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Multifaceted Effects of Obesity on Cancer Immunotherapies: Bridging Preclinical Models and Clinical Data

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Abstract

Obesity, defined by excessive body fat, is a highly complex condition affecting numerous physiological processes, such as metabolism, proliferation, and cellular homeostasis. These multifaceted effects impact cells and tissues throughout the host, including immune cells as well as cancer biology. Because of the multifaceted nature of obesity, common parameters used to define it (such as body mass index in humans) can be problematic, and more nuanced methods are needed to characterize the pleiotropic metabolic effects of obesity. Obesity is well-accepted as an overall negative prognostic factor for cancer incidence, progression, and outcome. This is in part due to the meta-inflammatory and immunosuppressive effects of obesity. Immunotherapy is increasingly used in cancer therapy, and there are many different types of immunotherapy approaches. The effects of obesity on immunotherapy have only recently been studied with the demonstration of an “obesity paradox”, in which some immune therapies have been demonstrated to result in greater efficacy in obese subjects despite the direct adverse effects of obesity and excess body fat acting on the cancer itself. The multifactorial characteristics that influence the effects of obesity (age, sex, lean muscle mass, underlying metabolic conditions and drugs) further confound interpretation of clinical data and necessitate the use of more relevant preclinical models mirroring these variables in the human scenario. Such models will allow for more nuanced mechanistic assessment of how obesity can impact, both positively and negatively, cancer biology, host metabolism, immune regulation, and how these intersecting processes impact the delivery and outcome of cancer immunotherapy.

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Keywords

Cancer; Obesity; Inflammation; Immunotherapy

1.0 Introduction

At its root, obesity has been defined as a condition of excess body fat and has been associated as a poor prognostic factor for many disease states, including cancer. Classically, obesity has been characterized by using the body mass index (BMI), a metric obtained by taking a ratio of an individual's weight in kilograms by height in meters squared, and is the standardized measurement used by the World Health Organization for setting overweight and obese criteria, which are a BMI ≥25 and ≥ 30 respectively (1). Obesity as a disease is on the rise globally with approximately 39% of the world's population classified as overweight or obese in 2015 (2). Projections indicate that the global incidence of adults that are either overweight or obese will reach 57.8% by the year 2030 (3,4). The increasing incidence of obesity is a major public health issue due to its association with exacerbating a number of diseases, including cancer, in which 14% of deaths in men and 20% in women are attributable to excess weight (5,6). Thirteen cancer types have been clearly identified as having an increased risk due to obesity including breast (post-menopausal), colon and rectum, corpus uteri, esophagus adenocarcinomas, gallbladder, gastric cardia, kidney (renal cell), liver, meningioma, multiple myeloma, ovary, pancreas and thyroid cancers (7,8) with likely more to be determined.

Obesity is characterized by a state of chronic inflammation, often termed "meta-inflammation" in which adipose tissue promotes secretion of adipokines and inflammatory mediators including interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) (9). While acute inflammation is a natural protective response, if sustained it can lead to chronic inflammation which can have deleterious effects both in the tissues and immune cells (10). Inflammation as it pertains to cancer, can also be a driver of cancer development as it can mediate changes in metabolism and inflammatory cell recruitment, which can promote cancer growth, angiogenesis, immune suppression, and tumor invasiveness (11,12). Examples of inflammation-induced tumorigenesis have been observed in cases of hepatocellular carcinoma in which elevated production of inflammatory cytokines directly promote tumor growth and autocrine growth factors for the cancer (13). Finally, this meta-inflammatory state in obesity has been correlated with heightened tissue damage as well as immune alterations termed "inflammaging", all of which have profound effects on cancer immunotherapy application (14).

While obesity as defined by BMI has been associated with an overall increased cancer incidence/progression (15,16), studies on obesity often demonstrate mixed results due to the heterogeneity of patient populations. Heterogeneity can be driven by numerous co-factors linked to obesity (i.e. diet), individual demographics (i.e. age, sex, presence of co-morbidities), and the types cancers and treatments (17-22). Surprisingly, while being primarily a negative prognostic marker in cancer and therapy, in the context of a particular type of immunotherapy "immune checkpoint inhibitors" (ICIs), obesity has been identified

as a potential prognostic parameter (23-25). The conceptual framework that obesity both promotes cancer incidence, yet also can be associated with improved immunotherapy outcomes is the basis of an “Obesity Paradox”. However, not all immunotherapies are the same and in the context of systemic immunostimulatory therapies, there are preclinical data that obesity leads to increased toxicities due to the heightened proinflammatory environment (26) which is analogous to increased morbidities observed in obese individuals during acute viral infections (27,28). This review will address how obesity can modify both metabolic and immune functioning, evaluate the role of both stimulatory and inhibitory immunotherapies in the context of obesity, discuss the potential variables affecting observations, and evaluate how preclinical modeling may be used to interrogate questions that remain.

1.1 How Do We Define Obesity and Limitations of BMI

Assessing the prognostic role of obesity as a predictor of cancer and immunotherapy outcomes can be highly useful but is only as meaningful as the definition used for obesity to capture this population. BMI has been, and still is, the standard metric of measuring obesity clinically, yet it can fail to adequately capture patients who have excess body fat but have a normal BMI (because of low muscle mass) or misclassify patients as obese who do not have excess body fat but have a high weight to height ratio because of high muscle mass (29). These limitations of BMI are primarily driven by an inability to discriminate between lean and fat body mass, which is increasingly appreciated as a revealing parameter affecting outcome, and an inability to consider fat distribution or adipose tissue type (30,31). Patient background can also be an important variable as studies assessing obesity have identified genetic variation in fat distribution in some Asian populations (32), and in some cases populations use different cutoffs for obesity such as a BMI >25 rather than >30 (33,34). BMI is also severely limited as metabolic status, presence of co-morbidities or medications, patient age, race, and sex are also critical cofactors often not considered especially in heterogeneous populations. These limitations of BMI to accurately capture excess adiposity and define an obese state is likely a significant contributing factor for the variance seen between studies evaluating the associations of BMI with cancer immunotherapy outcome. BMI also does not take into consideration the length of time the patient has been in an obese state as that also can have a major impact on what physiologic processes that are affected (35).

Methodologies have been developed to overcome some of the limitations of BMI including incorporation of waist and hip circumference measurements or ratios, which have demonstrated success in determining obesity (36,37). Waist and hip measurements are predominately aimed at assessing visceral adiposity and illustrate a clearer correlation between obesity and poor prognosis or increased cancer progression (38,39). Other means of measuring body fat include skinfold thickness measurements, bioimpedance analysis, dual energy x-ray absorptiometry (DEXA) and quantitative magnetic resonance analysis, hydrostatic weighing, and air displacement plethysmography. The distribution of body fat can be assessed through computed tomography (CT) and magnetic resonance imaging (MRI), and DEXA can be a valuable tool to evaluate body fat percentage (40).

Total body composition both lean and fat mass is important as studies have observed that even in cases where obesity is associated with higher survival rates circumstances of sarcopenic obesity do not benefit and in fact have the poorest prognosis (41). Sarcopenic obesity, and not obesity alone, appears to be better correlated with negative outcomes in solid tumors of the respiratory and gastrointestinal tracts, indicating that both lean muscle mass as well as fat tissue need to be assessed (42). In addition to poor overall outcome increased toxicities can be observed with sarcopenia as is illustrated in a study evaluating the treatment of esophagogastric cancers where sarcopenic obesity and not sarcopenia alone was associated with increased occurrence of toxicities (43). There is real need to develop better metabolic biomarkers as parameters in identifying an obese state given the likelihood that critical physiological processes (i.e., insulin resistance/diabetes, cardiovascular conditions) are also affected in addition to immune parameters (44,45). The prevalent use of drugs to counteract a number of parallel health effects (i.e., statins, metformin, etc.) also impact the obese environment and may therefore affect cancer immunotherapy outcomes confounding data interpretation (46-49). Thus, it is critical to develop metabolic markers in tandem with defined obesity that can further characterize the obese state and what physiologic processes, including those that are immune related, are most affected; this could allow for different classifications of obesity to be determined which may have more prognostic value.

