Nutrition and fasting mimicking diets in the prevention and treatment of autoimmune diseases and immunosenescence

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Abstract

Complex and coordinated signals are necessary to initiate and sustain the activation, proliferation, and differentiation of lymphocytes. These signals, which are known to determine T-cell fate and function, also depend on the metabolic state of the organism. Recent studies indicate that both the type and levels of nutrients can influence the generation, survival and function of lymphocytes and therefore can affect several autoimmune diseases. Here, we review the dysregulation of lymphocytes during autoimmunity and aging, the mechanisms associated with loss of immune function, and how fasting mimicking diets and other dietary interventions affect autoimmunity and immunosenescence.

Keywords

1. Introduction

Aging is associated with a progressive functional decline of the immune system, commonly referred to as immunosenescence. There are several consequences of age-dependent immunosenescence, including increased susceptibility to infection and autoimmune diseases, reduced response to vaccination, and chronic inflammation (Franceschi and Campisi, 2014; Franceschi et al., 2000). In general, men experience a stronger age-dependent alteration of immune function than women (Yan et al., 2010).

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T cells, which are derived from hematopoietic stem cells (HSCs), mature in the thymus. The T cell repertoire is generated in the thymus by TCR rearrangement, including the purging of thymocytes that recognize self-peptides via negative selection. Thymic activity progressively declines after puberty, and such involution has been thought to underline the age-dependent decline in T lymphocyte number/diversity and increase in autoimmunity (Coder et al., 2015; Britanova et al., 2014). However, recent evidence suggests that thymic involution itself may not be sufficient to account for the reduction of T cell repertoire and number (Denkinger et al., 2015). Another cause of the age-dependent decline in the adaptive immune system is the age-dependent decline of HSC function (Denkinger et al., 2015). Young HSCs possess a balanced potential to differentiate into myeloid and lymphoid lineage cells that later become components of the innate and adaptive immune system. However, aged HSCs preferentially give rise to myeloid cells rather than lymphoid cells, accompanied by a decline in common lymphoid progenitors (CLPs), and ultimately reduced T and B cell lymphogenesis that can cause stem cell exhaustion and reduced regenerative capacity (Geiger et al., 2013).

The rejuvenation of HSCs to reverse or postpone immunosenescence has recently received much attention (Denkinger et al., 2015). Dietary restriction (DR) is an effective and reproducible intervention to increase healthy lifespan in various model organisms (Lee and Longo, 2016; Fontana and Partridge, 2015). The major DR regimens include caloric restriction (CR) (Fontana et al., 2010), intermittent fasting (IF) (Fontana and Partridge, 2015), time-restricted feeding (TRF) (Chaix et al., 2014; Gill et al., 2015; Hatori et al., 2012), restriction of specific macronutrients (Lee and Longo, 2016; Miller et al., 2005; Mirzaei et al., 2014, 2016), ketogenic diets (KD), and periodic fasting (PF) or fasting-mimicking diets (FMDs) (Brandhorst et al., 2015) (Table 1). However, studies of the effects of many dietary interventions on the immune system have yielded different results, with chronic calorie restriction resulting in both positive and negative effects on the immune system and immune responses (Nikolich-Zugich and Messaoudi, 2005). In addition, CR requires significant life-style changes, making them challenging to adhere to, especially for frail patients and older individuals. However, certain periodic dietary restrictions have the potential to prevent and/or reverse age-dependent immune dysfunction by killing autoimmune cells and activating HSC-dependent regeneration while minimizing the burden of the intervention and the side effects (Tang et al., 2016; Mihaylova et al., 2014; Cheng et al., 2014). Here, we will discuss the potential of various DR regimens in the treatment of autoimmune diseases and the mechanisms that may mediate these effects.

2. Metabolism and immune response

The immune system is tightly regulated by nutrient availability and metabolism (MacIver et al., 2013). Leukocytes utilize oxidative metabolism in a resting state, but upon activation they switch to a more anabolic state that relies on aerobic glycolysis, a process that converts glucose into lactate even in the presence of sufficient oxygen to support oxidative phosphorylation (Franceschi and Campisi, 2014; Yan et al., 2010; Pearce, 2010) (Fig. 1). The switch to glycolytic metabolism increases the availability of carbon sources which can be converted to biosynthetic precursors that are required for cellular proliferation (Pearce, 2010). This metabolic reprogramming is, in part, regulated by hexokinase II (Chehtane and Khaled, 2010) and the phosphoinositide 3-kinase (PI3K)-dependent glucose transporter

