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Article

ARTICLE

Mechanisms by Which Obesity Impacts Survival from Acute Lymphoblastic Leukemia

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Abstract

The prevalence of obesity has steadily risen over the past decades, even doubling in more than 70 countries. High levels of body fat (*adiposity*) and obesity are associated with endocrine and hormonal dysregulation, cardiovascular compromise, hepatic dysfunction, pancreatitis, changes in drug metabolism and clearance, inflammation, and metabolic stress. It is thus unsurprising that obesity can affect the development of and survival from a wide variety of malignancies. This review focuses on acute lymphoblastic leukemia, the most common malignancy in children, to explore the multiple mechanisms connecting acute lymphoblastic leukemia, obesity, and adipocytes, and the implications for leukemia therapy.

The prevalence of obesity has steadily risen over the past decades (1). Obesity is associated with cancer mortality (2) and the development of all major leukemia subtypes in adults (3). Although childhood obesity has not been linked to acute lymphoblastic leukemia (ALL) incidence, pediatric obesity has been shown in multiple cohorts to have an adverse impact on ALL relapse and survival (4). A major question derived from these cohort studies was whether adipocytes (fat cells), independent of confounding environmental or socioeconomic factors, cause poorer survival. To test this, we developed mouse models of ALL and obesity and showed that obesity directly influences the development and cure of ALL (5–7). Given that up to one in three pediatric patients with newly diagnosed ALL are overweight or obese (8), understanding and breaking the obesity–ALL connection could yield significant improvements in survival.

Obesity-Associated Hormones and Leukemia

Systemic Signals

Obesity is associated with a number of complex physiological changes, many of which remain poorly understood. Among them, high insulin and insulin-like growth factor-1 (IGF-1) levels likely contribute to ALL incidence and outcome. Although increased insulin and free IGF-1 have not been directly associated with ALL survival, a large body of in vitro and ex vivo data strongly suggest they may be key mediators for ALL outcomes.

Insulin. Hyperinsulinemia associated with obesity-induced insulin resistance is likely a major mechanistic link between obesity and cancer. Insulin increases glucose uptake, protein synthesis, cell proliferation, and tissue growth. Insulin resistance impairs the effects of insulin on glucose metabolism, and the growth-promoting effects of insulin are even enhanced in the compensatory hyperinsulinemic state.

Insulin signaling through its receptor initiates a complex set of signaling cascades, including activation of phosphoinositide 3-kinase and protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), and extracellular signal-regulated kinase (ERK). These pathways are often dysregulated in ALL, with PI3K/AKT and STAT3 overexpression associated with poorer survival and chemotherapy resistance in pediatric B-precursor ALL (B-ALL) (9–11). Even more concerning, insulin promotes in vitro ALL resistance to daunorubicin, a common ALL chemotherapy agent, but not to several other chemotherapies (12). These implicated pathways and resistance patterns indicate a potential agent- and/or regimen-specific impact of hyperinsulinemia on outcome from ALL.

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IGF-1. IGF-1 may be a critical link between obesity and cancer in general and has been hypothesized to link fetal size and developing childhood ALL (13). Obese patients often have low or normal total concentrations but high free (active) IGF-1 because of lower levels of IGF binding proteins. The IGF-1 receptor (IGF1R) shares homology with insulin receptor, stimulating overlapping pathways including PI3K/AKT. IGF1R stimulation results in ALL proliferation and chemotherapy resistance (14,15), whereas its inhibition slows proliferation and enhances apoptosis (16). The micro-RNAs miR-99a and miR-100, which act in part by inhibiting IGF1R expression, are lower in ALL cells, and their restoration impairs ALL proliferation (15). Finally, IGF1R overexpression relieves stromal dependence of ALL cells (17).

Adipose Signals

One of the most obvious characteristics of obesity is excess body fat. Adipocytes secrete a large number of cytokines and hormones (collectively termed *adipokines*), which affect a myriad of paracrine and endocrine targets.

