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Contribution of lipid-reactive natural killer T cells to obesity-associated inflammation and insulin resistance

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Obesity is associated with a low-grade, chronic inflammation that promotes the development of a variety of diseases, most notably type 2 diabetes. A number of cell types of the innate and adaptive immune systems have been implicated in this process. Recent studies have focused on the role of natural killer T (NKT) cells, a subset of T lymphocytes that react with lipids, in the development of obesity-associated diseases. These studies have shown that invariant NKT (iNKT) cells, a population of NKT cells expressing a semi-invariant T cell receptor, become rapidly activated in response to lipid excess, and that these cells influence the capacity of other leukocytes to produce cytokines during the progression of obesity. The role of NKT cells in obesity-associated inflammation and insulin resistance has been investigated using NKT cell-deficient animals, adoptive transfer of NKT cells and an iNKT cell agonist. While divergent results have been obtained, it is now clear that NKT cells can modulate the inflammatory milieu in obesity, suggesting that these cells could be targeted for therapeutic intervention in obesity-associated diseases.

Introduction

Approximately 30% of the adult population in the United States is obese, and this obesity epidemic has also spread to children. Obesity is associated with susceptibility to a variety of diseases, including type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular disease, airway disease and cancer, resulting in reduced life expectancy. A common denominator that links these maladies to obesity is inflammation (for a review, see refs. 1–5). Inflammation represents the response of the host to pathogenic insults or tissue injury. Obesity is associated with a chronic low-grade inflammation, now referred to as "metainflammation," in metabolically active tissues such as adipose, liver and muscle, as well as pancreas and brain. While the signals that initiate these inflammatory processes remain unclear, emerging evidence suggests that nutrients and the modifications they cause in adipose tissue during situations of nutritional overload can activate immune sensors. Activation of immune sensors such as the Toll-like receptors (TLRs) in obese tissues results in the induction of inflammatory kinases and transcription factors, followed by production of pro-inflammatory cytokines. In turn, these cytokines may interfere with insulin signaling pathways in a variety of cell types, resulting in insulin resistance, which might ultimately progress to type 2 diabetes.

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A variety of cell types of the innate and adaptive immune systems have been implicated in regulating the inflammatory process during obesity (for a review, see refs. 1–5). Much research has focused on macrophages, which can adopt a pro-inflammatory M1 or an anti-inflammatory M2 phenotype and, thus, contribute either positively or negatively to the inflammatory process during obesity. Other innate cell types such as neutrophils and mast cells have been implicated in promoting inflammation and insulin resistance during obesity, whereas eosinophils and myeloid-derived suppressor cells have been suggested to play a suppressive role. Cells of the adaptive immune response are also involved, with B cells, $CD8^+$ T lymphocytes and T helper type 1 (Th1)-polarized $CD4^+$ T cells playing a pathogenic role, and $CD4^+CD25^+$ regulatory T cells playing a suppressive role. Recent studies have focused on another regulatory T cell subset, natural killer T (NKT) cells, in the development of obesity-associated inflammation and diseases.

Natural Killer T Cells

NKT cells are a group of T lymphocytes that react with lipid antigens bound with the antigen-presenting molecule CD1d, which is expressed by hematopoietic cells, such as macrophages, dendritic cells and B cells, as well as by other cell types such as hepatocytes (for a review, see refs. 6–11). NKT cells also express several surface markers such as NK1.1 that are characteristic of the natural killer (NK) cell lineage, which belongs to the innate arm of the immune system. Two subpopulations of NKT cells have been identified that differ in their lipid antigen-specificity and functions.[12] Type 1 or invariant NKT (iNKT) cells express T cell receptors (TCRs) with an invariant α chain (Vα14-Jα18 in mice and Vα24-Jα18 in humans), whereas Type 2 or variant NKT (vNKT) cells express more diverse TCRs. Hence, both of these cell types are absent in *CD1d*-deficient mice, whereas *Jα18*-deficient

