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Obesity Promotes the Ceramide-Mediated NADPH Oxidase in Acute Myeloid Leukemia

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Abstract

Acute myeloid leukemia (AML) is a type of blood cancer of the myeloid cell lineage. Obesity is characterized by an increase in body weight that results in excessive fat accumulation. Obesity has been associated with an increased incidence of many cancers, including blood cancers. This study evaluated the role obesity in AML progression in a novel transgenic mouse model developed by crossing $Flt3^{ITD}$ mice with $Lep^{ob/ob}$ mice. Leukemia burden was augmented in obese AML mice. In addition, it was determined that obesity upregulated the ceramide- mediated and ceramide-1-phosphate-mediated NADPH oxidase 2 (NOX2). Notably, increased oxidative pathways has been attributed to disease progression in AML. Taken together, this study demonstrates a direct link between obesity and the progression of AML in part by augmenting the ceramide mediated NOX2.

Keywords

Acute myeloid leukemia; Obesity; Ceramide; Acid sphingomyelinase; Ceramide-1-phosphate; Ceramide kinase; NADPH oxidase 2

Introduction

Cancer is a group of diseases involving abnormal cell growth that has the potential to invade into other parts of the body [1]. Acute myeloid leukemia (AML) is a type of blood cancer of the myeloid cell lineage. It most commonly occurs in older adults over 60 years old and accounts for the largest number of annual deaths from leukemia in the United States [2]. In recent years, obesity has been found to be an important risk factor for the development of cancer, including blood cancers. Obesity can promote the progression of cancer through several mechanisms, such as causing chronic inflammation; dysregulating various hormones and adipokines; as well as changing scaffolding properties surrounding cancer cells [3-5]. Chronic inflammation can take place at various organ sites, including the liver, pancreas, and gastrointestinal tract [1]. Obesity-associated inflammation can dramatically alter tissue composition, thereby creating a fertile environment for cancer development [6].

Sphingolipids are a class of lipids composed of sphingoid base and fatty acids with ceramide being a hypothetical central metabolite [7-10]. Sphingolipid metabolism is a complex network of interconnected pathways. Sphingolipids are formed via the metabolism of sphingomyelin, a constituent of the plasma membrane, through metabolism of other complex sphingolipids, or by *de novo* synthesis. In addition to functioning as structural elements, sphingolipids also participate in a variety of cellular pathways including apoptosis, cell senescence, the cell cycle, and cell differentiation

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[7-10]. Ceramide is recognized as being regulator of cell stress and death and an important component of lipid microdomains [7-10]. Additionally, several sphingolipid mediators including the ceramide metabolite ceramide-1-phosphate (C1P) have also been found to play important roles in inflammation [10-12].

NADPH oxidase 2 (NOX2) is a multi-subunit oxidoreductase originally ascribed as being responsible for the phagocytic respiratory burst [13]. There are seven different NOX-family oxidoreductases in eukaryotes, with NOX2 being the most prominent [13]. NOX2 has also been described as an important cellular regulatory responsible for redox signaling as well as being implicated in oxidative stress [13,14]. Notably, ceramide and C1P have been shown to regulate assembly and activity of NOX2 in response to the inflammatory mediator TNFα [14,15].

The current study evaluated a link between obesity, as a driver of chronic inflammation, and AML using a transgenic mouse model. The impact of obesity on the progression of AML was explored in this model by studying the expression of genes encoding sphingolipid-linked enzymes involved in inflammation and oxidative stress. Increased leukemia burden was observed in obese AML mice, which also upregulated inflammatory sphingolipid metabolism and NOX2.