1.2 The Impact of Sex on Obesity

Patient sex is a critical variable that can confound BMI interpretation of obesity due marked physiology differences, particularly those that are hormonally driven (50,51). Fat distribution between males and females is quite different with males having a preferential distribution of visceral fat while females preferentially store fat subcutaneously (52). Metabolically, this nuance in distribution is important given visceral fat is more metabolically active, while subcutaneous adipose tissue is inclined toward long term storage (53). The function of adipocyte secretion is another contrasting aspect in which females generally have higher circulating levels of adipokines such as leptin and adiponectin than males (54,55). Sex hormone production both affects and occurs in adipose tissue. The physiologic difference in fat distribution between male and females does have a consequence for the development of obesity and metabolic diseases, for while woman are more predisposed to developing obesity, men are more inclined to the development of obesity-related comorbidities (56). Visceral fat deposition correlates with increased susceptibility to metabolic diseases and in turn disproportionally impacts males (57). The disposition for fat distribution shifts in postmenopausal women as estrogen levels decline and testosterone increases, which results in increased visceral adiposity (58). This is further exacerbated in normal aging where lean body mass decreases, increased inflammation occurs, and alterations in hormonal production ensue (59-62). Distinctions in sex specific cancers including breast and prostate require additional study and offer potential opportunities when accompanied with the influence of patient age for elucidating the relationship between sex hormones, obesity and cancer (63-65). Obesity and age both can affect fat deposition as well as hormonal levels which in turn can influence both cancer and immune status. These insights may also partially account for some of the inconsistencies in the clinical outcome data, particularly in women after menopause or in cancer patients receiving hormonal blockade therapies.

2.0 The Importance of Appropriate Preclinical Modeling in Cancer Immunotherapy

The high heterogeneity in the human population highlighted by the considerable diversity in basic immune responses, as well as lack of access to primary tissues or cancer sites, confounds the ability to determine how obesity alone can affect cancer immunotherapy efficacy or even tumor progression. Clinical variables include outbred genetics, unique environmental conditions, dietary habits, medications used, comorbidities, age, and patient sex, as well differences in cancer type or tumor burden (defined as total tumor mass in the body) or immune history all have marked effects on overall immune response capabilities. Beyond this, simply obtaining an accurate picture of a patient's immune status is problematic since it often relies upon use of peripheral blood of immune cells in transit, which can be inadequate in reflecting the immune status within a tissue or tumor. The inbred laboratory mouse has been the foundation of biomedical research and for the development cancer therapies, particularly immunotherapy. However, aside from the species differences and inbred nature of the models, due to the cost and time for their use, there have been relatively few (especially considering the increasing prevalence of obesity in the population) assessing cancer immunotherapy in preclinical models of obesity. Both cost and time involved in obesity models represents a major hurdle. Another issue concerns the numerous pathways affected in obesity making definitive mechanistic studies highly problematic. The vast majority of preclinical cancer immunotherapy studies solely focus on the generation of successful anti-tumor effects in the most expeditious manner meaning that young, healthy, and lean, inbred mice are predominantly used. The other issue is the general skepticism on the relevance of rodent obesity models to the human condition to mirror the multiple facets that contribute to obesity.

As in humans, defining criteria for what is considered obese or not is also a challenge in pre-clinical models. Most preclinical models, including large animal models use simple weight differentials or body conditioning scores as the sole criteria analogous to BMI. Approaches including dual energy x-ray absorptiometry (DEXA), computed tomography (CT) scan, nuclear magnetic resonance (NMR), quantitative magnetic resonance (qMR), and magnetic resonance imaging (MRI) are similar to strategies used in humans but costly and are not often used. Rodent models, particularly the mouse, offer several benefits including short gestation period, ability to multi-house, smaller size, the ability to utilize genetically identical cohorts, and access to a variety of genetic manipulations. Inbred mouse models are by far the predominant model used for studying obesity in the context of cancer as they strike a balance between physiologic relevance and an ability to control for variables allowing for use of both diet induced and genetic models of obesity. A general overview of prevalent genetic and diet induced obesity models are outlined in Table 1. In most cases obesity is defined by a weight differential from control mice, through densitometry, or by post mortem assessment using chemical analysis (66,67). However, a key advantage of mouse models for the study of cancer is the presence of transplantable tumor lines and genetically engineered mouse models (GEMM) with spontaneous tumor development, which each can be used to assess immunotherapy approaches in the context of obesity.

Diet-induced obesity (DIO) modeling systems, commonly used in mouse studies, involve feeding high fat diets (HFD), usually 45-60% lard, but also other fats such as coconut oils, over a period time (usually several weeks to several months) at which there is significant weight gain in the mice compared to those on control diets. The range of both fat content and time on diet is an important variable in such studies (68). Some diets also add high sugar content to mirror what has been termed a "Western Diet" and as such, these diets often induce significant metabolic effects including insulin resistance/diabetes (69). Importantly, different mouse strains can have significant differences in weight gain. This is observed in contrasting phenotypes between different mouse strains exposed to HFD (70). Examples of this can be seen in the two commonly used mouse strains C57BL/6 and BALB/c in which the former is susceptible to diet induced obesity and uniform weight gain, while the latter is considered resistant with only a portion gaining weight (71-74).

Use of monogenic (genetically modified or mutated) mice has also been a strategy for implementing obesity studies. Leptin and its receptor are important in regulating energy balance and appetite and have both been characterized in leptin or leptin receptor deficient mice (referenced as *ob/ob* and *db/db,* respectively). Each has been used in models of both obesity and diabetes due to their unique phenotype in which mice develop overt obesity, insulin resistance and diabetes (75). It is important to acknowledge the total absence of leptin and its signaling on immunity. Part of this is also due to effects on the development and function on various immune cell-types. In *db/db* mice adaptive immune responses including proliferation and cytokine production are suppressed, yet innate inflammatory mechanisms including those in macrophages and NK cells are increased in activity (76,77). Further alterations in the gut microbiome and inflammatory profiles have also been identified in these mice (78). However, the distortion of having deficiencies from birth as well as the developmental role of the leptin system on immune cell development such as T regulatory cells (79,80) need to be considered as these can lead to a distortion or magnification of immune effects/alterations.

2.1 Accounting for Limitations in Murine Obesity Models

Although many murine models of obesity have been developed and have each offered insight into a growing understanding of many of the interacting factors of obesity many models have significant limitations or variables that cause difficulty in both interpreting data or extrapolating to humans. An excellent and thorough over-view on preclinical models of obesity and cancer has been published by Hursting et al (81). The commonly used monogenic murine models with spontaneous mutations in leptin and the leptin receptor (*ob*/*ob* and *db*/*db* strain mice respectively) have had profound impact on the metabolic study of obesity particularly in relation to diabetes but have also been used for immune assessment. However, these models are limited in that they have altered physiology from birth inducing a rapidly developed state of obesity that in many cases does not reflect human disease in which factors are often polygenic and complex. There is also an increasing appreciation and literature on the role of leptin on immune cell development and function (i.e. Tregs) which are affected indicating that not all immune effects are related to the obese state itself (82). Selectively bred polygenic obesity models with genetic dispositions toward obesity also can be helpful tools, but often do not universally develop an obese phenotype

with some models being sex or age dependent and similarly may not be applicable to a heterogenous human populations (83-88).

Use of diet induced obesity (DIO) models have the distinct advantage of taking into consideration polygenic and diet related factors the latter being of particular importance as a notable contributor to human obesity. DIO models both take into consideration steady progression of weight gain overtime as can be seen in human populations and given the time necessary to be on diet the model results in an age that can better accommodate human populations as opposed to young mice. We have observed the inflammatory effects of monogenic leptin models to be more severe than HFD models with some cancer immunotherapies which may also reflect the greater body fat accumulation of these models versus DIO compared to age-matched controls (26). The literature on the type of diet used to induce obesity is expansive and selecting a HFD whether it be high fat only (considering variables such as percentage of fat and duration of diet) versus the “Western Diet” which also contains high sugars and often accelerates or magnifies the metabolic permutations as well as effects on cancer growth (89). These metabolic effects, however, also can present difficulties in affecting mechanistic dissection depending on the extent of metabolic dysfunction.

