Obesity and adipose tissue impact on T-cell response and cancer immune checkpoint blockade therapy

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Summary

Many different types of cancer are now well known to have increased occurrence or severity in individuals with obesity. The influence of obesity on cancer and the immune cells in the tumor microenvironment has been thought to be a pleiotropic effect. In obese individuals, the highly plastic adipose tissue plays crucial roles in obesity pathophysiology, as they show alterations according to environmental cues. Adipose tissues of lean subjects present mostly anti-inflammatory cells that are crucial in tissue remodeling, favoring uncoupling protein 1 expression and non-shivering thermogenesis. Oppositely, obese adipose tissues display massive proinflammatory immune cell infiltration, driving adipocytes, and enhanced crown-like structure formation. In this review, we discuss how obesity can lead to derangements and dysfunctions in antitumor CD8+ T lymphocytes dysfunction. Moreover, we explain how obesity can affect the efficiency of cancer immunotherapy, depicting the mechanisms involved in this process. Cancer immunotherapy management includes monoclonal antibodies targeting the immune checkpoint blockade. Exhausted CD8+ T lymphocytes show elevated programmed cell death-1 (PD-1) expression and highly glycolytic tumors tend to show a good response to anti-PD-1/PD-L1 immunotherapy. Although obesity is a risk factor for the development of several neoplasms and is linked with increased tumor growth and aggressiveness, obesity is also related to improved response to cancer immunotherapy, a phenomenon called the obesity paradox. However, patients affected by obesity present higher incidences of adverse events related to this therapy. These limitations highlight the necessity of a deeper investigation of factors that influence the obesity paradox to improve the application of these therapies.

Key words: immunotherapy, obesity, cancer, adipose tissue

Obesity and adipose tissue

Obesity is currently considered a devastating pathology as it increases the individual risk for a plethora of diseases, such as heart disorders, dyslipidemia, chronic kidney disease, hypertension, type 2 diabetes (T2D), stroke, and cancer, and display intimate association with insulin resistance (IR) and chronic low-grade inflammation progressive worsening [1]. World Health Organization (WHO) defines overweight and obesity in terms of a body mass index (BMI), higher or equal to 25 kg/m² and higher or equal to 30 kg/m², respectively, and a significant increase in obesity’s prevalence has been of great concern worldwide [2]. The latest WHO’s global health report addressed that the prevalence of obesity has increased 50% from 2000 to 2016. Specifically, more than 1.9 billion adults were overweight in 2016 and of these 650 million adults were obese globally [3]. Previously, obesity was described as being solely an energy imbalance over time, due to excessive energy storage when compared with energy expenditure, hence accumulating adipose tissue (AT) [4]. Nonetheless, obesity is now seen as a result of AT dysfunctional expansion and as a multifactorial disease, since AT is a highly active endocrine organ, playing a central role in the orchestration of metabolic and immune homeostasis [5]. The augmented adiposity is related to alterations in the tissue physiological profile. Obesity-related dysfunctional expansion of fat depots results in hyperinsulinemia, dyslipidemia with an excessive release of many adipokines and proinflammatory molecules, which can cause an increase in insulin resistance (IR) in insulin-sensitive tissues [6]. Tumor cells that present in the microenvironment of adipose tissue (AT) uptake high levels of glucose via glucose transporter 1 (GLUT1), directing glucose towards the glycolytic pathway. Therefore, we hypothesize that adipose tissue contributes to cancer initiation and progression through metabolic reprogramming to drive tumor cell growth and proliferation. Obesity-related dysfunctional adipose depots can lead to an altered AT composition, favoring a proinflammatory macrophage phenotype and TGF-β expression, which stabilize tumor-infiltrating lymphocytes (TILs) and support cancer growth and progression. Tumor-associated adipose tissue (TAT) has been shown to drive cancer progression through many potential mechanisms. The TAT is characterized by a decrease in anti-inflammatory M2 macrophages and an increase in proinflammatory M1 macrophages, favoring an altered tumor immune microenvironment (TME) [7]. In this review, we discuss how obesity can lead to derangements and dysfunctions in antitumor CD8+ T lymphocytes dysfunction. As the tumor immune microenvironment is highly plastic, we analyze how the TAT can impact T-cell recruitment and expansion, as well as T-cell priming and function. The role of AT in cancer progression is highly influenced by the interplay of the TME, immune checkpoint blockade and other local factors, such as hypoxia and reactive oxygen species (ROS) [8]. Obesity and adiposity impact on T-cell response and cancer immune checkpoint blockade therapy.
of free fatty acids (FFA), and adipocyte hypoxia, inadequate oxygen supply, thereby promoting cell death, and the accumulation of proinflammatory mediators [6].

