Molecular and Cellular Endocrinology 455 (2017) 4–12

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

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

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ARTICLE INFO

Article history:
Received 9 June 2016
Received in revised form
25 January 2017
Accepted 25 January 2017
Available online 28 January 2017

Keywords:
Immunosenescence
Autoimmune diseases
Metabolism
Aging
Fasting
Fasting mimicking diet

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.

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).

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-

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http://dx.doi.org/10.1016/j.mce.2017.01.042
0303-7207/

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

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. 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.	Periodic PF: 2 or more days/2–4 weeks IF/ADF: 1 day on 1 day off	(4,5)
	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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