Another limitation that affects all murine obesity models is defining an obese state or differential to start assessing. Often, murine obesity models are defined by a simple weight differential of the DIO or obese mouse from control diet or wild-type mice with no set criteria as to what constitutes an acceptable differential. For some immunotherapy and tumor studies, basic metabolic parameters such as blood glucose levels or insulin resistance are sometimes used but there is a need for better characterizing key obesity parameters for investigators to use. These can involve body weight differential, serum metabolomics, ratios of fat and lean body mass, body fat deposition, and importantly, length of time in the obese state or on diet. Just as BMI is now increasingly viewed as too simplistic in clinical obesity studies, development of surrogate biomarkers analogous to the human clinical scenario need to be validated and incorporated in preclinical modeling. Thus, DIO models using other obesity biomarker readouts still offer the most reflective insights to the clinical paradigm, but use of older mice (greater than 12 months) would be still more reflective given the age of most cancer patients and that age can exacerbate the meta-inflammatory effects of obesity. Indeed, we have observed that, as opposed to the increased efficacy of immune checkpoint blockade in DIO mice versus control diet mice, aged DIO mice did not show this same differential (90). Whether this was due to the metabolic perturbations that occur in the aged DIO mice or other consequences of aging still needs to be determined.

3.0 Adipose Tissue, Adipokines and Free Fatty Acids

Adipose tissue (AT) is known predominately for its role at maintaining energy storage, however AT is also recognized as a major endocrine organ responsible for secretion of a vast array of adipokines. Under obese conditions AT can induce inflammation and alter several physiologic systems including immunity and metabolism (91).

Morphologically AT falls into three classifications including white, brown, and beige. White adipose tissue (WAT) is predominately associated with energy storage and hormone or adipokine secretion, while brown adipose tissue (BAT) is thermogenic and highly metabolically active (92,93). WAT is traditionally located either subcutaneously beneath the skin or viscerally within the abdomen, while BAT is found in a much smaller fraction of the body within axillary, cervical and paraspinal spaces (93,94). The third type of AT, beige adipose tissue, is defined as BAT that is found in traditionally WAT locations (i.e. subcutaneously) and is distinct with unique gene profiles particularly in areas of inflammation and metabolism (95).

The development of obesity manifests when an individual's energy intake exceeds their energy expenditures and accumulates through the generation and expansion of AT (96). AT expansion can take place either through an increase in adipocyte size (hypertrophy) or adipocyte number (hyperplasia). Expansion of AT is predominately associated with subcutaneous or visceral WAT and can lead to altered secretion of adipokines and free fatty acids, (97). Others have further reviewed and elaborated on obesity offering insight on how it induces changes in the tumor microenvironment including alterations in lipid metabolism (98)

Leptin was among the first adipokines identified following the characterization of the obese (*ob*) gene mutation in *ob/ob* mice, which have defective leptin production and manifest an obese phenotype (99). Leptin is an important regulator of food intake and appetite, which increased in abundance with adipose tissue. With increased adiposity leptin levels increase and reduce appetite. A lack of leptin signaling as seen in ob/ob mice results in an uncontrolled appetite, which leads to increased weight gain and obesity. However, beyond its role as a mediator of appetite leptin is also a key mediator of inflammation and promotes secretion of proinflammatory cytokines in macrophages and T cells, which can polarize each toward M1 and Th1 responses respectively (100). In conditions of obesity, leptin insensitivity can develop, which leads to elevated leptin levels without an appropriate response in reducing appetite. Leptin insensitivity results in conditions of chronically elevated leptin levels, which in turn can contribute to obesity induced chronic inflammation (101,102). Leptin insensitivity of immune cells and how cancers respond to leptin is less well characterized. Some cancers including prostate cancer have been shown to migrate and express increased growth factor through leptin signaling (103). Conversely, adiponectin another adipokine which is negatively corelated with elevated adiposity is anti-inflammatory. In cancer, leptin and adiponectin are each prognostic indicators of poor or favorable outcomes respectively and have been identified as therapeutic targets (104). Low levels of adiponectin are associated with greater risk across multiple cancer types including breast, colon, endometrial, multiple myeloma, and prostate cancers (105-108).

Increased secretion of free fatty acids (FFAs) and lipolysis occurs with the excessive expansion of AT, which can be seen in obese subjects whom demonstrate higher concentrations of free fatty acids than non-obese counterparts (109-111). Excess and chronic FFAs can lead to insulin resistance, while the reduction of FFAs in plasma during obesity can result in improving insulin sensitivity (112). Increases in FFAs have demonstrated an ability to activate inflammatory pathways including NF-κB, which can mediate increases

of hepatic expression of inflammatory cytokines including TNF, IL-6 and IL-1β (113). FFAs lipotoxicity stimulation of inflammatory cytokines such as TNF act as additional contributors to obesity induced inflammation (114). Indirect consequences of increased FFAs that promote tumorigenesis can be seen with the upregulation of the fatty acid receptor CD36 which is associated with induction of hepatocellular carcinoma (115). Thus, the metabolic and hormonal effects of obesity can be profound and need to be considered or assessed outside of simple adiposity.

3.1 Immunometabolomics: Measuring the Crosstalk Between Immune Cells and Metabolism

There is a growing appreciation that metabolic processes, especially those impacted by obesity, can impact immune cell function, resulting in altered immune responses (116). As such, the field of immunometabolism, which explores the relationship between immunology and metabolism, has burgeoned (117), resulting in both important biological findings, as well as, the development of novel assays. To this end, flow cytometry (118,119), scintillation counting (120,121), flux analyzers (122,123), mass spectroscopy (MS) (124) and Nuclear Magnetic Resonance (NMR) (125) based platforms have been used to characterize and quantify metabolites in immune cells and the immune milieu. Most of these techniques are steady-state, targeted approaches, from a bulk sample, covering predefined metabolic pathways, whether developed by a lab to measure specific pathways, or large panels like Biocrates (126,127) and Metabolon (128,129), which cover a broad range of metabolites. These assays have uncovered important immunometabolic changes in lipid, amino acid, and energy metabolic pathways (126,130,131), that facilitate immune cell alterations that results in disease progression, including both intrinsic and extrinsic mechanisms of immune cell activation (131-134), immune cell clonal expansion (135,136), and lineage differentiation (130). However, while steady state metabolomics are useful techniques, metabolomics is now expanding to include untargeted approaches (137-139) for discovery, isotope tracing (140-143) for better understanding metabolic flux in immune cells, and spatial (144,145) and single cell metabolomics (146-148) to assess crosstalk between metabolites and immune cells at higher resolution in both the tumor and immune milieu. The development of these techniques will help to further advance our understanding of metabolic dysregulation in the context of immune signaling and inflammation in obesity, cancer, inflammation, and other metabolic disorders.

4.0 Obesity and Inflammation

The inflammatory state promoted by obesity can result in altering immune function or phenotype (Figure 1). The term “inflammaging” refers to a state of chronic low-grade inflammation that can develop normally with age but can be exacerbated by several influences including stress, epigenetics, inflammation, macromolecular damage, metabolism, and obesity (14). This can affect every tissue and physiologic process and contributes to the off-target toxicities of many therapeutics.

Adipose tissue is composed of several cell types including adipocytes, fibroblasts, endothelial cells, and a wide spectrum of immune cells. As AT expands adipocyte

hypertrophy can result in increases of inflammatory adipokines including leptin, IL-6, TNF, MCP-1 and a number of others (149,150). Adipocytes undergoing hypertrophy in obesity are also more susceptible to injury and cell death. The combination of increased secretion of inflammatory adipokines and increased apoptosis of adipocytes in obesity contributes to the recruitment of immune cells to adipose tissue which promote a chronic inflammatory state (151). These increased inflammatory responses may also impact responses to conventional cancer therapies resulting in greater off-target effects or toxicities as well as impairing immune responses.