Glut1 (Swainson et al., 2007). Glut1 overexpression in mice resulted in an increase in not only the number of naïve T cells, but also the number of CD44^{high} T cells (activated T cells) (Macintyre et al., 2014). T-cell specific Glut1 deletion resulted in impaired CD4^{+} T cell activation, clonal expansion and survival (Macintyre et al., 2014). Amino acids, in particular glutamine, are key sources of biosynthetic precursors for activated T cells (Ardawi, 1988; Carr et al., 2010). Upon activation, T cells increase the expression of glutamine transporters; conversely, glutamine transporter deletion impairs T effector cell differentiation (Ardawi, 1988; Carr et al., 2010). Glutamine utilization, which requires ASC amino-acid transporter 2 (ASCT2), influences the development and differentiation of pro-inflammatory Th1 and Th17 cells and also T cell receptor (TCR)-stimulated activation of the metabolic kinase mammalian target of rapamycin complex 1 (mTORC1) (Nakaya et al., 2014). In a subsequent study, it was shown that proliferation and differentiation of T-cells upon activation require amino acid transporters, specifically system L transporter (Slc7a5) that mediates the uptake of large neutral amino acids (LNAAs) (Sinclair et al., 2013). Loss of Slc7a5 reduces the proliferation and differentiation of CD4^{+} and CD8^{+} T cells and promotes regulatory T cells (Treg). Deficient LNAA uptake due to loss of Slc7a5 leads to reduced c-Myc expression which is critical for boosting activation-induced glycolysis and glutaminolysis in T cells (Sinclair et al., 2013; Wang et al., 2011). Moreover, intracellular leucine concentration can affect mTORC1 activation via the regulation of cytosolic branched chain aminotransferases (BCATc) (Ananieva et al., 2014). BCATc expression was up-regulated in activated CD4^{+} T cells, and BCATc deficiency led to increased intracellular leucine and enhanced mTORC1 activity and glycolytic phenotype (Ananieva et al., 2014).

The importance of mTOR dependent T-cell fate has also emerged in recent years. The activation of mTOR, which is a catalytic subunit of mTORC1 and mTORC2, directs the proper activation and differentiation of effector CD4^{+} T cells. Suppression of mTOR1 with rapamycin promoted the generation of FoxP3^{+} Treg (Kopf et al., 2007), and T cell specific deletion of mTOR increased the production of Treg upon activation (Delgoffe et al., 2009). Interestingly, stimulation of HIF-1 activity, which is downstream of mTOR, shifted T cell differentiation into Th17, but deficiency of HIF-1 increased the generation of Treg cells. Consistently, Treg-specific deletion of raptor, an essential component of mTORC1, decreased the suppressive activity of Tregs *in vivo* and promoted the development of a fatal early onset inflammatory disorder (Delgoffe et al., 2009; Zeng et al., 2013).

2.1. Metabolism in autoimmune diseases and aging

Autoimmune and allergic diseases (e.g. asthma, lupus, multiple sclerosis (MS), and rheumatoid arthritis (RA)) are characterized by dysfunctional lymphocytes and metabolic dysregulation. In asthma patients, CD4^{+} T cells exhibit increased glycolysis, measured by increased lactate production levels (Ostroukhova et al., 2012). Notably, naïve CD4^{+} T cells from both asthma patients and a mouse asthma model resulted in higher amounts of lactate production upon stimulation, suggesting increased glycolysis (Ostroukhova et al., 2012). The inhibition of glycolysis in CD4^{+} T cells by dichloroacetate (DCA), an inhibitor of aerobic glycolysis, blocked T cell activation and the development of asthma, while promoting IL-10 production and Treg differentiation (Ostroukhova et al., 2012). In contrast, in a murine lupus model, splenocytes showed increased glucose oxidation level, possibly

indicating an increased activity of the TCA cycle (Wahl et al., 2010). In a recent study, normalizing CD4^{+} T cell metabolism by a combination treatment with metformin, a mitochondrial respiration inhibitor, and 2-deoxy-D-glucose (2DG), a glycolytic inhibitor, reversed disease biomarker in lupus-prone B6.*Sle1.Sle2.Sle3* (TC) mouse model and caused a reduction in IFN-γ production *in vitro* (Yin et al., 2015). In multiple sclerosis (MS), increased levels of glutamine and glutamate release have been detected at the site of demyelination and axonal degeneration, possibly correlating with disease severity (Frigo et al., 2012). CD4^{+} T cells from MS patients showed an over-activation of the mTOR pathway (Sarchielli et al., 2003; Tisell et al., 2013) which may indicate a dysregulation of the amino acid sensing signaling supporting a significantly lower percentage of nTreg (natural regulatory T) cells observed in relapse-remitting MS (RRMS) patients (Kraszula et al., 2012). In rheumatoid arthritis (RA), CD4^{+} T cells from the patients failed to produce as much ATP and lactate as healthy control T cells even under proliferating condition (Yang et al., 2013). In CD4^{+} T cells from RA patients, the enzyme 6-phosphofructo-2-kinase/ fructose-2,6-bisphosphate 3 (PFKFB3), which is a rate-limiting enzyme in the glycolytic pathway, was suppressed (Yang et al., 2013). Dysfunction of PFKFB3 leads to impaired glycolytic flux, apoptosis-susceptibility, and increased reactive oxygen species (ROS) production during T cell activation (Yang et al., 2013). It was further confirmed that several glycolytic enzymes in the lymphocytes of RA patients, such as glucose-6-phosphate isomerase, aldolase and enolase, have been identified as antigens recognized by autoantibodies (Saulot et al., 2002; Ukaji et al., 1999; Schaller et al., 2001).