mice only lack iNKT cells. iNKT cells are also distinguished from vNKT cells by their reactivity with α-galactosylceramide (α-GalCer), a glycosphingolipid derived from bacteria associated with a marine sponge.[13] Consequently, iNKT cells can be identified most reliably by staining with α-GalCer-loaded recombinant CD1d molecules (i.e., CD1d/α-GalCer-tetramers or -dimers).[12] iNKT cells also react with lipid antigens derived from several pathogenic bacteria (e.g., *Borrelia burgdorferi, Helicobacter pylori* and Streptoccoccus spp) and with endogenous lipids such as isoglobotrihexosylceramide (iGb3) and β-glucosylceramide (β-GluCer).[11] The antigen-specificity of vNKT cells is less clear, although many of these cells can react with the β-linked glycolipid sulfatide. NKT cells can contribute to a variety of diseases, including infections, cancer, autoimmunity, transplant rejection, airway disease and other inflammatory conditions. Although most of these studies have focused on iNKT cells, vNKT cells can contribute to some of these maladies as well, often exhibiting opposing effects to iNKT cells.[14] Because of their reactivity with lipids, their capacity to produce a variety of both pro- and anti-inflammatory cytokines, and their abundance in metabolically active organs, recent studies have investigated the role of NKT cells in the development of obesity-related inflammation and insulin resistance.

Functional Status of NKT Cells in Metabolically Active Organs During Obesity

NKT cells are abundant in the liver[15] and white adipose tissue,[16] two organs that play a critical role in the development of metainflammation. Several earlier studies, mostly employing surrogate markers for NKT cells, reported that hepatic NKT cells in mice on a high-fat diet (HFD), or in leptin-deficient *ob/ob* mice on a normal chow diet, gradually decline in numbers.[17-20] This finding was subsequently confirmed for iNKT cells, using α-GalCer/CD1d-tetramers to specifically identify this NKT cell subset in liver of wild-type C57BL/6 mice fed with a HFD, and in *ob/ob* or leptin receptor-deficient *db/db* mice fed with a normal chow diet.[21,22] Similar results were obtained for adipose tissue,[22] although only a partial loss of iNKT cells was observed in some studies.[21] Furthermore, it was found that within several days on a HFD, iNKT cells showed evidence of activation,[21,23] as demonstrated by early but transient expansion of this cell population, and increased expression of the activation marker ICOS (inducible costimulatory molecule) on these cells, concomitant with a reduction in the expression of the NK cell marker NK1.1. These alterations in iNKT cells, particularly in the white adipose tissue, occurred before significant increases in macrophages and $CD8^+$ T cells, two cell types that play a pathogenic role in the development of obesity-associated inflammation and insulin resistance, were observed.[21] These findings therefore suggested that iNKT cells are one of the first cell types that become activated in response to nutrient lipid excess.

Several research groups analyzed the functional properties of iNKT cells in obesity.[21,22,24,25] Although iNKT cells in adipose tissue were able to produce a variety of pro- and anti-inflammatory cytokines, divergent results were obtained regarding the profile of cytokines produced by iNKT cells during the progression of obesity. Some research groups reported that iNKT cells from adipose tissue, as compared with iNKT cells from spleen and liver, exhibit a Th2-biased cytokine profile.[22,24] Another group of investigators further reported that the cytokine profile of iNKT cells becomes progressively biased toward Th2 cytokine production in obese mice.[25] However, another study reported that iNKT cells gradually acquire increased capacity to secrete both pro- and anti-inflammatory cytokines during the progression of obesity.[21] In turn, these alterations in iNKT cells, regardless of their nature, correlated with the increased pro-inflammatory environment in liver and white adipose tissue.

Collectively, these findings suggested that iNKT cells are one of the first cell types that become activated in response to lipid excess, and that their chronic stimulation gradually modifies their functional properties, which contributes to the overall cytokine environment in metabolically active organs.

Although it is clear that iNKT cells become activated in response to lipid excess, mechanisms involved remain unknown. Based on studies that have investigated the response of iNKT cells to various microorganisms that lack cognate iNKT cell antigens (for a review, see refs. 10 and 11), we favor the idea that nutrient lipids can activate immune sensors on antigen-presenting cells, resulting in cytokine secretion and alterations in the endogenous lipid pool that is available for binding with CD1d molecules (**Fig. 1**). Additional studies will be needed to investigate this and other possible mechanisms by which NKT cells become activated during situations of nutrient excess.