Pre-adipocytes, fibroblasts, endothelial cells, immune cells, and mature adipocytes are the main cell types that constitute AT [7]. Four distinct types of adipocytes have already been described: white, beige, brown, and pink [8]. These cells differ in morphological and physiological characteristics. Brown adipose tissue (BAT) and white adipose tissue (WAT) are the most well-described types of AT in the literature because they are constitutively present in the organism. White adipocytes, predominant in WAT, are marked by a unilocular lipid droplet, smaller and less abundant mitochondria, and are classically associated with energy intake signaling and storage [9]. In contrast, BAT is mainly composed of brown adipocytes, characterized by their multilocular lipid droplets and high amounts of mitochondria, which express elevated levels of uncoupling protein 1 (UCP1). Accordingly, BAT is implicated in heat production (non-shivering thermogenesis) and weight loss, and showing modifications throughout the individual’s life [10].

BAT is maximally recruited in birth, when it shifts drastically from a quiescent form into its most activated state in terms of heat production to provide thermoregulation, being located in the interscapular region in newborns and small mammals [11]. During childhood, BAT is reduced, since the individuals have already been exposed to cold and start a skeletal muscle shivering heat production. Evidence indicate that there may be a transient increase in BAT’s volume near puberty [12], suggesting that BAT is implicated in other functions besides the replacement of an absent shivering thermogenic process. In adulthood, there is reduced detection of basal BAT activity and cold-stimulation of this tissue may significantly decline since middle age, along with a reduced expression of UCP1 [13]. Noteworthy, BAT also tend to morphologically change over time toward a more prominent lipid storage profile, emphasizing the changes in BAT’s composition and function throughout mammals’ lives [14].

ATs are extremely plastic and, thus, have the capability of expanding and remodeling. The expansion of ATs can be a result of hypertrophy, hyperplasia, and adipocyte differentiation and is sensitive to external factors, such as nutrition and exercise routines. AT types can undergo transdifferentiation. BAT can convert into an intermediate beige phenotype, through a process called whitening [15]. The inverse process also occurs, the conversion of WAT into brown-like AT is the result of a process called browning. Browning occurs in response to cold exposure, augmented physical exercise, the activation of sympathetic nerves on β-adrenergic receptors, triggering an intracellular signaling cascade. Alterations in cAMP levels can be detected by protein kinase A (PKA), which leads to the activation of mitogen-activated protein kinases, culminating in catabolic reactions that convert triglycerides (TGs) into fatty acids (FAs) and also in the activation and upregulation of UCP1, which allows the uncoupled production of ATP and heat dissipation [16]. This process is regulated by the influence of sympathetic nerves on β-adrenergic receptors, triggering an intracellular signaling cascade. Alterations in cAMP levels can be detected by protein kinase A (PKA), which leads to the activation of mitogen-activated protein kinases, culminating in catabolic reactions that convert triglycerides (TGs) into fatty acids (FAs) and also in the activation and upregulation of UCP1, which allows the uncoupled production of ATP and heat dissipation [16]. Currently, browning and BAT activation have been studied as promising therapeutic strategies against obesity [18].

Immune regulation in adipose tissue

Current research describes ATs as heterogeneous organs that regulate immunity, metabolism, and inflammation [19]. As studies show, both AT residing and infiltrating immune cells influence the inflammatory and metabolic status systemically and at tissue level. Diving into the mechanisms by which immune cell signaling modulates ATs’ function must occur to understand their influence on the onset, progression and treatment of many diseases [20]. Although efforts have been made in recent years, there is still scarce information regarding the characteristics of BAT immune cells. Macrophages and monocytes, eosinophils, B lymphocytes, and T regulatory (Treg) cells are present in BAT [21]. These immune cells are also key components in WAT architecture and, with unconventional lymphocyte subtypes innate lymphoid cells (ILCs), invariant natural killer T (iNKT) cells, and γδ T cells, influence WAT physiology [22–24].

Eosinophils residing in ATs are known to be sustained by IL-5 and CCL11 (eotaxin 1) tissue levels [25]. In addition to their crucial roles in allergic diseases and in the response against helminth infections, eosinophils play important roles in AT homeostasis maintenance, supporting type 2 (Th2)-associated immune profiles [26]. As described by Hasty and colleagues, macrophages represent only 30% of BAT’s leukocyte population [27]. B lymphocytes make up 20–30% of BAT immune cells and are regulated through the norepinephrine-beta2-adrenergic receptor (β2AR) interaction [27, 28]. In addition to its anti-inflammatory properties, Treg was described to display a BAT-specific phenotype that favors proper tissue function during cold exposure, as absence copes with impaired thermogenesis and diminished oxygen consumption [29].

