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Review Article

CD1d-restricted Natural Killer T Cells in Metabolic Disorders

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Abstract

Natural killer T (NKT) cells are a unique subset of innate immune cells, which express both T cell receptors (TCRs) and natural killer receptors. Among NKT cells, invariant NKT (iNKT) cells express in variant TCRs, recognize glycolipid antigens presented by CD1d, and produce both pro inflammatory and anti inflammatory cytokines. Recent findings showed that NKT cells, especially iNKT cells, play a regulatory role in metabolic abnormalities mainly through the interaction with CD1d. This review focused on NKT cells in obesity and their contribution to metabolic disorders, such as glucose intolerance, atherosclerosis, and non alcoholic fatty liver disease.

Keywords: NKT cell; CD1d; Metabolic abnormality; Glycolipid antigen; MTP

Introduction

Obesity has become a major problem around the world due to its contribution to morbidity and mortality. Obesity is one of the essential contributors to the development of metabolic diseases, such as hypertension, hyperlipidemia, atherosclerosis, and diabetes mellitus [1]. In addition, obesity is thought to be closely associated with systemic inflammation, which is an underlying contributor to many of these metabolic diseases [2, 3]. Natural killer T cells are innate immune cells, can acts either pro- or anti-inflammatory, and work as immune regulatory. Invariant natural killer T (iNKT) cells are a unique NKT cell population expressing invariant T cell receptors (TCRs) (Vα24 in humans and Vα14 in mice), recognize glycolipid antigens through CD1d, and can be either pro- or anti-inflammatory [4]. The subsets of NKT cells are found preferentially in the liver [5] and adipose tissue [6, 7], which are essential sites of lipid metabolic regulation, and are considered essential participants in metabolic abnormalities. This review summarizes and discusses the role of CD1d-restricted NKT cells in obesity and their contribution to metabolic disorders.

NKT Cells in Lipid Metabolism

Obesity develops as the result of increases in adipose tissues due to excessive energy intake. White adipose tissues is the primary site of energy storage, and white fat storage is associated with the metabolic complications of obesity [8]. On the other hand, microsomal triglyceride transfer protein (MTP) mainly located in the endoplasmic reticulum (ER) of hepatocytes and intestinal epithelial cells plays an essential role in the transfer of lipids, including phospholipids, triglycerides, and cholesterol. Dietary lipids are taken up by the enterocytes through various transporters as free fatty acids, monoacylglycerols and free cholesterol, transferred to the ER by MTP, and used for the synthesis of phospholipids, triacylglycerols and cholesterol esters [9]. These lipids are stored in the cytosol as lipid droplets. MTP is a key protein in the assembly and secretion of triglyceride-rich lipoproteins (apolipoprotein B, apoB) in the intestine and liver, and the abnormality of such lipoproteins predispose individuals to various metabolic diseases, such as obesity, atherosclerosis, diabetes, and nonalcoholic fatty liver disease [10].

In addition, iNKT cells are lipid antigen-specific lymphocytes that recognize glycolipid antigens presented on CD1d molecules and produce large amounts of T helper (Th)1 cytokines, including interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α); and Th2 cytokines, including interleukins (IL)-4 and IL-10 [4]. CD1d is a major histocompatibility complex (MHC) class 1-like molecule widely found in systemic organs [11, 12]. The function of glycolipid antigen presentation by CD1d has been shown to be regulated by MTP [13]. MTP deficiency is associated with impaired activation and reduced number and phenotypic alterations of NKT cells, resulting in resistance to immune pathogenesis associated with NKT cell-mediated diseases [13 – 15]. The regulation of CD1d function by MTP occurred not only in apoB-secreting cells, such as hepatocytes and intestinal epithelial cells (IECs) [13], but also antigen presenting cells (APCs) [14, 15] and adipocyte [16]. The precise function of MTP in adipocytes or APCs is unknown. MTP is presumed to load the first endogenous lipid into the CD1d in APCs, where it was suggested to play a role in lipid droplet formation [16]. Moreover, NKT cell-mediated inflammation was recently shown to be regulated by interactions among CD1d, MTP, and cytokines [17]. Thus, MTP is an essential protein not only in lipid metabolism but also the lipid antigen presentation function of CD1d.

Furthermore, proteins involved in lipoprotein metabolism other than MTP, such as low-density lipoprotein receptor (LDLr) [18, 19], scavenger receptors [20], and cholesterol membrane transporters [21], are able to modulate NKT cells homeostasis and activation. LDLr-related protein has been shown to be expressed in macrophages and to be necessary for the production of Th2 cytokines not but Th1 cytokines [19]. These data suggest that not only the modification of antigen presentation on CD1d by MTP but also lipid transfer and metabolism by lipid receptors may affect the functions of NKT cells.