4.1 Adipose Tissue Immune Infiltration and Polarization

Obesity affects not only the quantity of adipose tissue but also its metabolic and inflammatory qualities. In a non-obese lean state, adipose tissue is dispositioned toward an anti-inflammatory type two polarization typically associated with cells including T helper 2 cells (Th2) and M2 macrophages. However, in obesity both T cells and macrophages undergo increased infiltration into adipose tissue shifting an anti-inflammatory environment to a proinflammatory environment with a polarization toward T helper 1 (Th1) cells and M1 macrophages (152). Macrophages in particular have been identified as major contributors to the adipose inflammatory environment with reports of macrophages composing as much as 50% of AT in obese mice and 40% in obese humans compared to lean controls in which macrophages only composed 10% of AT (151,153). The obesity mediated shift in macrophage polarization begins with the recruitment of macrophages to AT. Adipocyte death provoked by adipocyte growth and hypertrophy produces cellular debris which act as a catalyst responsible for the recruitment and localization of macrophages (154). In models of *ob/ob*, *db/db* and DIO mice, it has been observed that an obese phenotype can induce stress to adipocytes that eventually leads to cell death (155). These preclinical observations are paralleled with human obesity in which increased adipocyte necrosis is observed. Obesity induced adipocyte death correlates both with adipose tissue expansion and macrophage inflammatory polarization (156).

Adipose tissue immune infiltrate and composition has been observed to be time dependent. Studies in diet induced obesity (DIO) models have observed that while macrophages do become the dominant immune subset, this is only after initial infiltration by lymphocytes, notably memory T cells (157). Additional studies have indicated that recruitment of adipose tissue macrophage is facilitated by CD8 T cells and that they are also crucial for maintenance of AT inflammation, which was observed through CD8 antibody depletion that resulted in amelioration of inflammation (158). Thus, both macrophages and T cells directly contribute to obesity induced inflammation which can have substantial systemic effects that alter anti-tumor immunity. This dual interplay between the immune system and adipose tissue suggests that a cascade develops which may be difficult to intercede in with obesity, especially in aging.

4.2 Macrophages in Obesity Promote Inflammation and Immune Suppression

Elevated adiposity modulates macrophage polarization by promoting shifts from an M2 to an M1 proinflammatory macrophage phenotype (149). AT M1 macrophages promote inflammation through secretion of cytokines including interleukin 6 (IL-6) and TNF (151).

AT macrophages also have increased expression of inflammatory products NOS2 and CCR2 (150).

Adipokines have been identified as key contributors to promoting inflammatory macrophages in conditions of elevated adiposity. When the adipokine adiponectin is knocked-out mice display a phenotype with increased M1 macrophages and elevated cytokines TNF, IL-6 and MCP-1 (159). Contrastingly, the adipokine leptin, which is increased with greater adiposity, has been demonstrated to induce activation of macrophages and promote increased cytokine production and phagocytosis (160).

Depletion of M1 macrophages in DIO mice exposed to HFD resulted in normalization of insulin activity and decreased inflammatory marker expression both systemically and locally (161). These data implicate that M1 macrophages are instrumental in facilitating obesity induced inflammation. The increased inflammation and changes in metabolism can have meaningful impacts on cell proliferation and tumorigenesis. Even distally from within the adipose tissue macrophages have been recognized to contribute toward angiogenesis (162).

In cancer an increased M1/M2 ratio within the tumor is associated with extended survival and favorable response (163). Several studies across different cancer types have confirmed these observations and have implicated that the presence of M2 tumor associated macrophages is an indicator or poor prognosis and survival (104,164-167). Although obesity is characterized by proinflammatory processes and M1 macrophages the inflammatory shift in obesity can lead to immune suppression notably through induction of myeloid derived suppressor cells (MDSCs) (168). MDSCs are a heterogeneous population of immature myeloid cells that are immunosuppressive. In models implementing high fat diets (HFDs) it was observed that in obesity MDSCs play a multifaceted role in which they can protect against metabolic dysfunction and to some extent could reduce obesity related inflammation, but also were responsible for increased fat accumulation, tumor progression and metastasis in tumor models (169). Thus, in obesity there can polarization to immunosuppressive tumor-associated macrophages (TAMs) and MDSC’s which also can promote tumor progression as well as tumor evasion.

4.3 Obesity Induces NK Cell Dysfunction and Paralysis

Natural killer (NK) cells represent a key component of innate immunity and due to their ability to kill transformed cells in an MHC-unrestricted manner, have been intensively examined for use in cancer immunotherapy approaches. Reports of both human clinical data and preclinical models have demonstrated that obesity results in NK cell dysfunction (170,171). Both reductions in NK cell numbers and function have been reported in obese patients (172). Further studies have identified that NK cells from people with obesity are metabolically defective and have impaired NK cell “training” due to cytokine influences on IL-12, IL-15, and IL-18 (173). NK cell functionality can be restored through reduction of fat mass and bariatric surgery (174,175). Interestingly, in preclinical mouse models studies have characterized decreased activation and responsiveness of NK cells as “paralysis” driven in part by peroxisome proliferator-activated receptor (PPAR) driven by lipid accumulation, which halts NK cell metabolism (172). These studies would then suggest that diet also can play a pivotal role outside of increased adiposity. These clinical and preclinical studies do

raise important questions as to whether BMI needs to be considered in clinical trial design when therapies seeking to augment NK cell activity or ACT involving NK cells (including CAR NK cells) are being evaluated.

4.4 Obesity Promotes T Cells Memory Conversion, Polarization, and Exhaustion

T lymphocytes are substantially affected by the inflammation experienced in obesity and as result can both further contribute to obesity-induced inflammation and undergo several changes that can alter T cell functionality including anti-tumor responses. The immune system relies on naïve T cells to induce new antigen-specific responses. Normal aging results in thymic involution and reduction of this population which correlates with the reduced ability of aged individuals to mount primary T cell responses to vaccines and other antigens. Obesity has been demonstrated in infectious disease and other models to augment this dysfunction. Furthermore, obesity has been correlated with increased memory T cell numbers at the expense of naïve T cells. Obesity induced inflammatory mediators promote T cell immune polarization, which can provoke an imbalance in T cell subsets such as T regulatory (Tregs), T helper 1 (Th1), and T helper 17 (Th17) cells (176,177). The obese environment promotes Treg depletion specifically within AT, allowing for further inflammatory escalation and insulin resistance (178,179). Secreted adipokines can be major influencers on T cell polarization as is seen with leptin which promotes both Th1 and Th17 cell expansion through upregulation of glycolytic metabolism (180,181). Other mediators of polarization within AT such as IFN-α can contribute to the depletion of Tregs (182).

T cells can be potent actors in the tumor microenvironment (TME), yet they also undergo substantial changes in conditions of elevated adiposity and chronic inflammation, which can alter their function and effectiveness by decreasing antigen sensitivity, restricting T cell receptor (TCR) repertoire, and increasing T cell exhaustion.

DIO models have demonstrated that adipose tissue CD8 T cells also have an intrinsic decrease in antigen responsiveness and can lose the ability to effectively respond to TCR stimulus suggesting an epigenetic alteration is occurring (183,184). Assessments of human visceral adipose tissue T cells have demonstrated decreased inflammatory response to TCR specific stimuli (185). Adipose tissue (AT) resident T cells also have a restricted TCR repertoire when compared to peripheral T cells seen in the spleen and has been accompanied by increased production of proinflammatory mediators such as IFNγ and TNF (186). The increased secretion of IFNγ and TNF by CD4+ T cells has been linked to increased levels of MHC II in obese AT (187).

Systemically, obesity accelerates T cell senescence and thymic involution increasing $CD44^{hi}$ $CD62L^{lo}$ memory T cells that accumulate in visceral adipose tissue (188-190). Interestingly, initially, thymic size in obese mice has been reported to be increased but is then followed by more profound thymic involution which may account for the increased memory T prevalence observed (90). The inflammatory changes and alterations in the ratio of memory and naïve T cells may account for both impaired memory responses to viral pathogens such as influenza and impaired responses to vaccines observed in experimental conditions of obesity (183,191-193). Similar observations of obesity related impairments with response to vaccination have also been observed (194,195). These effects may therefore have significant

consequences in cancer patients using immune therapy approaches where generation of new T cell responses such as with cancer vaccines to neoantigens are attempted.

Obesity has also been identified as a mediator of T cell exhaustion a state of diminished proliferative capacity and effector functionality often identified by several cell surface markers such as programmed death protein 1 (PD-1), lymphocyte activation gene 3 (Lag-3), T- cell immunoglobulin and mucin-domain containing 3 (Tim-3) and others (24,90) . Obesity has been observed to induce increases in peripheral exhaustion markers including PD-1 and is accompanied by a diminished proliferative disposition as indicated by decreased levels of Ki67 (24,196). An upregulation of a number of exhaustion markers alongside decreased indicators of proliferation and functionality has suggested that obesity promotes T cell exhaustion (185). In obesity, AT T cells exhibit enrichment of exhaustion related genes and increased expression of coinhibitory receptor *Btla* (185).