Materials and Methods

Animal studies

B6.129-Flt3^{tm1Dgg}/J transgenic mice (homozygotes: *Flt3*$^{ITD/ITD}$) (Jackson Laboratory, strain #011112) develop a myeloproliferative neoplasm that evolves to AML [16]. FMS-like tyrosine kinase-3 (FLT3) is a receptor tyrosine kinase that is important for the development of the hematopoietic and immune systems. The internal tandem duplication (ITD) variant of FLT3 mutation is one of the most common molecular abnormalities in AML [17-19]. Mice that are homozygous for this molecular defect develop a progressive myeloproliferative disease. For this study, *Flt3*$^{ITD/ITD}$ mice were crossed with B6.Cg-Lep^{ob}/J mice (homozygotes: *Lep*$^{ob/ob}$) (Jackson Laboratory, strain #000632). *Lep*$^{ob/ob}$ mice have a spontaneous mutation in the gene encoding for the hormone leptin, which normally regulates energy homeostasis and appetite [20,21]. Homozygous leptin-deficient mice develop obesity with typical associated metabolic ysfunction. Therefore, crossing *Flt3*$^{ITD/ITD}$ mice with *Lep*$^{ob/ob}$ mice resulted in a transgenic mouse that develops AML in the context of obesity. Notably, homozygous *Flt3*$^{ITD/ITD}$ mice were bred with heterozygous *Lep*^{ob} mice due to infertility associated with homozygous *Lep*$^{ob/ob}$ mice. Genotyping was performed to identify double homozygous (*Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$) offspring. For *Flt3*$^{ITD/ITD}$, genotyping was carried out as reported by Lee *et al*. using 5'-AGGTACGAGAGTCAGCTGCAGATG -3' as the forward primer and 5'- TGTAAAGATGGAGTAAGTGCGGGT-3' as the reverse primer [16]. Briefly, native gel electrophoresis was used to visualize the *Flt3* locus following amplification using these PCR cycling parameters: initially 95°C for two minutes and then 35 cycles of 95°C for one minute, 60°C for one minute, and 72°C for 50 seconds. For *Lep*$^{ob/ob}$, genotyping was carried out as recommended by the Jackson Laboratory using an end point analysis approach that is a modification of Real-Time qPCR methodology and using a fast Taq polymerase. This used 5'- GTGCTGCAGATAGCCAATGAC-3' as a forward primer, 5'- GAGAAGGCCAGCAGATGGA-3' as a reverse primer, 5'-TGGAGAATCTCCGAGACC-3' with a 5'-fluorophore and 3'-quencher as a wildtype probe, and 5'-CTGGAGAATCTCTGAGACC-3' with a second 5'-fluorophore and 3'-quencher as a mutant probe. These PCR cycling parameters were used: initially 95°C for three minutes followed by 40 cycles of 95°C for 15 seconds and 60°C for one minute, and then the system is held at 40°C.

Bone marrow cells were isolated from the femurs and tibias of 4–8-month-old (male and female) transgenic mice and their respective wildtype littermates for Real-Time qPCR analysis. Mice were submitted to the New Hampshire Veterinary Diagnostic Laboratory (NHVDL) at the University of New Hampshire for necropsy and histopathological evaluation. Leukemia was confirmed by the investigative team and the NHVDL based on spleen or bone marrow histopathology, and/or peripheral blood smear evaluation.

All animal studies were approved by the Institutional Animal Care and Use Committee of the University of New Hampshire.

Peripheral blood smears

Peripheral blood smears were prepared by placing a drop of blood on one end of a slide and using a spreader slide to disperse the blood over the slide's length. Slides was left to air dry and then stained with Wright-Giemsa stain to distinguish cells from each other. The eosin Y dye stains red blood cells a faint pink color, while the methylene blue and azure B dyes stains lymphocytes a purple-blue color [22]. Slides are air dried for approximately 24 hours before being observed using light microscopy.

Real-Time qPCR

Total cellular RNA from mouse bone marrow samples was first extracted and cleaned. RNA quality was then evaluated with a NanoDrop 8000 spectrophotometer, and then RNA was reverse transcribed using Taq polymerase to generate cDNA. PrimeTime™ Predesigned qPCR Assays (Integrated DNA Technologies) were then used to evaluate murine gene targets using a Bio-Rad CFX96 Real-Time PCR System. Gene expression was determined using the $2^{-\Delta\Delta Ct}$ method using cycle threshold (Ct) values for target genes as well as two reference genes (*Actb* and *Tbp*). Data analysis and graphing was carried out using GraphPad Prism software and 1-way ANOVA and student's t-tests were performed to asses statistical significance.