NKT Cells and Intestinal Microbiota

Innate immune cells, including NKT cells, can also be activated

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by intestinal microbiota-derived antigens through Toll-like receptor (TLR) signaling [22 – 24]. Recently, commensally microbiota was also shown to regulate the development and function of CD1d-restricted NKT cells through interactions with lipid antigens [25-27]. Intestinal microbiota-derived lipids and metabolites, as well as cytokines and chemokines produced in response to microbial recognition, may contribute to systemic NKT cell development [28]. The intestinal microbiota is different between healthy and obese subjects [29]. The relative proportion of the fecal microbiota are also altered in obese human subjects but change with weight loss [30]. Furthermore, transplantation of intestinal microbiota from obese mice resulted in greater adiposity in recipients than transplantation of microbiota from lean donors [31]. These differences in the intestinal microbiota associated with obesity may affect the function of NKT cells. Probiotic antigens may stimulate hepatic NKT cells and restore the number of hepatic NKT cells in mice fed a high-fat diet through interactions between lipid antigens and CD1d, but not through TLR4 signaling [32]. Thus, NKT cells are regulated by not only glycolipid antigen presentation through CD1d but also intestinal microbiota-derived factors. NKT cells may be associated with the development of systemic inflammation through metabolic modifications from lean to obese.

The Contribution of NKT Cells to Metabolic Abnormalities

a. Obesity

Recent studies have suggested that NKT cells are involved in systemic metabolic disorders. For example, iNKT cells were found to be depleted in the adipose tissue of obese individuals [6, 7, 33], while restoring iNKT cells by adoptive transfer induced weight loss [7]. This iNKT cell depletion was correlated with proinflammatory macro phage infiltration [7]. The numbers of iNKT cells could be restored after weight loss [7]. CD1d-deficient mice fed a high-fat diet have been shown to aggravate metabolic parameters, such as glucose homeostasis and hepatic lipid metabolism [34]. Furthermore, CD1d-deficient mice fed a high-fat diet were more susceptible to weight gain, along with increased adiposity and greater induction of inflammatory gene expression in the liver and white adipose tissues [35]. These findings suggest that CD1d-restricted NKT cells protect against diet-induced obesity through the regulation of cytokine production [36].

On the other hand, obesity-induced inflammation is known to induce various metabolic disorders [37]. CD1d is expressed at high levels in adipocytes and CD1d-expressing adipocytes regulate iNKT cells. The iNKT cell population and CD1d expression level were shown to be reduced in the adipose tissues of obese mice and humans, and iNKT cell-deficient mice became more obese and exhibited increased adipose tissue inflammation at an early stage of obesity [38]. Furthermore, lack of iNKT cells was shown to affect lipid metabolism in the adipose tissue of diet-induced obese mice [39]. Jα18-deficent mice, which lack iNKT cells, were resistant to diet-induced obesity and showed increased lipogenesis counter balanced by elevated lipase expansion and basal lipolysis [39].

Adoptive transfer of iNKT cells and α-galactosylceramide treatment were shown to protect against weight gain and adipocyte hypertrophy and to reverse obesity-associated metabolic disorders [7]. Thus, iNKT cells are associated with obesity and obesity-induced metabolic disorders, and may be a potential therapeutic target for obesity-induced metabolic disorders.

b. Glucose intolerance

CD1d-deficient mice, which lack iNKT cells, were shown to worsen glucose homeostasis when they had been fed a high-fat diet [34, 35], while adoptive transfer of iNKT cells improved glucose intolerance [7]. Adoptive transfer of iNKT cells or treatment with glycolipid antigens has been shown to improve glucose intolerance in ob/ob mice, which are deficient in leptin and are regarded as a model for obesity [40, 41]. CD1d-restricted iNKT cells in adipose tissue were shown to play an essential role in preventing insulin resistance [42]. NKT cell function was directly modulated by adipocytes, which acted as lipid antigen presenting cells in a CD1d-dependent manner [42]. These findings suggest that CD1d-restricted iNKT cells protect against glucose intolerance [36].