In murine cancer models tumor growth and progression has been observed to increase with HFD exposure which evidence has suggested is in part mediated by the accumulation of PD-1^{+} exhausted T cells, although this can be cancer dependent (24,197,198). Obesity and HFD exposure in murine models can decrease numbers of tumor infiltrating T cells, alter metabolism of the TME and promote T cell dysfunction (198). Leptin, which increases with adiposity, has been identified as vital for activated T cells to upregulate glucose uptake and metabolism (199). However, leptin is also positively associated with increased expression of exhaustion markers such as PD-1. Interestingly, reduction in leptin signaling, which has been simulated through use of adoptive transfer of T cells from leptin receptor deficient mice into DIO RAG$2^{-/-}$ mice, was able to rescue T cells from exhaustion in an obese environment (24). These data illustrate that although obesity is associated with an exhausted and immunosuppressive environment, this could be potentially overcome which may partially explain the “Obesity Paradox” in which greater efficacy can be observed with some types of immunotherapies. The data indicating that obesity impairs T cell priming also suggests that these may be issues to consider when evaluating cancer vaccine approaches.

5.0 Obesity and Cytoreductive Cancer Therapies

The effect of obesity on traditional cytotoxic therapies (radiotherapy and chemotherapy) is controversial. There is a body of clinical evidence that suggests that obese patients may not respond as well to radiotherapy or chemo-radiotherapy. Four large studies of prostate cancer patients, ranging from 700-1400 patients, treated with definitive RT found that those with higher BMI were more likely to experience biochemical failure, distant metastases, cause-specific mortality, and overall mortality (200-203). Similarly, poor outcomes after combined chemotherapy and radiotherapy have been reported in several rectal cancer trials, where obesity was found to be significantly associated with higher rates of recurrence (13-15). Additionally, a large prospective analysis of 2,303 patients diagnosed with colorectal cancer demonstrated that obese patients had higher rates of colorectal cancer specific mortality (204). The same trend was seen in studies of nasopharyngeal cancer and breast cancer patients where obesity was linked to poorer outcomes in patients treated with cytotoxic therapies (205-208). Obesity has also been linked to a higher incidence of melanoma (209,210), and there is evidence to suggest that adiposity may lead to RT resistance in

this type of cancer (211). These findings are not universal as others have reported improved outcomes in melanoma patients treated with chemotherapy and targeted therapies and others have reported no effects of BMI on outcomes (212,213).

5.1 Cancer Immunotherapies: Diverse Approaches

Contemporary cancer immunotherapy strategies have revolutionized the cancer treatment landscape adding a fourth arm to cancer treatment alongside the traditional strategies of surgery, radiation, and chemotherapy (Outlined in Figure 2). However, one must be careful not to use the umbrella term of “cancer immunotherapy” so broadly as different approaches in cancer immunotherapy can have markedly different effects particularly in the context of obesity. Classically, cancer immunotherapy approaches initially involved means to stimulate the immune system to attack the cancer. The initial systemic use of recombinant human cytokines including interleukin 2 (IL-2) and interferons paved the way for other immunotherapies with a proof of concept that the immune system could be stimulated to mount a more efficacious response to cancers. Cytokine therapies demonstrated success in the context of melanoma and renal cell carcinoma with durable complete responses, but these response were confined to a subset of patients and were associated with severe toxicities (214-216). Immunotherapy approaches have dramatically expanded over the years but the application of immune checkpoint blockade initially targeting CTLA-4 and PD-1/PD-L1 have now made such approaches front-line therapy options and importantly, applied to solid cancers (217).

Other immunotherapy approaches involve oncolytic viruses, tumor vaccine application, as well as monoclonal antibody-based approaches. Cellular based therapies such as adoptive transfer of immune cell-types such as tumor infiltrating lymphocytes (TILs) as well as NK cells have been applied in the past but have now progressed to more sophisticated approaches involving genetic manipulation to improve targeting or be resistant to immunosuppression. Chimeric antigen receptor (CAR) T cells in which antibody-based targeting is applied, have built on these approaches and are being increasingly applied first in hematologic malignancies but now for solid tumors. Due to both the cytoreductive conditioning applied to the patient and effects of the CAR T cells themselves, a significant risk for cytokine release syndrome (CRS) can result necessitating the use of anti-inflammatory approaches such as IL6 blockade. Given the preclinical and clinical data indicating that obesity predisposes to CRS by other stimuli such as viral infection, LPS or cytokine administration, it will be important to determine if this also is associated with greater off-target toxicities with CAR application or less efficacy with obesity or altered nutritional status (218). Initial studies do not appear to demonstrate decreased efficacy or benefit of CAR T cells in obesity (219), but there have been glimpses of greater risk as seen in a study of patients receiving CD19 CAR T cells, for treatment of refractory B cell malignancies, in which increased body composition and VAT were associated as a risk for severe and early CRS (220). However, larger cohorts of patients receiving CAR T cell therapy allowing stratification on BMI, body composition and other parameters are still needed. Effects of obesity on application of oncolytic viral therapy as well as tumor vaccines has not been robustly examined in preclinical models and clinical trials lack the numbers to allow for sufficient stratification. Preclinical models demonstrating that systemic high

dose IL-2 alone or in combination with immune agonists such as CD40 resulted in marked anti-tumor effects in young mice (221,222) but resulted in CRS and multiorgan pathology in DIO or *ob/ob* mice (26) highlights the need to incorporate obesity models in evaluation of potential immunotherapies. Targeting inflammatory pathways as shown by targeting TNF preclinically and not impacting anti-tumor efficacy suggests that similar approaches may be applied with other forms of immunotherapy (223).

5. 2 Obesity and allogeneic HSCT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has played an important role by establishing a potentially curative immunotherapeutic approach in some hematologic cancers. Allo-HSCT initially involved infusion of donor hematopoietic cells into a recipient that had received myeloablative cytoreductive conditioning. The presence of donor alloreactive cells resulted in the occurrence of graft-versus-host disease (GVHD), which was, and still is, a significant cause for morbidity, but also resulted in a significant anti-tumor effect. This graft versus leukemia (GvL) effect or, more broadly as a graft versus tumor (GvT) effect provided the first clear evidence that successful immune responses to a cancer could occur. However, minimizing GVHD while maintaining GVT is still a major hurdle. The effect of obesity in these conditions which has been difficult to decipher given all the variables associated with allo-HSCT, however, obesity has been identified as an indicator of increased incidence of acute GVHD (aGVHD) and increased transplant related survival (224). Other reports have observed that obesity is an independent variable for mortality risk in patients treated with HSCT and has a positive association with death within 100 days of treatment (225). Increased toxicities have been reported in high BMI HSCT recipients (226). However, results depicting the predictive role of obesity in HSCT outcomes are mixed with a few other reports finding either no difference or a benefit to those with high BMI (227). An example is seen in conditions of autologous HSCT where overweight and obese patients treated for lymphoma have reported to not have decreased survival (228). Delineating the effects of different conditioning regimens or therapies, heterogeneity of the cancers and prior therapies, and the previously described other variables, has been highly problematic as well as inherently small sample sizes in determining the real impact of obesity on outcome.

Preclinical murine modeling of obesity and allo-HSCT has paralleled some of the clinical reports by demonstrating a negative impact of obesity on allo-HSCT outcomes. Using a DIO model, it was observed that obesity markedly impacted acute GVHD pathology even in models where such severe GVHD would not normally occur (139). This was in part due to increased gut permeability resulting in increased endotoxin translocation, as well as increased radiation induced gastrointestinal damage, all of which fueled GVHD processes and pathology. This was correlated with clinical allo-HSCT and preclinical mouse DIO models showing higher proinflammatory cytokines (139). Interestingly, it was found that both preclinical DIO mice and obese human microbiomes had a markedly restricted diversity which also augmented GVHD pathology as administration of antibiotics could partially ameliorate the GVHD (229). While obesity clearly alters the microbiome, the question arose as to whether this was the sole cause for increased pathology versus effects of the diet as well as body fat deposition. Additional preclinical studies using mouse models

where some mice on diet did not gain weight demonstrated the increased body fat as well as HFD both directly contributed to the increased GVHD induction whereas the altered microbiome appeared to play an amplifying role (230). Thus, obesity has a significant effect on gut permeability as well as susceptibility to radiation-induced damage which further augments the heightened proinflammatory responses and tissue pathology. The microbiome alterations associated with obesity also appear to play an immunomodulatory role which needs further exploration.