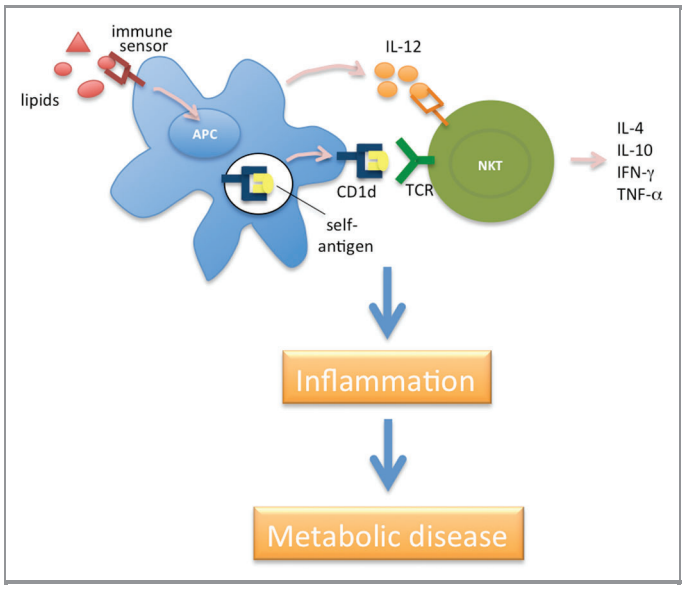

Figure 1. Proposed role of NKT cells in obesity-associated inflammation and metabolic diseases. In this model, nutrient lipids activate immune sensors expressed on antigen-presenting cells (APCs), inducing these cells to produce cytokines such as IL-12, and to induce the synthesis of NKT cell antigens. The pro-inflammatory cytokines subsequently synergize with the CD1d-bound lipid antigens to activate NKT cells. In turn, the NKT cells produce cytokines such as IL-4, IL-10, interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) and contribute to the overall inflammatory milieu, which influences the development of insulin resistance and other metabolic maladies.

Table 1. Effect of NKT cells on insulin resistance reported in different studies

Study*	Mice†	Diet‡	Manipulation§	Effect on insulin resistance‖
Elinav et al.[20]	*ob/ob*	chow	Transfer of B6 NK1.1$^+$CD3$^+$ cells, then 12 d rest	amelioration
Margalit et al.[32]	*ob/ob*	chow	β-GluCer, chronic (daily)	amelioration
Ma et al.[26]	B6	HFD	Transfer of B6 NK1.1$^+$TCR$^+$ cells, then 4 d rest	amelioration
Ohmura et al.[27]	*β2m* KO	HFD	-	amelioration
	B6	HFD	α-GalCer, single, then 8 d rest	exacerbation
	ob/ob	chow	α-GalCer, single, then 8 d rest	no effect
Mantell et al.[28]	*CD1d* KO	HFD	-	no effect
Kotas et al.[29]	*CD1d* KO	HFD	-	mild exacerbation
	Jα18 KO	HFD	-	no effect
	CD1d KO	chow	-	no effect
Satoh et al.[30]	*CD1d* KO	HFD	-	amelioration
	Jα18 KO	HFD	-	no effect
	CD1d KO	HFD	Transfer of *Jα18* KO HMNC, then 14 week HFD	exacerbation
	CD1d KO	LFD	-	no effect
	Jα18 KO	LFD	-	no effect
	B6	HFD	α-GalCer, chronic, then 1 wk rest	exacerbation
Wu et al.[21]	*CD1d* KO	HFD	-	amelioration
	Jα18 KO	HFD	-	amelioration
	db/db;CD1d KO	chow	-	amelioration
	db/db;Jα18 KO	chow	-	amelioration
	B6	HFD	α-GalCer, chronic, then 2 week rest	exacerbation
Ji et al.[31]	*CD1d* KO	HFD	-	no effect
	B6	HFD	α-GalCer, day 0 and 2, then 2 d rest	amelioration
Ji et al.[23]	*CD1d* KO	HFD, 4 d	-	exacerbation
Schipper et al.[24]	*CD1d* KO	HFD	-	mild exacerbation
	Jα18 KO	HFD	-	mild exacerbation
	CD1d KO	LFD	-	exacerbation
	Jα18 KO	LFD	-	exacerbation
	B6	LFD	NK1.1$^+$ cell depletion	exacerbation
	B6	LFD	α-GalCer, single, then 3 d rest	no effect
Lynch et al.[22]	*CD1d* KO	HFD	-	exacerbation
	Jα18 KO	HFD	-	exacerbation
	CD1d KO	LFD	-	exacerbation
	Jα18 KO	LFD	-	exacerbation
	Jα18 KO	HFD	transfer of B6 hepatic iNKT cells, then 4 d rest	amelioration
	B6	HFD	α-GalCer, single, then 4 d rest	amelioration

*Individual studies are listed in chronological order of publication date. †All mice employed were on a C57BL/6 (B6) background. ‡Although diets are listed here as high-fat diet (HFD) and low-fat diet (LFD), these differed in their fat content and source, as well as other nutritional components. §For details about the different manipulations, including dosing and timing of treatments, please see the original studies. ‖The effects listed are as compared with control mice, which are either wild-type, db/db, untreated or treated with PBS, vehicle or isotype antibody. Diverse measurements of insulin resistance or glucose intolerance have been employed in these studies and only the main outcomes, as reported by the authors of the original studies, are listed. Abbreviations: -, none; α-GalCer, α-galactosylceramide; β-GluCer, β-glucosylceramide; β2m, β2-microglobulin; HMNC, hepatic mononuclear cells; KO, knockout; TCR, T cell receptor.