Results

An obese AML mouse model was developed by crossing *Flt3* transgenic mice with *Lep*$^{ob/ob}$ mice. The Lep$^{ob/ob}$ mouse is a major model of obesity that arises due to a spontaneous mutation in the gene encoding the hormone leptin [23]. Leptin is produced predominantly by adipocytes [24]. It helps regulate energy balance by inhibiting hunger and diminishing fat storage in adipocytes. During obesity, the body develops insensitivity to leptin and so is unable to detect satiety [25]. Homozygous leptin-deficient mice are phenotypically indistinguishable from their unaffected littermates at birth, but rapidly gain weight throughout their lives. They ultimately reach a weight over twice that of unaffected mice. The *Flt3*$^{ITD/ITD}$ transgenic mouse is a myeloproliferative neoplasm model that evolves to AML. FLT3 is a proto-oncogene involved in crucial steps of hematopoiesis such as proliferation, differentiation, and survival. The ITD variant of FLT3 has been strongly associated with poor prognosis, leukocytosis, high blast count, increased risk of relapse, and shorter overall survival of AML patients [26]. These individual models were crossed to develop the *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mouse to further study the role of obesity in AML development and progression. Notably, the *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mouse had similar weight gain and overall appearance as the *Lep*$^{ob/ob}$ mouse (**Figure 1**). In addition, peripheral blood smears demonstrated that this transgenic obese AML model (*Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mice) developed a robust leukemia as evidenced by the substantial appearance of blasts as compared with the *Flt3*$^{ITD/ITD}$ transgenic AML mouse model (**Figure 2**).

The impact of obesity on inflammatory ceramide metabolism and associated redox signaling in AML was further investigated to explore a mechanism where obesity can promote AML progression. Obesity can induce several pathological conditions including

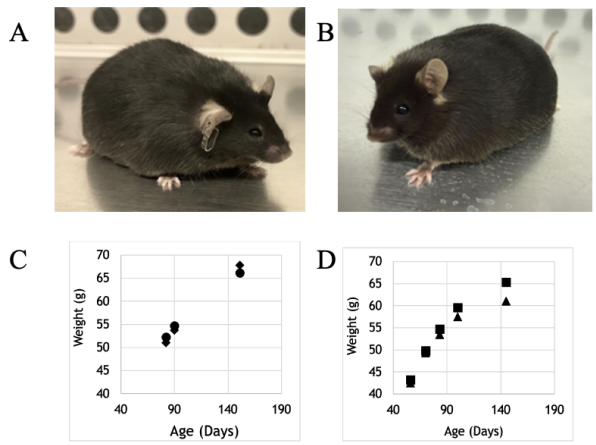

Figure 1: *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mice have similar weight gain as *Lep*$^{ob/ob}$ mice.

A representative aged *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mouse (A) and a representative aged *Lep*$^{ob/ob}$ mouse (B). Weight gain patterns of *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mice (C) and *Lep*$^{ob/ob}$ mice (D). As the age of these transgenic mice approaches 160 days, their weight plateaus around 65 grams.

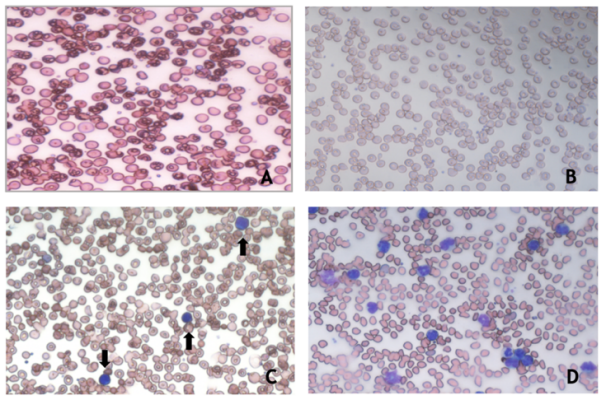

Figure 2: *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mice developed robust AML compared with *Flt3*$^{ITD/ITD}$ mice.