Potential means of compensating for increased toxicities in obese patients following HSCT while maintain GvT effects have targeted inflammatory cytokines. Examples including IL-6 receptor block, which can lower mobilization of free fatty acids, or TNF block, which has been demonstrated to reduce pathology under inflammatory conditions (223,231). Preclinically the feasibility of cytokine blockade was explored in a DIO model of GVHD, where the use of dual cytokine block of IL-6 and TNF provided significant protection against acute GVHD when compared to untreated mice (232). These data suggest that conditions of obesity while disposed to increased GVHD toxicity may lend an opportunity to maintain strong GvT effects through control of inflammatory cytokines or pathways.

5.3 Immune Checkpoint Inhibitors (ICI) and The Obesity Paradox

The phenomenon in which obese patients unintuitively have more favorable cancer outcomes despite a greater risk of developing cancer has been referred to as the “obesity paradox”. While not universal obesity has been identified as a positive predictive indicator of cancer treatment outcome particularly in the context of immune checkpoint inhibitors (ICIs). There have been key observations in several cancer types in which obesity has been correlated with more favorable outcomes and a number of studies have evaluated particularly in melanoma, lung and renal cancer patients (233,234).

McQuade et al. were among the first to report on the concept of an “obesity paradox” in a retrospective study which identified that melanoma patients with obesity (as determined by BMI) had improved progression free and overall survival involving a variety of cancer therapies, including ICI (212). These data highlighted that high BMI melanoma patients had an association with increased survival particularly in targeted therapy and ICI immunotherapy, with a caveat showing increased efficacy only in high BMI male patients (212). In another study, a grouped analysis of both male and female lung, melanoma and ovarian cancer patients undergoing ICI identified that obesity, defined by BMI, was associated with improved survival across several cancer types (24). A smaller cohort study evaluating melanoma identified that BMI was predictive of response to ICI (ipilimumab), but this study classified patients into only two groups normal (BMI<25) and overweight (BMI ≥ 25) (235). Placing into two groups ignores those patients that are underweight and obese. Similarly, a multi-center study analyzing patients with NSCLC, melanoma and kidney cancers identified that “overweightness” and not necessarily obesity was associated with improved outcomes and was observed in both male and female patients (236). A study that further evaluated the intersection between patient sex and BMI identified that overweight/Class I obese patients (BMI > 25 and BMI < 35) were associated with greater survival, but predominantly in males (237). This study also identified that there was

not a positive association of ICI outcome in more severe Class II/III obesity (BMI ≥ 35). These data confirm the obesity paradox illustrated by McQuade et al but suggests a nuance in the classification of BMI severity and body composition. Some of these questions concerning body composition are addressed in a retrospective study that evaluated melanoma patients based on visceral adiposity and systemic inflammation status instead of BMI and observed that under these criteria obesity was also associated with improved outcome (25). Importantly, this sex-linked difference has been observed in some preclinical models where increased responses to ICI using anti-PD1 were observed in female mice that were estrogen-receptor deficient (238). This raises an interesting question as to whether patients, particularly female, on hormone blockade therapy for hormonally-responsive cancers also have altered immune function in the settings of obesity or if estrogen levels can be associated with body fat deposition differences or immune changes as well as therapeutic responses.

In a pooled analysis of NSCLC patients treated with atezolizumab, BMI was associated with improved survival following treatment with immunotherapy (239). Retrospective analysis of 513 NSCLC patients who received ICIs (nivolumab/pembrolizumab/atezolizumab) illustrated that BMI was associated with improved efficacy of ICI targeting the PD-1 axis and was independently associated with longer progression free survival (240). A meta-analysis performed in 2020 which encompassed 5140 patients across 12 studies identified that higher BMI is associated with improved overall and progression free survival (241).

Examples of studies evaluating the role of obesity and BMI in renal cancers have had mixed outcomes with the extent of an “obesity paradox” being inconsistent. High BMI was identified as predictive of improved survival in a retrospective study of metastatic renal cell carcinoma (RCC) where tyrosine kinase inhibitors demonstrated improved outcome with high BMI, but this was not seen for immunotherapy (i.e. nivolumab, atezolizumab or avelumab) (242). Similar results were observed in another study investigating clear cell renal cell carcinoma where obese patients demonstrated increased survival following a number of treatments including surgery, targeted tyrosine kinase inhibitors, and ICI, with the latter not being significant following adjustments based on International Metastatic RCC data base risk score (243). There has been some success of immunotherapy in renal cancer as is seen in a study evaluating clear cell renal cell carcinoma that observed that high BMI patients have an initial survival advantage and that they are also corelated with occurrence of immune related adverse events (244). Other studies have found that obesity actually diminishes immunotherapy responses in RCC (245).

Although a number of studies support the “obesity paradox” in the context of ICI immunotherapy not all studies are in agreement and even those that do agree vary in their findings depending on a number of variables including cancer type, treatment regimen, age, and sex (246-253). Studies incorporating body composition criteria including subcutaneous and visceral fat area have demonstrated conflicting results with BMI (254). A study taking into consideration immune inflammation observed that while BMI was associated with increased survival low BMI patients with a high inflammatory index were at a three times greater risk of mortality (255). The role of immune related adverse events from ICI and their relation to obesity also needs further interrogations and can add complexity as some studies

have identified greater incidence of conditions such as immune-mediated diarrhea and colitis (IMDC) with increased BMI without increases in severity or impacts on overall patient outcome (256). The multiple variables and factors associated or known to affect obesity need to be considered rather than simply relying on BMI as the sole means for stratification, but these may be difficult to include given heterogeneity and patient sample size limitations. This is where more robust preclinical modeling may offer insights.

6.0 Concluding Remarks: Obesity and Immunotherapy, Many Unanswered Questions Remain

Despite the rising incidence of obesity within the population, obesity has not been rigorously assessed with regard to cancer and cancer immunotherapy application. In part, this is hampered by the complex physiological pathways all impacted by obesity and in part by how obesity is defined both in the clinic and the laboratory. There is a real need for more metabolic biomarkers to be applied in conjunction with fat deposition. Given all the other factors that affect obesity (age, sex, diet, presence of co-morbidities and medications, cancer type, immune status), it is imperative that more robust preclinical modeling be applied where delineations of the different components and factors can be mechanistically addressed. Another issue revolves around the increasing diversity and application of what is called “immunotherapy” as it is apparent that completely opposite results regarding efficacy/outcome can result in obesity depending on what is applied in part due to the meta-inflammatory state in obesity (Figure 3). Use of cytoreductive conditioning and systemic immune stimulation may result in increased CRS and tissue pathologies whereas use of ICI can potentially result in greater anti-tumor efficacy. The question arises as more immunotherapeutic approaches are applied in combination which outcomes will dominate. In an era of personalized medicine in cancer, tailoring treatment strategies to a patient’s metabolic factors will be critical to improving outcomes and this requires more rigorous assessment of patient parameters beyond BMI. There is still great need to determine what aspects of obesity (body fat deposition, diet, microbiome alteration, immune alterations, hormonal effects) most affect immunotherapy outcome, and it is likely age and sex may be critical drivers along with cancer type. The immune cells or pathways being targeted in cancer immunotherapy also may be critically impacted in obesity and therefore more understanding on the immune alterations that occur in obesity, and whether they are permanent or reversible, is needed.