c. Atherosclerosis

Atherosclerosis is one of the major disorders due to metabolic abnormalities, which leads to induce various serious complications. CD1d-restricted iNKT cells were shown to exacerbate atherosclerosis through the production of proinflammatory cytokines [43, 44]. Atherosclerogenic ApoE-deficient mice crossed with CD1d-deficient mice lacking iNKT cells were shown to have a 25% reduction in atherosclerosis lesion size [43]. Furthermore, ApoE-deficient mice treated with α-galactosylceramide, a glycolipid that activates iNKT cells, showed a 50% increase in atherosclerosis with inflammatory Th1 and Th2 cytokines [43]. Increasing the complement of iNKT cells exacerbated aortic atherosclerosis and inflammation in obesogenic diet-fed LDLr-deficient mice, which are susceptible to dyslipidemia, hyperinsulinemia, insulin resistance, and hepatic triglyceride accumulation [45]. Furthermore, α-galactosylceramide treatment of ApoE-deficient mice with established atherosclerosis lesions had no significant effect on lesion size, but decreased their collagen content in atherosclerosis [46]. Thus, CD1d-restricted iNKT cells play a role in the formation of atherosclerosis through proinflammatory factors.

d. Nonalcoholic fatty liver disease (NAFLD)

CD1d-deficient mice, which lack iNKT cells, fed a high-fat diet showed increased susceptibility to fatty liver, along with increased adiposity and greater induction of inflammatory genes in the liver compared to normal controls [35]. Depletion of NKT cells has also been reported in ob/ob mice, which are regarded as a model of obesity-related fatty liver, through hepatic sensitization toward proinflammatory conditions induced by endotoxins from the gut, by increased production of adipokines, or by ER stress [47 – 50]. In wild-type mice fed a choline-deficient or high-fat diet, which are also regarded as a model of NAFLD, reductions in the numbers of hepatic NKT cells were accompanied by increased Th1 cytokine production [51, 52]. Hepatic NKT cells were also reported to be decreased in hepatosteatosis through KC- [53] and IL-12 [54]-dependent mechanisms. In addition, administration of probiotics has been reported to improve high-fat diet-induced hepatic steatosis by increasing hepatic NKT cells through reductions in TNF-α production and nuclear factor-κB binding activity [55].

Adoptive transfer of NKT cells or treatment with glycolipid antigens has been shown to reduce hepatic steatosis in ob/ob mice [40, 41]. Moreover, adrenergic activation by norepinephrine has

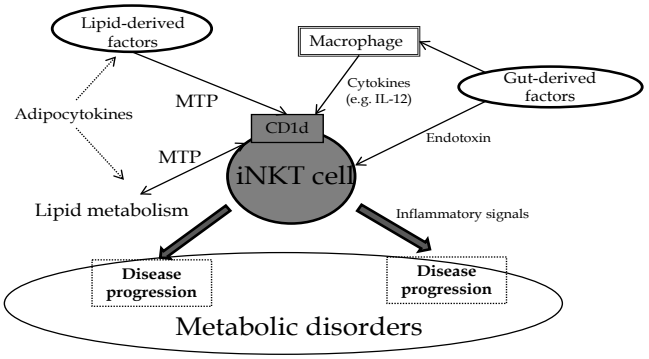

Figure 1: Schema of interactions of NKT cells in metabolic disorders. MTP: microsomal triglyceride transfer protein.

been reported to induce the expansion of NKT cell populations and improve hepatic steatosis [48]. In humans, NKT cell numbers were decreased in the livers of patients with relatively mild NAFLD [54]. Taken together, these findings indicate that hepatic NKT cells are preferentially protective during the process of hepatic steatosis through various metabolic factors and cytokines, especially those produced by KCs and associated with gut-derived factors, such as endotoxin.

During advanced stages of NAFLD, the number of hepatic NKT cells was increased in the liver. These increases were accompanied by increased activation of the hedgehog (Hh) pathway and increased osteopontin production, leading to promotion of liver fibrosis through activation of hepatic stellate cells [56, 57]. In human NAFLD, the number of hepatic NKT cells increases with disease progression [58, 59]. Furthermore, disease progression is accompanied by increased activation of antigen presenting cells, such as KCs, and increased expression of CD1d [58]. Thus, CD1d-restricted NKT cells are activated in the livers of patients with NAFLD, at least in those with advanced disease.

Summary and Conclusion

CD1d-restricted NKT cells may play an essential role in the interaction between metabolism and the immune system to regulate energy balance through factors derived from the gut (Figure 1). Antigen presentation of CD1d through the interaction of lipid-derived factors and sensitization of NKT cells from gut-derived factors through macrophages may have important roles in metabolic disorders. The modulation of NKT cells may be a therapeutic target in various metabolic diseases.

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