A peripheral blood smear from a representative wildtype mouse (A) displays all small, pink, and normal red blood cells, indicative of normal and nonmalignant cells. A peripheral blood smear from a representative *Lep*$^{ob/ob}$ mouse (B) displays a similar appearance, indicative that obese mice likewise do not have notable and malignant phenotypic changes in the peripheral blood. In contrast, a peripheral blood smear from a representative *Flt3*$^{ITD/ITD}$ mouse (C) displays a handful of blasts (noted by arrows), indicative of the mouse's circulating leukemia. Most notably, a peripheral blood smear from a representative *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mouse (D) shows a considerably greater number of blasts (numerous, throughout the image), indicative that the malignancy has more robustly developed.

insulin resistance, in which ceramide metabolism can play a key pathological role [27]. Obesity-driven increases in ceramide have been linked to glucose intolerance [28]. Acid sphingomyelinase (gene name: *Smpd1*) is an enzyme that hydrolyzes sphingomyelin to liberate ceramide, modulating membrane domains and signal transduction pathways including those mediated by inflammation [29]. Ceramide kinase (gene name: *Cerk*) is a lipid kinase that is responsible for the phosphorylation of ceramide to generate C1P at both the plasma membrane and Golgi apparatus [30]. NOX2 is a superoxide generating enzyme. Superoxide is crucial in killing foreign bacteria in the human body. Decreased activity of NOX2 can lead to an increased susceptibility to organisms such as catalase-positive microbes, while its increased activity in response to inflammation can lead to oxidative stress [13,31]. We have previously shown that both neutral sphingomyelinase-generated ceramide [14], as well as ceramide kinase-generated C1P [15], can coordinately activate NOX2 in response to inflammatory stimuli as part of a deleterious oxidative stress process [15].

In the present study, obesity associated with the *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ AML mouse model led to aberrant gene expression involving aspects of inflammatory ceramide metabolism and redox signaling. This was reflected by increased gene expression of *Smpd1*, *Cerk*, and *Nox2* (encodes the gp91^{phox} membrane-bound subunit of NOX2; gene also known as *Cybb*) (**Figure 3**). Collective upregulation of these genes enables the ceramide- and C1P-mediated NOX2 (**Figure 4**). In this manner, inflammatory stress can provoke ceramide and C1P generation to promote activation of NOX2. Activation of this pathway enables redox-mediated progression of AML, as observed with the *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ obese AML transgenic mouse model.

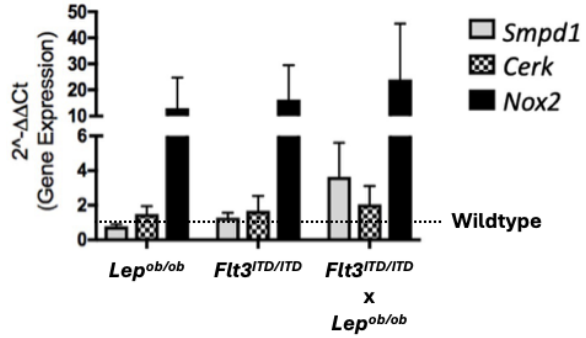

Figure 3: *Smpd1*, *Cerk*, and *Nox2* are upregulated in *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mice.

Bone marrow from age-matched wildtype, *Lep*$^{ob/ob}$, *Flt3*$^{ITD/ITD}$, and *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/ob}$ mice was harvested and analyzed by Real-Time qPCR (wildtype mice were used as a normal control). Expression of *Smpd1*, *Cerk*, and *Nox2* (also referred to as *Cybb*) were significantly ($p \leq 0.05$) elevated as compared to the wildtype control in the *Flt3*$^{ITD/ITD}$ x *Lep*$^{ob/b}$ obese AML mouse model, while *Nox2* expression was elevated as compared to the wildtype control in all mice. $n \geq 3$ per group.

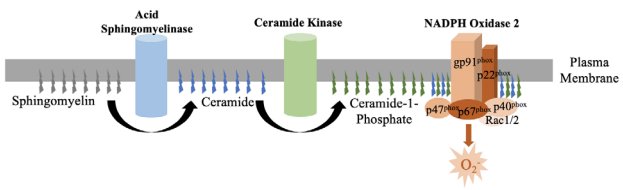

Figure 4: Diagram of ceramide- and C1P-mediated NOX2 activity.

Acid sphingomyelinase (or other sphingomyelinases) generate ceramide from sphingomyelin, including in response to obesity-driven inflammation. Ceramide kinase coverts ceramide to ceramide-1-phosphate (C1P), which collectively promote assembly and activation of NADPH oxidase 2 (NOX2) The multi-subunit NOX2 generates superoxide (O_2^-) following assembly of the membrane subunits (gp91^{phox} and p22^{phox}) and cytosolic subunits (p47^{phox}, p67^{phox}, and p40^{phox}), as well as the small GTPase Rac1/2.

