption and weight loss.

Intermittent fasting: an eating pattern that cycles between periods of fasting and food intake (e.g. food intake is restricted to a period of 24 h, followed by fasting for 24 h).

Group 2 innate lymphoid cells (ILC2), a distinct subset of innate lymphoid cells, responsible for maintaining tissue homeostasis at barrier sites. Chronic activation of ILC2 cause allergen-induced airway inflammation by increasing mucus production and eosinophil recruitment.

Ketogenic diet (KD): a diet mimicking a fasting state through reduced protein and carbohydrate but increased fat contents. This diet forces the liver to produce ketone bodies from fat, which are subsequently used as the major fuel supply for distal organs such as the brain.

Lipotoxicity: toxicity caused by the accumulation of free fatty acids in non-adipocyte cells.

Lipopolysaccharide (LPS): a signature component of the cell wall of gram-negative bacteria. LPS binds to and activates toll-like receptor 4 (TLR4).

***Listeria monocytogenes*:** Is a Gram-positive pathogenic species of bacteria causing a disease known as listeriosis.

Lymphocytic choriomeningitis virus (LCMV): a rodent-born virus that infects a large number of humans causing lymphocytic choriomeningitis, a disease characterized by neurological problems, including meningitis, encephalitis, and neurologic birth defects.

Malnutrition: A condition referring to deficiencies, excesses, or imbalances in energy and nutrient uptake. Malnutrition encompasses under- and over-nutrition.

Mammalian target of rapamycin (mTOR): a central metabolic sensor promoting anabolic metabolism and cell growth by suppressing catabolic processes.

Memory T cells: long-lived antigen-specific T cells that remain in the body after the elimination of an infection and are rapidly reactivated upon re-exposure to their specific antigen.

NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome: a multimeric intracellular protein complex. Activation and assembly of this complex activates caspase-1, the release of the cytokines IL-1β and IL-18, and triggers an inflammatory form of cell death called pyroptosis.

Pentose phosphate pathway (PPP): branch of glucose metabolism, important for nucleotide synthesis and generation of NADPH.

Peroxisome proliferator-activator receptor alpha (PPARα): a nuclear hormone receptor and master regulator of lipid metabolism.

Plasmodium bergei: protozoan parasite that causes malaria in mice.

Polyinosinic:polycytidylic acid (Poly (I:C)): a synthetic analogue of double-stranded RNA that activates TLR3. Poly (I:C) is a widely used ligand to mimic viral infections.

Reactive oxygen species (ROS): a byproduct of metabolic pathways, which serve both as cellular signaling molecules and antimicrobial agents. An imbalance between ROS production and anti-oxidant systems results in oxidative stress.

***Salmonella* Typhimurium:** a primary enteric pathogen that infects both humans and animals through contaminated food or water.

Sickness-behaviors: coordinated set of adaptive behavioral changes such as lethargy, social withdrawal and loss of appetite, that develop during the course of an infection.

Staphylococcus aureus: Gram-positive bacteria, normally residing on the skin and in the upper respiratory tract but which can also cause infections as opportunistic pathogen.

Type 1 T helper (Th1) cells: Th1 cells are a distinct subpopulation of CD4+ effector T cells mediating immune responses against viral and bacterial infections. Th1 cells are characterized by the expression of the transcription factor T-bet and the production of the cytokines IFN-γ.

Type 2 T helper (Th2) cell: Th2 cells are a distinct subpopulation of CD4+ effector T cells mediating immune responses against parasites, allergens and toxins. Th2 cells are characterized by the expression of the transcription factor GaTA-3 and the production of the cytokines IL-4, IL-5 and IL-13.