In addition to autoimmune and inflammatory diseases, aging promotes immune dysfunction. Age largely affects the adaptive immune response, especially that based on T and B lymphocytes (Boraschi et al., 2013; Valenzuela and Effros, 2012; Frasca and Blomberg, 2011). Immune cells in older organisms shows a skewed metabolism toward glycolysis, which is associated with immunosenescence (Cannizzo et al., 2011). Such age-dependent changes include a general decline of total T lymphocytes, with a significant reduction in the number and proportion of naïve T cells and both helper/inducer (CD4^{+}) and suppressor/ cytotoxic (CD8^{+}) cells (Yan et al., 2010; Sansoni et al., 1993; Vescovini et al., 2014). Also, the T lymphocyte repertoire, generated by excisional T cell receptor (TCR) gene rearrangement, diminishes with age as measured by TCR-rearrangement excision circles (TREC) (Douek et al., 1998) and the TCR signaling cascade, including Raf-1/MEK/ERK kinases, JNK protein kinase, ZAP-70 kinases, and Ca^{2+} release, can be impaired in elderly people (Hasler and Zouali, 2005). Contributing to immune dysfunction is also the reduced efficiency of the aged immune system in eliminating self-recognizing antibodies, increasing the incidence of autoimmunity resulting from the combination of dysfunctional T and B lymphocytes (Goronzy and Weyand, 2012; Rosenblum et al., 2015).

2.2. Nutrition and autoimmunities

Different forms of dietary restrictions can increase lifespan and protect multiple systems from aging (Brandhorst et al., 2015; Mattison et al., 2012; Longo and Mattson, 2014; Yu et al., 1982; Goodrick et al., 1990; Jiang et al., 2000; Sohal and Weindruch, 1996). However, the view that all types of dietary restriction can be somehow equivalent leading to similar changes, including those related to autoimmunities, is simplistic and probably incorrect. In

fact, it is now clear that CR can be either effective or ineffective in promoting longevity or disease reduction depending on its dietary composition. For example, a study done by the National Institute on Aging (NIA) in 2012 shows that there are no significant health benefits and no difference in life-span extension for caloric restricted rhesus monkeys, regardless of whether the CR regimen implemented in young or older age rhesus monkeys (Rosenblum et al., 2015). In contrast, another study done by the Wisconsin National Primate Research Center in 2014 shows improved survival associated with 30% CR initiated in adult rhesus monkey (7–14 years). In this study the *ad lib* control monkeys had a threefold increased risk of death and a risk of disease 2.9 times higher than that of the calorie-restricted monkeys (Sohal and Weindruch, 1996). These contrasting CR results on the longevity and the healthspan of monkeys may be due to differences in dietary composition and varying protein content which can have an impact on CR-induced cellular protection (Colman et al., 2014). Thus, it is essential to begin to consider and discuss the effects of different forms of restriction, whether they involve calories or composition, separately and also use terminology and abbreviations that accurately identify the type of restriction, duration, and the mode of use. For example, CR is generally understood to describe a 20–40% restriction of calories below *ad libitum* levels, whereas DR is a much more inclusive term that can refer to the restriction of calories or of specific macronutrients (Lee and Longo, 2011, 2016) (Table 1). IF, which can also be interchangeable with alternate day feeding (ADF), instead refers to the alternation of a day of feeding and a day of either water only fasting or a very low calorie diet. In contrast, periodic fasting (PF) refers to two or more consecutive days of fasting that is done periodically; this can range from every week to every several months. These definitions and classifications are particularly important in the identification and understanding of the dietary interventions that affect autoimmunity since they can have drastically different, and in some cases opposite, effects on both immune cells and on the regeneration of cells and tissues damaged by the autoimmunity.