Role of NKT Cells in Metainflammation and Obesity-Associated Insulin Resistance

Earlier studies using adoptive transfer of NK1.1-expressing T cells suggested a suppressive role of NKT cells in the generation of obesity-associated insulin resistance (**Table 1**).[20,26] However, a subsequent study argued for a pathogenic role of NKT cells in this process, using *β2-microglobulin*-deficient mice,[27] which lack not only NKT cells but also other T cell subsets such as CD8$^+$ T cells that play a pathogenic role in

obesity-associated inflammation. To investigate the role of NKT cells in the development of obesity-associated diseases more directly, several research groups employed models of selective NKT cell-deficiency. This included *CD1d*-deficient mice, which lack both iNKT and vNKT cells, and *Jα18*-deficient mice, which only lack iNKT cells. These studies were performed with both diet-induced and genetic models of obesity. While most studies showed that NKT cell-deficiency only has minor effects on the development of obesity, food uptake, energy expenditure and blood lipid levels,[21,24,28-31] one group of investigators found that NKT cell-deficient animals gained more weight than their wild-type controls when fed either a high-fat or low-fat diet.[22] Widely divergent results have been obtained for the effects of NKT cell-deficiency on the development of obesity-associated fatty liver and insulin resistance (**Table 1**). Some of these studies found a pathogenic role of NKT cells,[21,30] whereas others found no significant role[24,28,29,31] or evidence for disease amelioration.[22,23] One study further suggested that NKT cells played a protective role in the development of insulin resistance in lean animals.[24] In most of these studies, similar results were obtained for *CD1d*- and *Jα18*-deficient mice, pointing toward iNKT cells as the main contributors. However, in one study, reduced insulin resistance was observed in *CD1d*-deficient but not *Jα18*-deficient mice, as compared with wild-type animals,[30] suggesting that vNKT cells might contribute to obesity-associated disease as well.

To complement these studies with a gain-of-function approach, several groups treated mice with the iNKT cell-specific agonist α-GalCer during the development of diet-induced obesity (**Table 1**). Again, divergent results were obtained, with studies reporting disease exacerbation,[21,27,30] no effect[24,27] or disease amelioration.[22,31] Yet another study reported that β-GluCer ameliorated insulin-resistance in *ob*/*ob* mice, possibly by antagonizing iNKT cell functions.[32]

When investigated, mechanistic studies revealed that the effects of NKT cells on obesity-associated disease correlated with alterations in macrophage accumulation, macrophage polarization and levels of pro-inflammatory cytokines in liver and white adipose tissue, and in the size of adipocytes and levels of the adipokines leptin and adiponectin in white adipose tissue.[21-24,27,30,31]

Although precise reasons remain unclear, a variety of factors might explain these divergent effects of NKT cells and their subsets on obesity-associated inflammation and disease. Possible contributing factors include differences in the genetic backgrounds of the animals employed, diet compositions, feeding durations, experimental procedures such as the protocol for α-GalCer treatment, as well as the endogenous microbiota that are present in the animal facilities where the mice were housed. With respect to the latter possibility, it is interesting to note that NKT cells can influence microbial colonization in the gut[33] and, conversely, that the normal microbiota can impact NKT cell numbers and functions.[34-36] In this context, it has been suggested that NKT cells can contribute to the protective effects of probiotics on obesity-associated inflammation and glucose intolerance.[26]

Concluding Remarks

The studies discussed here have provided strong evidence that NKT cells are one of the first cell types that become activated in response to nutritional lipid excess. These cells can contribute to the low-grade inflammation that is associated with obesity and influence the development of metabolic diseases (**Fig. 1**; **Table 1**). Outstanding questions in this field include the mechanisms that activate NKT cells during lipid excess and the effects of the endogenous microbiota on the functional status of NKT cells that impacts their role in the development of metainflammation and metabolic diseases. Collectively, these studies place NKT cells within the complex network that links nutrient excess to inflammation in obesity. These findings also suggest NKT cells as potential therapeutic targets for obesity-associated disorders. NKT cells could be targeted by lipid antigens, TCR antagonists, blocking or activating CD1d antibodies or NKT cell-depleting antibodies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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