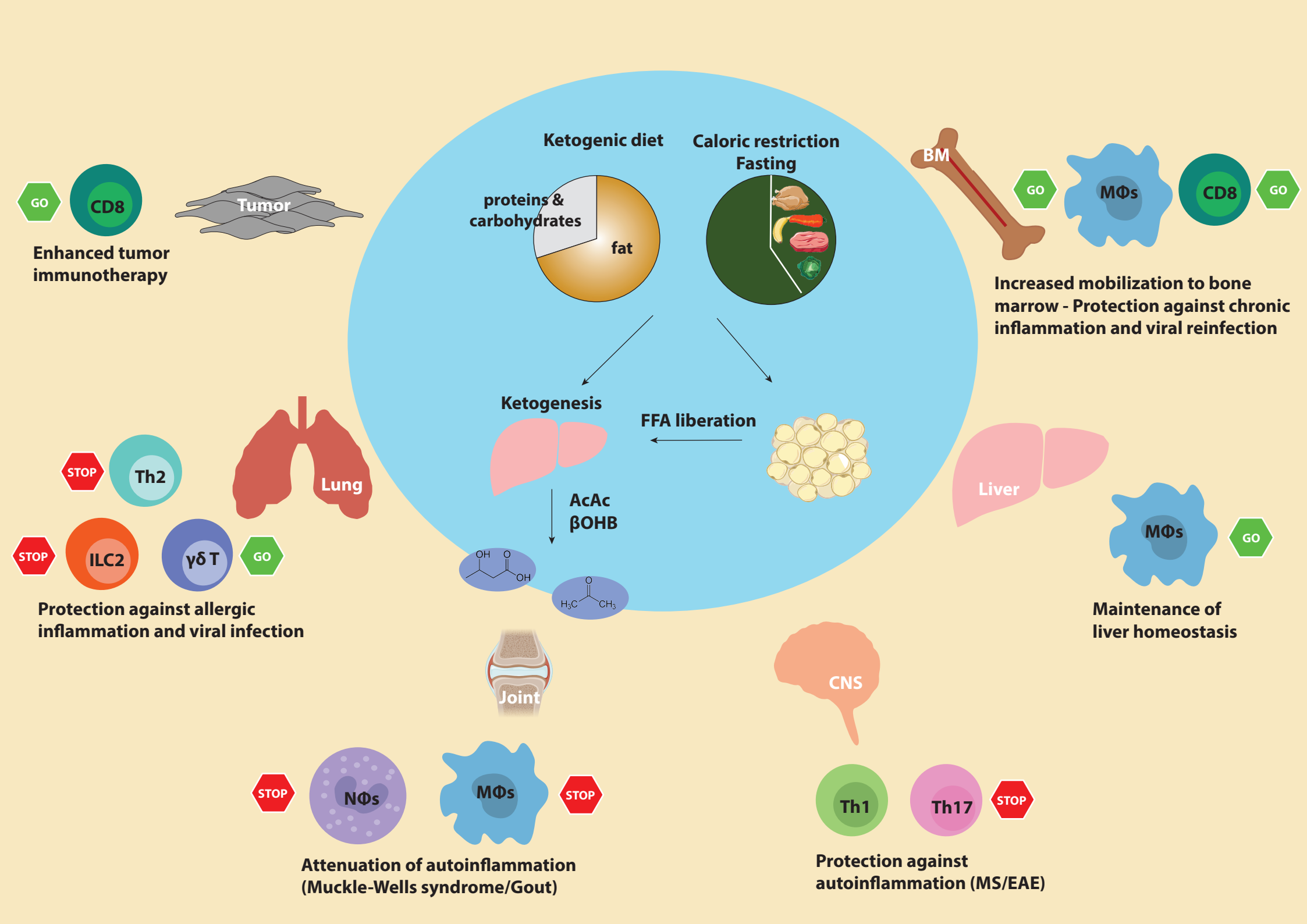
Type 17 T helper (Th17) cells: Th17 cells are a distinct subpopulation of CD4+ effector T cells, playing an important role in host defense against extracellular pathogens but also in autoimmune diseases. Th17 cells are characterized by the expression of the transcription factor RORγt and the production of the cytokines IL-17 and IL-22.