PF or a low protein and sugar and high fat 48–72 h FMD, which provides calories in a quantity and form that does not interfere with the effects of water only fasting, can result in a 40% or greater decrease in serum glucose levels in rodents (Brandhorst et al., 2015) and a 20% or greater decrease in serum glucose in humans (Longo and Mattson, 2014). During the initial fasting period, cells utilize liver glycogen as the main energy source, and then switch to a metabolic mode in which non-hepatic glucose, fat-derived ketone bodies and free fatty acids are used for energy (Longo and Mattson, 2014). PF also leads to a dramatic reduction in certain growth factors, particularly the insulin-like growth factor 1 (IGF-1), which is a key signaling molecule for cellular growth and an inhibitor of both cell protection and regeneration (Longo and Mattson, 2014). Some of the changes that are shared by chronic CR and PF in mice are reduced protein synthesis rate, reduced AKT activity (Du et al., 2003) and mTOR/S6K activities, increased 4E-BP1 activity (Sans et al., 2004) and increased activity of FOXO transcription factors (Longo and Mattson, 2014; Imae et al., 2003) all of which have been implicated in both CR and PF-dependent longevity extension. These changes in metabolic sensing pathways upon CR and PF have shown to be clinically relevant for cancer treatment and prevention including potentially ameliorating several side effects cause by chemotherapy in humans (Safdie et al., 2009), and protection from chemotherapy-induced toxicity and sensitization from a range of cancer cells to chemotherapy in mice (Lee

et al., 2012a,b). It is widely known that cancer cells rely more on glycolysis than on oxidative phosphorylation: a phenomenon known as the Warburg effect. Fasting-based reduction in glucose but also in other nutrients and factors on which cancer cells rely, contribute to the increased cancer cells' sensitivity towards the chemotherapy (Lee and Longo, 2011). As described in the previous sections, immune cells, during hyper-activation following antigen-specific T cell activation or during autoimmune response, utilize a similar strategy to generate the energy carriers and metabolic intermediates needed to produce biomass and inflammatory mediators (Yang et al., 2015). Therefore, PF may kill cancer and immune cells, particularly the more active autoimmune cells, by partially overlapping mechanisms that are poorly understood.

2.3. Multiple sclerosis

MS is an autoimmune disorder characterized by T cell-mediated demyelination and neurodegeneration of the central nervous system (CNS) (Friese and Fugger, 2005; Pender and Greer, 2007; Rasmussen et al., 2007; Sospedra and Martin, 2005), whose exact etiology remains unclear. The autoimmune view of MS is strongly supported by the use of the animal experimental autoimmune encephalomyelitis (EAE) model, which displays some of the key MS characteristics. For example, during the activation phase, the antigen presenting cells migrate to the lymph nodes and present the immunodominant peptide to naïve T cells (Dhib-Jalbut, 2007; Fletcher et al., 2010; Hemmer et al., 2002; Goverman, 2009), and the histocompatibility (MHC) Class II-restricted $CD4^+$ T cells secrete many inflammatory cytokines such as IFN-y, TNFα, IL-6, and IL-17. During the effector phase, $CD4^+$ T cells that recognize antigen proliferate, cross the blood-brain barrier and subsequently activate macrophages and microglia (Benveniste and Benos, 1995) that cause demyelination, oligodendrocyte death, and axon degeneration. As the disease progresses, remyelination and regeneration of oligodendrocyte become inefficient and ultimately fail (Chang et al., 2002; Wolswijk, 1998), resulting in disease progression. Several MS treatment drugs have been effective in reducing immune responses, but their impact on long-term disease progression, accrual of irreversible neurological disability, and the function of the immune system remains largely unclear (Wingerchuk and Carter, 2014). The limitation of pharmacological immune-modulating treatments is due to both the relatively non-specific inhibition of immune responses leading to immunosuppression and the failure to repair the damaged myelin in the affected tissues.

Although we are only beginning to understand the relationship between nutrients, fasting and autoimmune disorders, the dietary treatment of MS and other autoimmune diseases has high potential, since it may stimulate and take advantage of the ability of the organism to repair and replace its damaged cells without interfering with the function of normal cells and systems.

3. Dietary restriction and multiple sclerosis prevention

3.1. Dietary restriction in MS prevention in murine models

Virtually all chronic CR studies in mouse MS model have shown effects on prevention and not treatment, possibly because cycles of the combination of restriction and re-feeding as

well as the severity, type and length of the restriction, not simply chronic CR optimizes the effects on MS pathology and symptoms. Chronic moderate to severe CR (33–60%) has been shown to promote protective effects in the prevention of EAE in various MS models (Piccio et al., 2008; Esquifino et al., 2004). After chronic CR, 33% or 40% of mice showed a minor decrease in the EAE induction and disease severity but were protected from EAE induced inflammation, demyelination, and axon injury (Piccio et al., 2008; Esquifino et al., 2004). Interestingly, only severe CR (66% caloric restricted group) completely prevented EAE induction (Piccio et al., 2008; Esquifino et al., 2004). Similarly, a chronic ketogenic diet, consisting of a 4:1 ratio of fat to carbohydrate and protein (DeVivo et al., 1978), has been reported to serve as a preventive measure against EAE (Kim do et al., 2012). However, similar to the effect of chronic moderate CR, KD did not completely prevent the EAE disease induction but reduced the severity of the disease (Kim do et al., 2012). Intermittent fasting (IF), where fasting is applied every other day, was also shown to help reduce EAE disease severity (Kafami et al., 2010). Eight weeks of IF prior to the EAE immunization completely protected mice from EAE induction compared to 75% incident rate of *ad libitum* group (Kafami et al., 2010). Although the exact mode of these protective effects is still under active investigation, these dietary interventions caused similar changes in immune response including a significant reduction in circulating and CNS-derived $CD4^+$ and $CD8^+$ T cells and $CD11b^+CD45^+$ cells (macrophages and microglia) compared to the control diet group, and markedly reduced cytokines (IL-1β, IL-6, TNF-α, IL-12, IL-17) and chemokines (IFN-γ, MCP-1, MIP-1α, MIP-1β) (Piccio et al., 2008; Esquifino et al., 2004; Kim do et al., 2012; Kafami et al., 2010).