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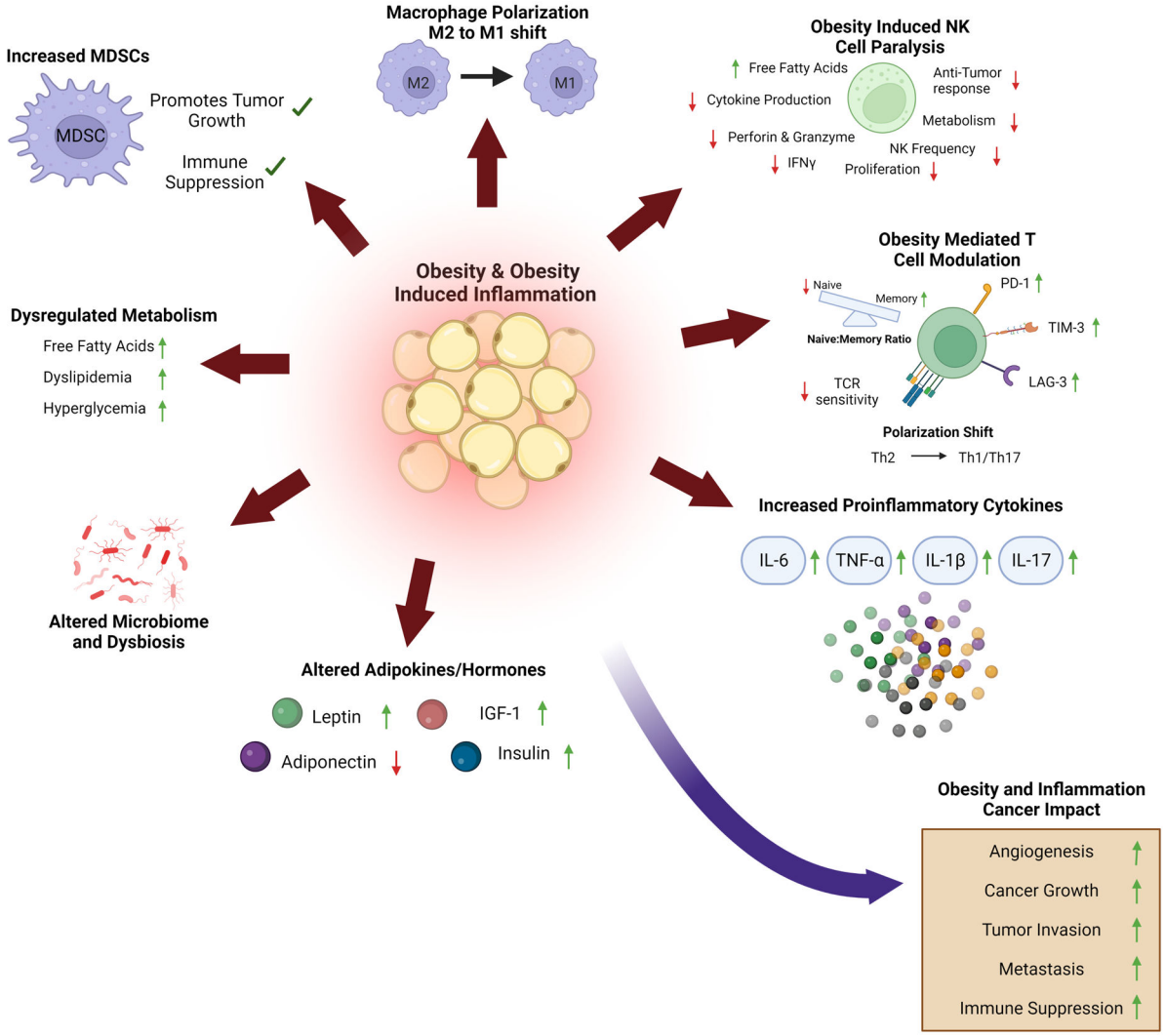

Figure 1. Obesity Influences Cancer Through Multiple Pathways.

Obesity can facilitate several processes that promote inflammation, immune suppression, and cancer growth. The schematic outlines some key aspects of obesity mediated effects on metabolism, adipokine secretion and immunity. Myeloid derived suppressor cells (MDSCs) can increase during obesity which foster both exert immune suppression and promote Tumor Growth. Obesity dysregulates metabolism elevating free fatty acids (FFAs) promoting insulin resistance and hyperglycemia. Obesity can cause dysbiosis, which can alter microbiome composition. With elevated adiposity during obesity proinflammatory adipokines such as Leptin increase, while anti-inflammatory adiponectin decreases. Obesity also increases hormones including Insulin-like growth factor 1 (IGF-1) and insulin. Proinflammatory cytokines including interleukin 6 (IL-6), tumor necrosis factor-alpha (TNFα), interleukin 1-Beta (IL-1β), and interleukin 17 (IL-17) are each elevated in conditions of obesity. T cells undergo several obesity mediated changes including an increased shift in naïve: memory ratio, decreased T cell receptor (TCR) sensitivity, a polarization shift from T helper 2 (Th2) to T helper 1 and 17 (Th1 & Th17), and increases in exhaustion markers PD-1, TIM-3 and LAG-3. Natural Killer (NK) cells undergo paralysis in

obese conditions with decreases in cytokine production (including Interferon γ -IFNγ) and decreased proliferation. Similar to other cell types, macrophages also undergo polarization shifts from M2 to M1 proinflammatory macrophages.

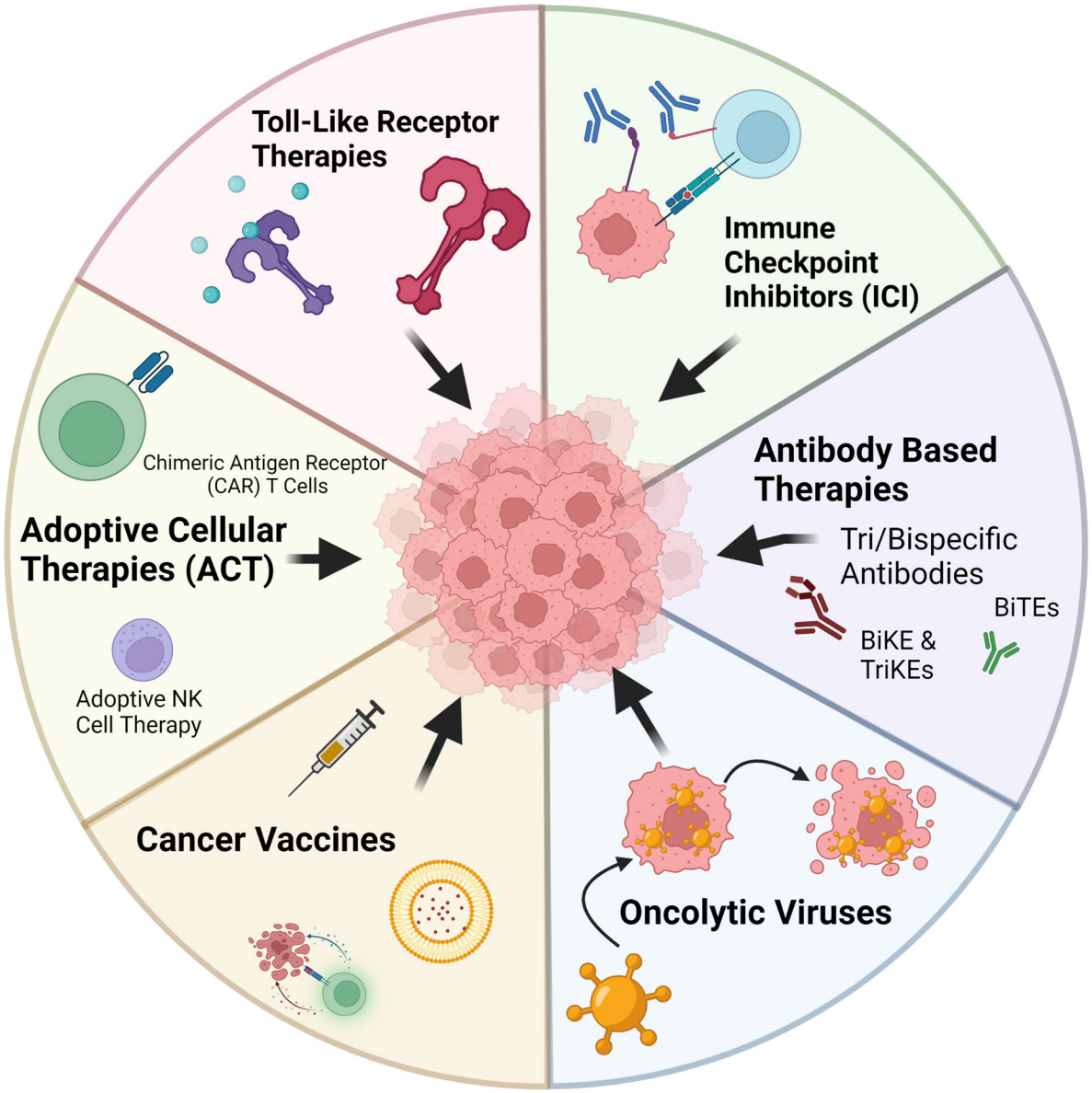

Figure 2. Cancer Immunotherapy Approaches.