CXCL12. We observed in a mouse model of obesity and ALL that, after chemotherapy, ALL cells had migrated into adipose tissues (Figure 1) (5). We showed that this was mediated via adipocytes secretion of CXCL12 (also known as SDF1α), an important factor in lymphocyte migration (18). Importantly, this migration was prevented by blocking the CXCL12 receptor, CXCR4. As described below, this intercalation of ALL cells and adipocytes in bone marrow and adipose tissue microenvironments could result in a distinct, chemoprotective niche from the metabolic protection described below.

Leptin. Leptin is an adipokine secreted in proportion to obesity and adiposity (19,20). Whereas leptin in the bone marrow enhances ALL cell engraftment (21), higher leptin receptor expression on ALL blasts is associated with improved prognosis in patients (22,23). Further, fasting induces leptin receptor expression, which stimulates ALL cell differentiation and inhibits initiation and progression (24). Therefore, although elevated leptin levels in obesity may promote ALL initiation, they are unlikely to directly worsen ALL survival.

Adiponectin. Adiponectin is one of the most abundant systemic hormones (25). Unlike most adipokines, adiponectin circulates in inverse proportion to obesity and generally has beneficial metabolic effects. Adiponectin simulates the AMP-activated protein kinase (AMPK) pathway, which in ALL cells would be expected to promote apoptosis (26). In vitro, adiponectin does not influence proliferation of lymphoid precursors in vitro (23), and thus does not appear to play a major role in ALL chemoresistance.

Visfatin. Visfatin, also known as nicotinamide phosphoribosyltransferase and pre-B cell colony-enhancing factor, is secreted by adipocytes and elevated in obesity. However, its intracellular form, which has enzymatic activity, is likely more relevant to cancer cells. So, although visfatin expression is upregulated in many cancer cells, including ALL, and its inhibition is cytotoxic (27), it is unlikely to mediate obesity and ALL survival.

The adipocyte secretome therefore has multiple points of interaction with ALL, yet no clear *direct* influence on ALL cell survival. However, adipocytes also secrete a myriad of other hormones and cytokines (eg, adipsin, RBP4, FGF21, resistin, omentin), most of which have yet to be explored in ALL. Leptin and other adipokines also contribute to obesity-associated insulin resistance and inflammation, which themselves can influence ALL outcomes. The secretome may therefore play an *indirect* role either as a mediator or indicator of the systemic impact of obesity.

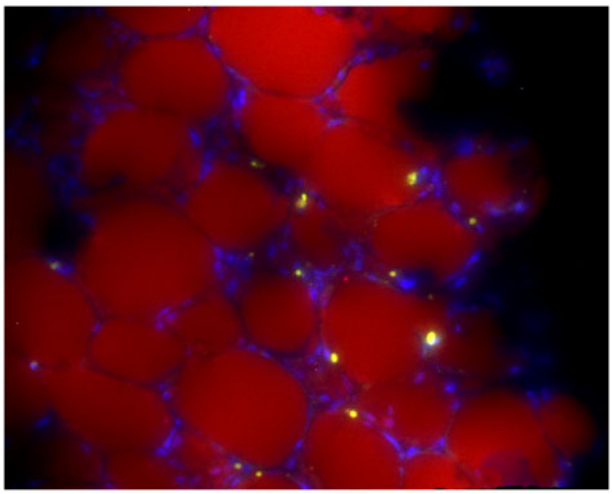

Figure 1. GFP+ 8093 acute lymphoblastic leukemia cells in the perirenal fat pad of a transplanted obese mouse that developed progressive leukemia during vincristine treatment. Lipid is stained with Nile Red, and the image is counterstained with 4', 6-diamidino-2-phenylindole. Image was taken on a Leica DM RXA2 with a x20 objective with x1.6 Optovar magnification (x32 final). Image is representative of fat pads obtained from the other four mice after vincristine treatment. Reprinted with permission from (5).