4. Fasting mimicking diets as a treatment for MS and other autoimmunities

4.1. Fasting and murine MS models

Some of the major limitations of the chronic dietary restrictions listed above are: 1) that they would be very difficult to adopt for the great majority of the population, 2) that they can cause both protective and detrimental effects including impaired immune responses and would healing, 3) that they are effective in the prevention but not treatment of MS. Furthermore, these dietary interventions fail to address one of the core aspects of MS treatment, which is the need to stimulate both the regeneration of functional white blood cells and the remyelination at the demyelinated lesions either by stimulating myelin production or regenerating oligodendrocyte from oligodendrocyte precursor cells. Periodic treatment with a fasting mimicking diet (FMD) with a very low calorie and protein content has the potential to overcome the limitations listed above. FMD cycles were shown to attenuate EAE symptoms by modulating immune cells and promoting oligodendrocyte precursor cell regeneration (Choi et al., 2016). This study showed that a periodic fasting mimicking dietary intervention has potent MS treatment effects in mice but also that it has the potential to minimize side effects as well as compliance issues. FMD cycles not only resulted in a reduction in dendritic cells which are known to play an important role as antigen presenting cells (APC) that secrete cytokines responsible for activating T lymphocytes, but also reduced circulating MOG_{35-55} specific $CD4^+$ T cells, Th1 and Th17 cells and reduced serum cytokines such as IFN-γ, IL-17 and TNF-α. Furthermore, the FMD treatment increased anti-inflammatory $CD4^+$ Treg. It was previously shown that during the

cycles of the prolonged fasting, the immune cells undergo system-wide apoptosis followed by hematopoietic stem cell based regeneration upon re-introduction of nutrients (re-feeding period) in a IGF-1-PKA dependent manner (Cheng et al., 2014). Similarly, FMD cycles cause apoptosis of autoreactive T cells, which are replaced by newly generated naïve T cells during the re-feeding period (Choi et al., 2016) (Fig. 2). More importantly, the FMD treatments promoted oligodendrocyte precursor cell dependent regeneration, which is known to participate in remylelination of demyelinated axons.

4.2. Dietary restrictions in human clinical trials

In a human clinical trial, a 7-day cycle of a FMD followed by 6 months of a Mediterranean diet, was reported to be safe and feasible (Choi et al., 2016). A chronic KD intervention also resulted in potentially positive effects on relapse-remitting MS (RRMS) patients. Moreover, both the FMD and the chronic KD were associated with positive changes in self-reported Health-Related Quality of Life (HRQoL) and an improvement in Expanded Disability Status Scales (EDSS) compared to what was reported by the control diet group. Similar to the rodent study, the clinical trial also reports a reduction in lymphocyte upon FMD intervention which indicates that the diet may work in a similar manner in mice and humans. However, whether or not FMD cycles will reduce MS pathology in humans is still unclear and must be tested in larger randomized clinical trials. One of the possible mechanisms of the FMD-dependent modulation of autoimmunity involves the up-regulation of serum glucocorticoid, adiponectin and the reduction of IL-6 and leptin (Piccio et al., 2008). RRMS patient had significantly higher leptin and resistin levels and lower levels of adiponectin and Treg cells (Kraszula et al., 2012). Therefore, PF and FMDs may stimulate endogenous production of glucocorticoid and adiponectin which may contribute to a system-wide suppression of specific immune responses.

4.3. Autoimmune diabetes

Type 1 diabetes is an autoimmune disease commonly diagnosed in children and young adults, leading to the destruction of the insulin-producing pancreatic beta cell in the islets of Langerhans leading to a lack of insulin production (King, 2012; Hyttinen et al., 2003). Type I diabetes is associated with the infiltration of innate and adaptive immune cells that produce cytokines which promote beta cell apoptosis and increase infiltration of islet-specific T cells. Infiltrating T cells, predominantly CD4^{+} or CD8^{+}, play an important role in the induction type 1 diabetes mellitus (Hanninen et al., 1992; Conrad et al., 1994). Studies using human and murine models of diabetes have demonstrated that the destructive autoimmune process in type 1 diabetes requires both CD4^{+} and CD8^{+} T cells and macrophages (Yoon and Jun 2001; Wong and Janeway, 1997). Although DR has been widely studied for the prevention and treatment for type 2 diabetes, the effect of different forms of DR in autoimmune type 1 diabetes is poorly understood.