Outlined are several immunotherapy approaches for the treatment of cancer. Immune checkpoint inhibitors (ICIs) are antibodies that target inhibitory proteins and their ligands including CTLA-4 and the PD-1/PDL-1 Axis. Other antibody therapies including tri-specific killer engagers (TriKEs), bi-specific killer engagers (BiKEs), and bi-specific T cell engagers (BiTEs) are strategies which use antibodies to direct a host's immune cells such as T and Natural Killer cells toward a target. Oncolytic viruses are viruses that preferentially infect cancer cells and promote tumor cell lysis, which can assist with release of tumor antigens and stimulate host immunity. Cancer vaccines can be either preventative or therapeutic and rely on exposing the hosts immune system to antigens derived from a given cancer. Adoptive cellular therapies involve the infusion of immune cells, notably T or NK cells, into a patient; examples include chimeric antigen receptor (CAR), or tumor-infiltrating lymphocyte

(TIL) therapies as well as NK cell-based therapies. Therapies targeting pattern recognition receptors that can initiate immune responses such as Toll-like receptors are also of interest in cancer treatment.

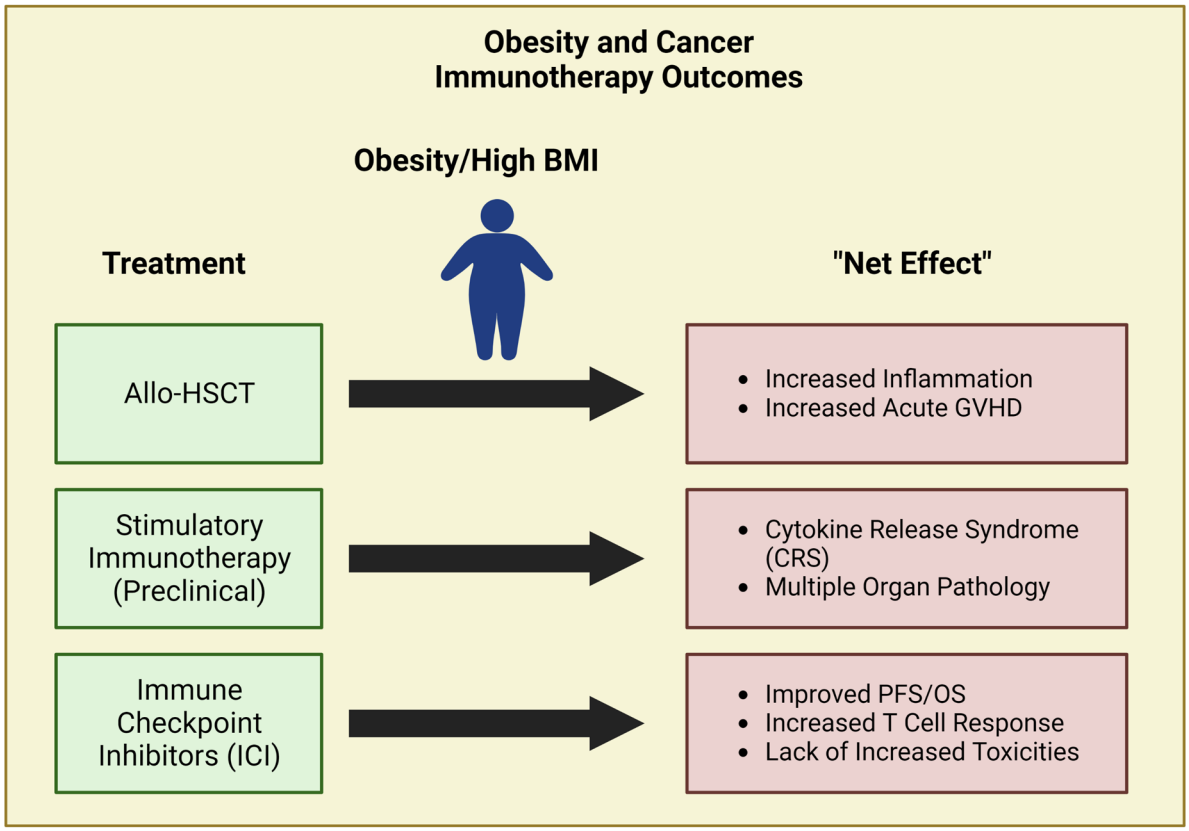

Figure 3. Effects of Obesity on Immunotherapy.

Obesity influences cancer treatments in differently depending on the approach taken which can result in either increases or decreases in both the efficacy and toxicities of a given regimen. The high inflammatory environment of obesity can lead to increased toxicities such as in allogeneic hematopoietic stem cell transplantation (Allo-HSCT), which can result in increased inflammation and acute graft versus host disease in obese patients. Similarly immune stimulatory therapies have shown preclinically that they can exacerbate inflammation in obesity and lead to cytokine release syndrome and organ pathology. Immune checkpoint inhibitors (ICIs) have demonstrated both increased efficacy in obese patients, but also a lack of increased toxicities in the obese inflammatory environment.

Table 1:

Brief Overview of Monogenic and Diet Induced Murine Obesity Models

Means of Inducing Obesity	Model Examples	Model Descriptions	Advantages	Disadvantages
Monogenic	ob/ob	Mice with the ob/ob mutation (often C57BL/6 background) are deficient in leptin, exhibiting an inability to control food intake which results in these mice undergoing marked weight gain at an extremely rapid rate. These mice outwardly have increased weight and demonstrate an obese phenotype accompanied with diabetes, insulin resistance and hyperinsulinemia (99,257)	• Reliably induced weight gain and "obese" phenotype. • Defective leptin production • Develops metabolic disorders. • Develops phenotype on a "normal" chow diet.	• Limited translation to human obesity which predominately does not. result from mutations in leptin signaling. • Metabolic disorders begin at birth. • Mice suffer from an altered immune system.
	db/db	Mice with the db/db mutation have a leptin receptor deficiency which also results increased body weight gain. This model is often used for the study of type II diabetes (often C57BLKS/J background), in which these mice are also insulin resistant and have increased insulin levels. (75,258,259)	• Reliably induced weight gain and "obese" phenotype. • Defective leptin receptor signaling. • Develops metabolic disorders. • Develops phenotype on a "normal" chow diet.	
Polygenic Diet Induced	C57BL/6 (High Fat Diet)	C57BL/6 mice are a common inbred strain used for immune research are a model used for diet induced Obesity (DIO). These mice exhibit increased weight gain when placed on high fat diets (HFD) when compared to those on control diets. Both male and female C57BL/6 demonstrate increased weight gain, but at different rates. Severity of weight gain for this model varies depending on duration, and composition of diet which can range in fat percentage and type used. (260,261)	• Gain increased weight and develop "obese" phenotype." • Diet induced obesity resembles conditions of human obesity. • Increased tumor growth in DIO mice resembling human disease.	• Diet duration can be lengthy and costly. • Diets used can vary on composition. • Variability in obese phenotype which can be influenced by factors including age and sex. • Metabolic parameters (blood glucose, insulin etc.) can vary and be strain dependent.
	BALB/c (High Fat Diet)	The BALB/c mouse strain is considered DIO resistant with only a percentage of mice placed on a HFD manifesting increased body weight over controls (particularly females). DIO susceptible mice undergo increased body weight and increases in white adipose tissue, although this is not as pronounced as other models (e.g., C57L/6)(73,74)	• Gain increased weight in only a portion of those exposed to diet allowing for interrogation of questions concerning diet and adiposity. • Diet induced obesity resembles human condition.	