Providing Metabolic "Fuel" for Leukemia Cells

Obesity is characterized by excess fuel storage. The obese, insulin-resistant state, particularly when it is not completely compensated by hyperinsulinemia, is associated with increased levels of circulating glucose, free fatty acids, and certain amino acids (28,29). In the adipose tissue microenvironment, interstitial levels of adipocyte-released fuels are likely extremely high.

Glucose

Many cancers, including ALL, exhibit increased aerobic glycolysis, termed the Warburg effect (30). This serves to support both energy production and macromolecule synthesis in rapidly dividing cells. Targeting glucose uptake or glycolysis in cancer cells, as has been done in BCR/ABL+ ALL cells, can reduce proliferation, impair nucleotide synthesis, and increase sensitivity to chemotherapy (31). A recent study showed that acute myeloid leukemia cells reprogram cells in their microenvironment, impairing their glucose uptake and resulting in increased available glucose for the cancer cells (32). Additionally, clinical studies revealed that hyperglycemia during induction was associated with decreased duration of complete remission in adult patients with ALL (33), although this association was not detected in children (34). Thus, it seems likely that higher glucose levels seen in obesity could contribute to ALL cell proliferation and chemotherapy resistance and thus help explain the links between obesity and poorer ALL outcome.

Free Fatty Acids (FFA)

Arguably, the primary role of adipocytes is the storage and provision of lipids. In the obese state, adipocytes are insulin resistant, resulting in higher circulating triglycerides and FFA. Many

cancers rely heavily on FFA as both a source of energy (through beta-oxidation) and a precursor for synthesis of macromolecules, such as phospholipids. Cancers often overexpress enzymes involved in lipogenesis, such as fatty acid synthase and acetyl-coenzyme A carboxylase (35,36), and lipid uptake, including lipoprotein lipase (37), fatty acid binding protein 4, and CD36 (38). Inhibition of CD36 and fatty acid binding protein 4 can impair cancer proliferation and induce apoptosis (35,39). Further, some cancers induce nearby adipocyte release of FFA (40,41), an effect we have observed in ALL cells (42). In fact, we found that ALL cells take up adipocyte-derived FFA and incorporate them into phospholipid membranes and lipid droplets. The direct connection between adipocyte provision of FFA to ALL cells as a source of energy and chemotherapy resistance and proliferation is currently being investigated.

Amino Acids

Glutamine (GLN) is an important fuel and macromolecule precursor for most cancers, including ALL. Generally lacking asparagine (ASN) synthetase, ALL cells depend on uptake of extracellular ASN. Asparaginase treatment exploits these needs by hydrolyzing ASN and to a lesser extent, GLN, reducing their availability in the ALL microenvironment. Adipocytes release both ASN and GLN into the local microenvironment (6,43), thereby potentially fueling ALL cells and circumventing asparaginase activity.

Branched chain amino acids (BCAA), including leucine, isoleucine, and valine, are important for protein synthesis and energy and as signaling molecules in cancer cells. Circulating BCAA levels are increased in obesity, insulin resistance, and type 2 diabetes (44), although the reasons for this are not clear. Importantly, exogenous BCAA partially reduces reliance on endogenous BCAA synthesis, although BCAA metabolism has not yet been studied in ALL. Thus, BCAA, ASN, and GLN all may contribute to enhanced ALL cell metabolic health and chemotherapy resistance in obesity.

Inflammation, Obesity, and Cancer

Obesity is associated with chronic inflammation, a well-known contributor to solid tumor oncogenesis (45). Adipocytes secrete pro-inflammatory cytokines such as IGF-1, interleukin (IL)-1β, IL-6, IL-7, and tumor necrosis factor α (TNFα) (46), as well as FFA. Obese adipose tissue accumulates immune cells and induces their polarization toward a pro-inflammatory phenotype, further promoting systemic inflammation. Inflammatory cytokines activate traditional leukemia signal transduction cascades, primarily PI3K/AKT, MAPK, and STAT3 pathways (47). IL-7, which is increased in morbidly obese subjects, is associated with T-cell ALL (T-ALL) oncogenesis (48) and glucocorticoid chemotherapy resistance (49). Obesity-associated inflammation and its downstream signaling overlaps with obesity-induced systemic triggers, all of which may contribute to poorer survival for obesity-associated ALL.