4.3.1. Dietary restriction in diabetes type 1 murine models—Studies have shown that CR improves glycemic homeostasis and reduces oxidative stress and lipid peroxidation in streptozotocin (STZ)-induced type 1 diabetic (T1D) rats model (Anson et al., 2003; Mattson and Wan, 2005; Wegge et al., 2004). Chronic CR (30% reduction in daily caloric intake) for 9 weeks prior to STZ-induced diabetes showed a protection against diabetic

insults (Ugochukwu and Figgers, 2007). CR inhibits up-regulation of inflammatory cytokines (IL-1β, IL-4, and IL-6) and TNF-α, activates IL-10 and haptoglobin in the plasma of streptozotocin-induced diabetic rats (Ugochukwu and Figgers, 2007). IF, performed for 30 days from 5 p.m. to 8 a.m., minimized the increase in pancreatic, hepatic and renal weight, which is commonly observed in the STZ-treated rats (Belkacemi et al., 2012). IF improved glucose tolerance, insulin sensitivity and percentage of apoptotic B cells in the pancreas of STZ-induced diabetic rats (Belkacemi et al., 2012). Moreover, an alteration in the dietary protein content has been shown to exacerbate diabetes. High-protein diet accelerated the onset of disease in spontaneous autoimmune models are the non-obese diabetic (NOD) mice (Schneider et al., 1996). It was shown that the types of dietary protein have a major impact on the incidence of diabetes in the NOD mouse. NOD mice fed with meat or casein result in an early onset of the disease while mice fed with casein hydrolysate, a denatured form, or lactalbumin-based diet was relatively protected against the disease (Beales et al., 2002; Elliott et al., 1988).

Recently, cycles of FMD were shown to promote the reprogramming of pancreatic islet cells, leading to the induction of a gene expression profile with similarities to that observed during fetal development and able to reverse insulin deficiency in mouse models of Type 1 and Type 2 diabetes (Cheng et al., *Cell*, in press). Fasting mimicking conditions also reversed insulin deficiency defects in human cells derived from autoimmune type 1 diabetes patients, indicating that FMD has the potential to treat human diabetes.

Thus, we are only beginning to understand the relationship between nutrition and the autoimmunity related to T1D. However, FMD cycles appear to have high potential for the treatment of both Type 1 and Type 2 diabetes. In fact, a recent pilot study showed a long-lasting reduction in fasting glucose in subjects who completed 3 monthly cycles of the FMD, although it is not known whether this effect involves pancreatic regeneration (Brandhorst et al., 2015). Additional animal and randomized studies are needed to confirm these results and serve as the foundation for dietary FDA approved treatments for autoimmune diabetes.

4.4. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease, characterized by synovial hyperplasia, production of autoantibody, destruction of cartilage and bone and malformation and destruction of multiple joints (Harris, 1990; Firestein, 1992). The pathogenesis of RA is complicated involving both genetic and external factors (Symmons, 2003). Similar to other autoimmune disease, RA involves an aberrant pathway of T cell activation in both the initial and progression phases of the disease (VanderBorght et al., 2001; Cope et al., 2007). However, it has become clear that pathogenesis of RA cannot simply be explained in terms of a classical antigen-driven expansion of effector T cells, but that disease progression involves a more complex autoimmune response. It is largely accepted that RA is closely associated with CD4+ T effector cells (both Th-1, 2, 17) which can be detected in RA synovial joints (Yudoh et al., 2000; Chabaud et al., 1999; Ronnelid et al., 1998; Kanik et al., 1998). Moreover, patients with RA have a premature immune aging phenotype including accumulation of CD4+ CD28− T cells, telomeric shortening in hematopoietic stem cells, proliferation defects of naïve CD4 T cells, premature loss of naïve

CD4 T cells telomeres, loss of telomerase in T cells, and impaired DNA damage repair due to ATM insufficiency (Weyand et al., 2014). Different dietary interventions have been shown to or have the potential to attenuate and possibly reverse the symptoms of RA.