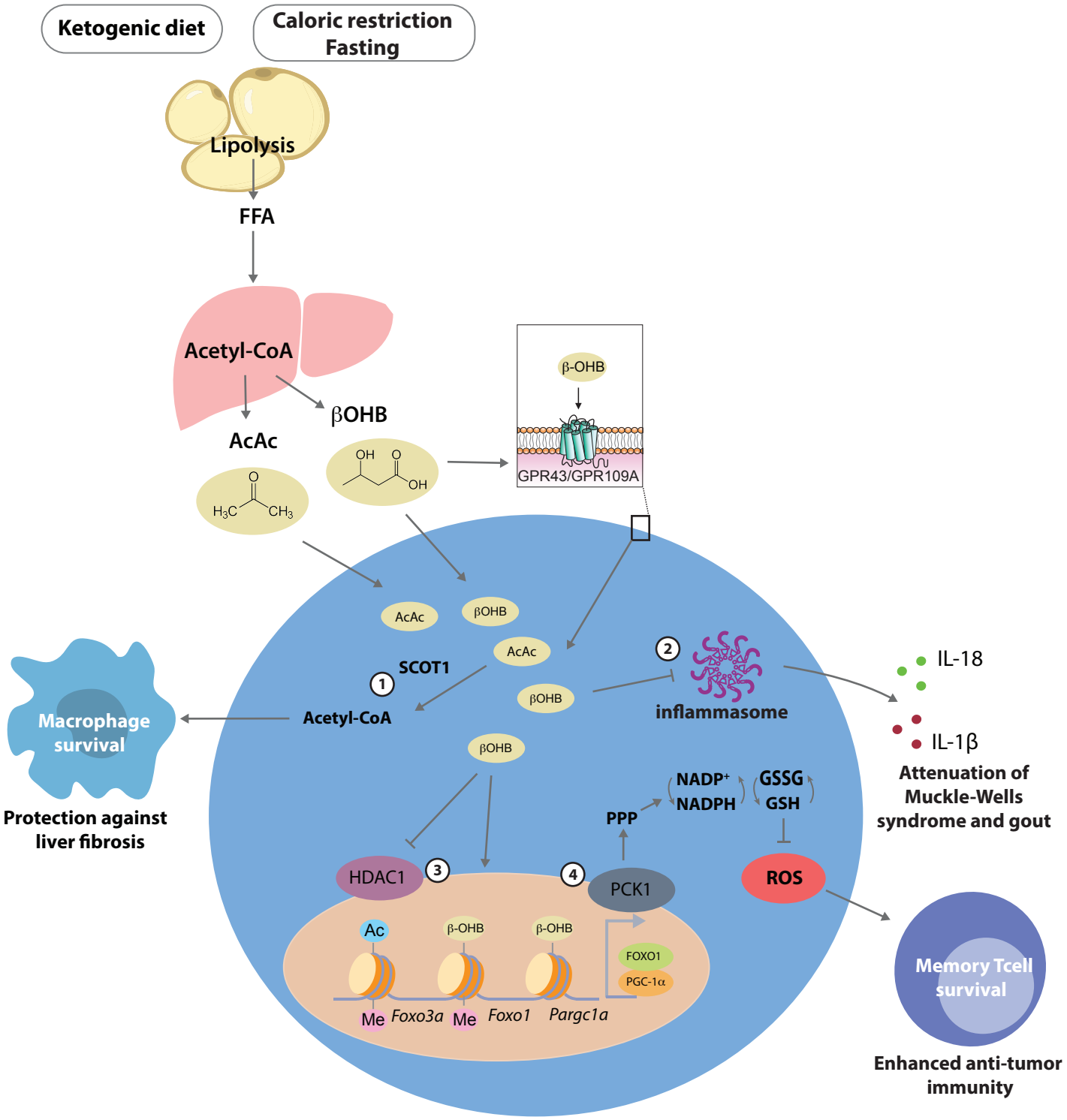
T regulatory cells (Treg); Treg are a distinct subpopulation of CD4+ effector T cells expressio, critical for maintaining self-tolerance and immune cell homeostasis. Treg are characterized by the expression of the transcription factor FOXP3.

Type 2 immune response: the immune response characterized by the production of the cytokines IL-4, IL-5, IL-9, and IL-13 by GATA-3+ cell types; involved in the defense against parasitic infections and in allergic diseases.

Unfolded protein response: is acellular stress response activated in response to an accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum.

***Yersinia pseudotuberculosis*:** Gram-negative bacterium that causes Far East scarlet-like fever in humans.


Ketogenic diet
Caloric restriction
Fasting
proteins &
carbohydrates
fat
Ketogenesis
FFA liberation
AcAc
βOHB
GO
CD8
Tumor
Enhanced tumor
immunotherapy
BM
GO
MΦs
CD8
GO
Increased mobilization to bone
marrow - Protection against chronic
inflammation and viral reinfection
STOP
Th2
Lung
STOP
ILC2
γδ T
GO
Protection against allergic
inflammation and viral infection
Liver
MΦs
GO
Maintenance of
liver homeostasis
Joint
CNS
STOP
NΦs
MΦs
STOP
Attenuation of autoinflammation
(Muckle-Wells syndrome/Gout)
Th1
Th17
STOP
Protection against
autoinflammation (MS/EAE)


Ketogenic diet
Caloric restriction
Fasting
Lipolysis
FFA
Acetyl-CoA
AcAc
βOHB
β-OHB
GPR43/GPR109A
AcAc
βOHB
AcAc
βOHB
βOHB
SCOT1
1
Acetyl-CoA
2
inflammasome
IL-18
IL-1β
Attenuation of Muckle-Wells syndrome and gout
Macrophage survival
Protection against liver fibrosis
NADP+
NADPH
GSSG
GSH
PPP
HDAC1
3
4
PCK1
ROS
Ac
β-OHB
β-OHB
FOXO1
PGC-1α
Me
Foxo3a
Me
Foxo1
Pargc1a
Memory Tcell survival
Enhanced anti-tumor immunity