Pharmacokinetics and Pharmacodynamics (PK/PD) in the Obese

Several physical and physiological changes in obesity may affect the PK of drugs. Increased adiposity can alter a drug's volume of distribution in either direction, depending on its lipophilicity. Alterations in volume of distribution can affect a drug's peak concentration and area-under-the-curve (AUC), both of which can impair efficacy or increase toxicity, depending on the direction of change. Obesity-associated alterations in gastrointestinal, hepatic, and renal function can further affect chemotherapy PK/PD. Chemotherapy dosing is routinely based on body surface area, which increases disproportionately slower with increasing weight and body fat mass. Extensive PK modeling has not been done for most chemotherapies in obese subjects, and there is almost no data in extreme obesity. In 2012, the American Society of Clinical Oncology recommended that "full weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer" (50). Limited PK data from the St Jude Total trials showed no influence of body mass index (BMI) on the PK of many common ALL chemotherapies (methotrexate, cytarabine, mercaptopurine) (51). However, two core chemotherapy classes integral to ALL treatment were not assessed and are discussed below. For a more extensive review of the literature on obesity and chemotherapy PK/PD, we refer the reader to (52).

Vincristine (VCR)

Vincristine is part of the backbone of ALL therapy. For yet unknown reasons, a high degree of variability is observed in the PK of VCR among individuals (53). Across ALL regimens, VCR dosing is capped at 2 mg, such that patients larger than an average 8-year-old ($\sim$1 m^2) receive a capped dose. We found that diet-induced obesity in mice altered the PK of VCR, leading to a lower overall AUC of the drug in blood over time, a faster clearance from spleen and bone marrow, and accumulation in adipose tissue (54). This is particularly worrisome, as decreased VCR AUC has been linked with higher relapse risk in children with ALL (55). In adolescents, one study reported no impact of increased size on VCR PK (56). Better understanding of body fat's contribution to VCR PK is necessary to optimize dosing across ages and in the obese.

Anthracyclines

Daunorubicin and doxorubicin are commonly used to treat ALL. PK studies showed no effect of BMI or body fat on the plasma clearance of either drug in children (57,58), whereas obese adults were found to have lower systemic clearance and higher AUC of doxorubicin (59). In contrast, we recently reported that adipocytes absorb and metabolize daunorubicin to its largely inactive form, daunorubicinol (Figure 2) (60). We found human adipocytes express high levels of the aldo-keto reductase and carbonyl reductase enzymes responsible for this inactivation, leading to a reduced concentration of active daunorubicin within the nearby environment. Although this may not alter the plasma PK of daunorubicin (and potentially other anthracyclines), it may result in subtherapeutic concentrations in the leukemia-adipose marrow microenvironment. Further work is ongoing to evaluate this effect in patients.

Breaking the Link Between Obesity and Leukemia Outcome

Although the evidence for obesity to worsen ALL outcomes is strong, clinical and preclinical data provide a glimmer of hope that this association may be reversible. An improved understanding of the obesity-ALL biology could provide new