4.4.1. Dietary restriction in RA patients—Fasting has been actively studied as an alternative therapy for RA and a number of clinical trials has been conducted to test its efficacy (Muller et al., 2001; Kjeldsen-Kragh et al., 1991; Skoldstam et al., 1979; Darlington et al., 1986). Fifty-three RA patients were randomly grouped into either a control diet or fasting group in which subjects underwent fasting only once for a period ranging from 7 to 10 days followed by a vegan diet for 3.5 months (Kjeldsen-Kragh et al., 1991). Patients in the fasting group reported a significant improvement in all clinical parameters and half of the laboratory parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) that are correlated with RA disease severity (Kjeldsen-Kragh et al., 1991). In a similar study, twenty RA patients were subjected to either a control or fasting (7–10 days) period followed by a strict vegan diet. Patients in the fasting group reported significantly less pain and an improvement in symptoms (Skoldstam, 1986). Thus, either periodic fasting or a FMD have the potential to treat RA, although larger randomized studies are necessary to test this possibility. It will be important to test the effect of cycles of FMD that are applied every 1–2 months on RA patients, with or without the need to undergo drastic dietary changes, which are unlikely to be feasible for the majority of patients.

5. Conclusion

We are now just beginning to understand the complex connections between metabolism and the regulation of T cells in relation to autoimmune diseases development and progression. In the development of novel therapeutics for autoimmune disorders, targeting T cell metabolism by dietary interventions provides an alternative way to control T cell fate and function (O'Sullivan and Pearce, 2015). CR or various other dietary restrictions and particularly relatively long-term fasting, or FMDs cycles followed by refeeding appear to decrease the biological rate of aging and promote anti-inflammatory effects, and may contribute to alleviate and possibly reverse a variety of autoimmune disorders as well as immunosenescence by killing old and damaged cells and replacing them with young and functional ones. However, the limited number of studies and of participants in studies described in this review, underlines the need for a set of larger randomized clinical trials testing both the feasibility and efficacy of FMDs, fasting and other DR-based interventions on the treatment of autoimmunities. Notably, whereas patients can undergo water only fasting only in a clinic, FMDs are already recommended by physicians in the U.S. and Europe, and do not require hospitalization.

In summary, chronic CR and other chronic dietary restrictions have shown some efficacy in the prevention but not the treatment of autoimmunities. Thus, chronic CR and other DRs have the potential to prevent many age-related diseases, including autoimmunity, possibly by delaying aging. However, chronic CR is associated with poor compliance and long-term studies in monkeys indicate that diet composition, more than the restriction, may have a key role in disease prevention (Mattison et al., 2012; Colman et al., 2014). In contrast, FMD cycles followed by refeeding are emerging as both an effective and feasible intervention with

the potential for long-term and wide use. They are also emerging as potentially powerful interventions in the treatment of other age-related diseases and conditions including immunosenescence. The ability of periodic cycles of PF/FMD to suppress autoimmune cells and the ability of the re-feeding phase to help repair the damaged sites, and to activate hematopoietic cells to provide healthy immune cells indicate that they stimulate highly sophisticated repair and regenerative programs with similarities to those activated during development (Fig. 2). Notably, the periodic PF/FMD combines a period of severe restriction sufficiently long to promote the death of a significant portion of damaged cells with a period of high nourishment re-feeding able to promote the opposite effect on growth and other factors leading to multi-system regeneration. These programs, which may have been frequently activated under the normal conditions in which famine periods were commonly encountered, may remain dormant in individuals constantly exposed to food intake and in which fasting periods lasting for over a few days are generally absent.