Discussion

Obesity is an important risk factor for the development of cancer, although the relationship is not as clear as that between tobacco use and lung cancer [32]. Nearly 25% of the relative contribution to cancer has subsequently been linked to obesity [33]. It is accepted that obesity can promote the growth of primary tumors as well as metastatic progression through various mechanisms [6]. Obesity-associated oxidative stress has been shown to cause genomic damage, which can lead to the transformation of premalignant cells [34]. Moreover, NOX2- dependent redox-signaling has been shown to promote proliferative signaling [13,31]. Importantly, obesity has been shown to be a risk factor for the development of both myelodysplastic syndrome and AML, with poor prognosis and survival outcomes in these patients that are obese [35]. Since obesity has been demonstrated to be a driver of chronic inflammation [6], perhaps contributing to the increased risk of diseases such as AML, this has rationalized studies to evaluate these links. Interestingly, sphingolipids have been shown to play key roles in mediating inflammatory pathways [7-12,14,15], yielding a potential explanation for the increased instances of myeloproliferative disorders in the obese population.

In this study, the role of obesity in the progression AML was evaluated in a newly described obese AML mouse model ($Flt3^{ITD/ITD}$ x $Lep^{ob/ob}$). Interestingly, these mice had similar weight gains as their obese, but otherwise normal, littermates. However, they developed a more robust AML than non-obese $Flt3^{ITD/ITD}$ transgenic AML mice, indicative that obesity can augment the development and progression of AML. It was further demonstrated that the combination of obesity and AML in these $Flt3^{ITD/ITD}$x $Lep^{ob/ob}$ mice upregulated the expression of genes encoding for the: 1) ceramide-generating enzyme acid sphingomyelinase (*Smpd1*), 2) C1P-generating enzyme ceramide kinase (*Cerk*), and 3) primary membrane-bound NOX2 subunit (*Nox2*, also known as *Cybb*). We have earlier and separately shown that ceramide and C1P can activate the NOX2 to promote oxidative stress in response to inflammatory stimuli [14,15]. It has also been shown that stimulation of acid sphingomyelinase can promote NOX2 activation as part of a vascular reperfusion effect during radiation therapy [36]. Altogether, this suggests that transgenic obese AML mice upregulate inflammatory aspects of ceramide metabolism as well as linked oxidative pathways. By increasing oxidative stress and redox signaling within AML cells, obesity may accelerate the molecular evolution of the disease [37], as well as promote a more proliferative cellular state.

There are other mechanisms through which obesity can promote cancer progression. For example, at a primary tumor site obesity can increase myofibroblast content to subsequently stiffen the extracellular matrix and enhance the growth of cancer cells. Inflammasome activation in tumor-infiltrating myeloid cells has also been shown to promote increased IL-1β signaling. In response, adipocytes express additional VEGF-A to augment tumor angiogenesis [38].

Furthermore, cholesterol metabolites have been shown to promote metastasis by regulating the epithelial-mesenchymal transition [39]. In addition, IL5Rα+ monocytes at metastatic sites. generate GM-CSF to promote neutrophil expansion [40]. Circulating neutrophilia in response to elevations of GM-CSF has been shown to promote outgrowth and seeding of disseminated cancer [6].

Altogether, various interventions are being investigated to mitigate the effects of obesity in cancer. Caloric restriction has been shown to have a better effect than bariatric surgery in obese murine models of breast cancer [41]. In preclinical studies, lifestyle interventions such as exercise and fasting have been found to improve immune function. Specifically, fasting has been shown to increase lymphoid progenitor cells and cytotoxic CD8+ lymphocytes, enhancing the targeted killing of cancer cells [42]. In conclusion, it is imperative to understand mechanisms by which obesity affects cancer progression including for blood cancers such as AML. In this way, better personalized approaches to treat obese patients with cancer, including AML, can be developed. This study developed an obese AML transgenic mouse model, which demonstrated dysfunction of inflammatory sphingolipid metabolism and associated redox pathways. Moreover, this model could be further used for preclinical evaluation of sphingolipid-directed and NOX2- targeted anti-AML therapies.

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