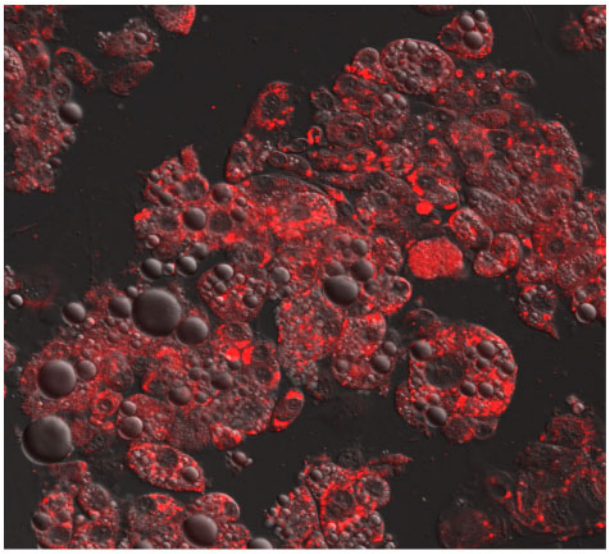

Figure 2. Confocal microscopy of adipocytes treated with 60 nM daunorubicin (red) for 4 hours. Photo taken on a LSM 700 confocal system mounted on an AxioObserver.Z1 microscope equipped with a 63/1.4 Plan-APOCHROMAT objective lens and controlled with ZEN 2009 software (Carl Zeiss Microscopy). Reprinted with permission from (60).

opportunities to develop nonchemotherapy integrative approaches to augment therapy and reduce risk for relapse.

Targeted Therapy for Obesity-Associated ALL

Multiple commercially available biologics are available to target mTOR and the other obesity-associated leukemia signaling pathways described above. Metformin is one of the best characterized and stimulates AMPK, a potent mTOR inhibitor. Metformin has pro-apoptotic and antiproliferative activity in leukemia cell lines (61,62). When tested with traditional chemotherapy, in vitro synergy was observed for some T-ALL cell lines, representing a variety of leukemia phenotypes (63). Metformin had promising results in a phase 1 study of relapsed pediatric ALL patients (64) and is currently being tested by the Children's Oncology Group to target constitutive Janus kinase (JAK)/STAT activation due to cytokine receptor-like factor 2 (CRLF2) fusions (NCT02723994). If successful, a similar approach could be envisioned for ALL with obesity-mediated pathway activation. Alternatively, future targeted therapy may instead focus on obesity's adverse influence on metabolism of traditional chemotherapy, such as incorporating drugs targeting enzyme-mediated sequestration and deactivation of anthracyclines. Although our understanding of the biology of obesity-associated leukemia remains incomplete, data offer promising glimpses for future augmentation of chemotherapy via pathway inhibition.

Metabolic Manipulation of ALL

Adipocytes directly and obesity indirectly enhance fuel availability to rapidly proliferating leukemia cells. Restricting fuels, such as with a low-glycemic index or calorie-restricting diets, could prove efficacious, particularly in obese patients, although data remain limited. Glucose restriction was as effective as the drug rapamycin in vitro for inhibiting mTOR and inducing apoptosis in multiple cell lines (65). Serum restriction, which simulates the hormone and growth factor changes of calorie restriction, can also sensitize ALL cells to chemotherapy (66). In mouse models, intermittent fasting completely halted the engraftment and progression of B-ALL and markedly reduced both for T-ALL (24). We have shown that switching obese mice from a high-fat to a low-fat diet when starting chemotherapy substantially improved ALL outcome with vincristine, although not with L-asparaginase or dexamethasone (66). Identifying the most advantageous interventions, and how best to incorporate these into standard chemotherapy regimens remain important goals.

Based on the above, we launched a prospective obesity-intervention trial during ALL induction (NCT02708108). In this trial, we are investigating a metabolic intervention consisting of a 10% dietary calorie restriction and a 10% increase in energy expenditure through exercise. The intervention takes place during the first month of induction chemotherapy, with the goals of reducing body fat accretion and decreasing the incidence of minimal residual disease. To our knowledge, this is the first trial in pediatric ALL to investigate the use of metabolic modification as an integrated treatment modality to increase chemotherapy efficacy.

The evidence that obesity impairs ALL outcome is strong, and our understanding of the mechanisms responsible for this association is growing. In the era of immune therapy and biologics for treatment of childhood leukemia, metabolic therapy offers a potential avenue with few side effects for augmenting chemotherapy to reduce relapse and improve survival.

Notes

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