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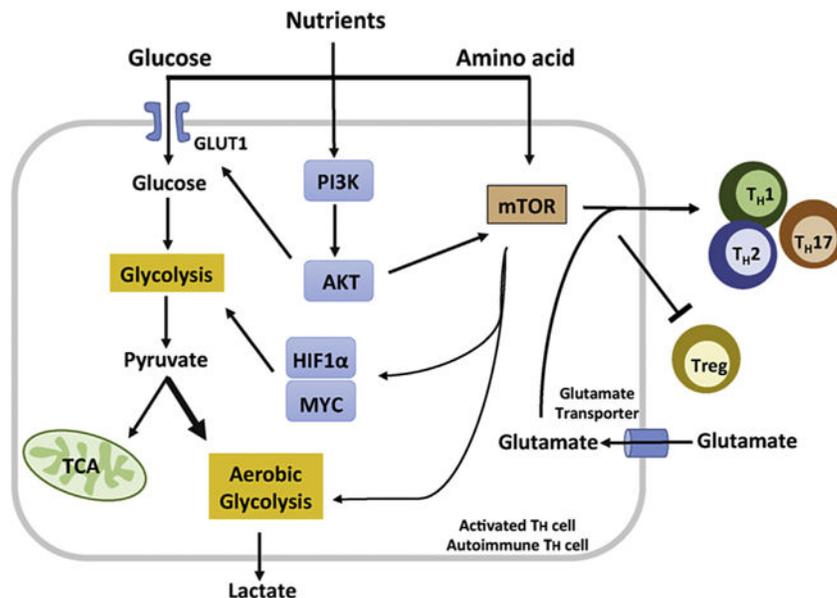
Fig. 1. Change in metabolism of the activated T cells and autoimmune T cells
Metabolism plays an important role in T cell proliferation and differentiation and dysregulation of metabolism is often linked to autoimmune diseases. Upon activation, T cells primarily use aerobic glycolysis and produce lactate as a byproduct to support the biosynthetic precursors that are required for cellular proliferation. Increased lactate and abnormal glycolytic function are frequently observed in T cells from asthma and rheumatoid arthritis patients. During activation, T cells increase the expression of glutamine transporters and glutamate metabolism to support T cell proliferation and differentiation. Interestingly, increased levels of glutamate and glutamine are observed at the site of demyelination and axonal degeneration in MS patients. Mammalian target of rapamycin (mTOR) promotes activation and differentiation of the T effector cells, and down-regulates Treg differentiation. Also, the Akt-mTOR pathway act as a negative regulator of Treg cells. Activation of mTORC1 promotes glycolysis through hypoxia-induced factor 1α (HIF1α), and dysregulation of mTOR is frequently observed in MS patients. These changes in metabolism provide a unique opportunity to target specific pathways for disease treatment purposes.
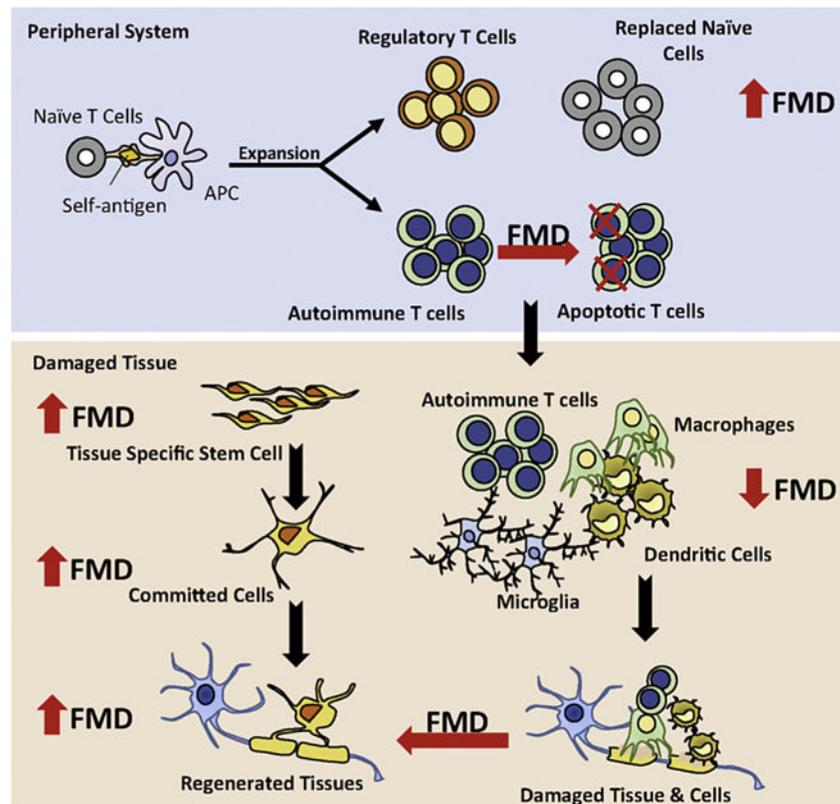
Fig. 2. FMD-dependent modulation of autoimmunity and tissue-specific regeneration of damaged cells

FMD causes a systemic anti-inflammatory effect and specific suppression of autoimmune cells whereas the re-feeding period stimulates hematopoietic cells to generate naïve cells to replace the immune cells eliminated. FMD also promotes tissue-specific stem cells that repair the damaged sites.

Table 1

Calorie and Dietary restriction.

Types		Definition	Duration	Ref
Calorie Restriction (CR)		20–40% Reduction in total calorie intake	Chronic	(1,2)
Dietary Restriction	Ketogenic Diet (KD)	High-fat, low-carbohydrate diet. In human, diets with caloric contents of up to 75–80% fat and 15% protein are commonly used to treat various neurological disorders.	Chronic	(3)
	Fasting/Prolonged Fasting (PF)/Intermittent Fasting (IF)/Alternative Day Feeding (ADF)	Fasting: Complete absence of food intake. PF refers to at least 2 and usually 3 or more consecutive fasting days, which can be repeated periodically.	Periodic PF: 2 or more days/2–4 weeks IF/ADF: 1 day on 1 day off	(4,5)
		IF and ADF eliminate or greatly reduce daily intake of food/calories intermittently (usually every other day or every 2–3 days). Usually ADF refers to alternation of a day of feeding and a day of either water only fasting or a very low calorie diet.		
	Fasting mimicking diet (FMD)	Formulations composition of macronutrients and micronutrients specifically formulated to trigger responses such as reduced glucose and insulin-like growth factor 1 (IGF-1) level, and increased ketone bodies, while maximizing caloric intake	Periodic (2–7 days every 15–365 days)	(6)

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