Also described in lean WAT, the Treg cell is one of the main actors in controlling tissue inflammation and modulating its plastic phenotype [30]. In subcutaneous WAT (scWAT), activated Treg increases anti-inflammatory markers and augments the tissue thermogenic capacity through increasing UCP1 expression [31]. Lean visceral WAT (vWAT) is associated with a Treg profile that is preferentially adapted to fatty acid (FA) metabolism, the visceral adipose tissue Treg [32]. B lymphocytes also present a regulatory cell subset (Breg), which, in addition to secreting antibodies, restrain pathological tissue inflammatory responses through the secretion of interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) [33]. Treg and Breg immunomodulatory activity favor AT accumulation of alternatively activated macrophages (M2), which, through type 2 cytokine secretion, aid in conserving tissue immune and metabolic homeostasis. In addition, M2 participates in AT vasculogenesis and remodeling processes [34]. Also, a key factor in AT homeostasis, CD4+ T lymphocytes (T Helper 2-Th2) are known to orchestrate anti-inflammatory immune profile in ATs, inhibiting the occurrence of an immunologically harsh environment, and favoring adequate wound healing [35].

The innate-like T cells, iNKT cells, are enriched in ATs of human and mice and account for 15–20% of total T cells [36]. Regulatory iNKT influences other anti-inflammatory immune cells homoeostasis and avoid tissue inflammation through secretion of Th2-associated cytokines, including interleukin-5 (IL-5) and IL-13 [23]. Also linked to elevated anti-inflammatory cytokine levels, active innate lymphoid cell 2 (ILC2) stimulate beige fat biogenesis [37]. Another unconventional T lymphocyte, γδ T cells, are enriched in ATs and also present immunomodulatory roles and are crucial for promoting sympathetic innervation, as ablation of these cells impairs this process [38].
Obesity-associated adipose tissue inflammation and system physiology derangements

During homeostasis, ATs show an increased number and activation of type 2 cytokine-secreting immune cells [35]. In contrast, the ATs associated with the obese phenotype present tissue inflammation due to proinflammatory profiles displayed by residing and infiltrating immune cells [39] (Fig. 1). BAT’s function is impaired during obesity, as cold-induced thermogenesis, insulin sensitivity, and glucose consumption are disrupted in the BAT of subjects affected by obesity [40]. In an elegant study, Alcala and colleagues informed that diet-induced obese mice showed BAT dysfunction due to the infiltration of immune cells (including lymphocytes and macrophages), cytokine release, and oxidative stress [41]. Another important study confirmed that B cells from BAT of individuals with obesity are increased in number [27].

B lymphocytes are also enriched in obese WAT, are associated with higher levels of proinflammatory mediators and decreased amounts of anti-inflammatory cytokines, and with the secretion of pathogenic IgG [42]. CD8- and CD4-expressing cells also play key roles in the induction of AT inflammation in the context of obesity. Effector CD8+ T lymphocytes are known for mediating antiviral and antitumor immunity by inducing apoptosis in other cells and systemically secreting the proinflammatory cytokine interferon (IFN-γ) [43]. Antibody depletion of CD8+ T cells from obese models decreases vWAT inflammation and increases insulin sensitivity, while adoptive transfer of these cells to CD8-deficient mice copes with proinflammatory mediators’ secretions, IR, and glucose intolerance [44]. CD4+ T cells (Th1) drive type 1 cytokine release (as IFN-γ) in ATs of individuals with obesity, amplifying tissue chronic inflammation [45]. Shirakawa and others linked a unique subpopulation of CD153+PD-1+CD44hiCD4+ T lymphocytes with WAT inflammation and systemic insulin resistance under influence of an obesogenic diet and affirmed that these cells accumulate in obese WATs [46]. The saturated FA palmitate, common in the high-fat diet, dose-dependently activates T cells, favoring cytokine secretion, and reactive oxygen species generation [47]. After re-stimulation, T cells from ATs present higher inflammatory cytokine secretion and cells derived from subjects with obesity display decreased T-cell receptor (TCR) diversity [48, 49]. In the context of the obese phenotype, CD8+ T cells and Th1 cells favor macrophage M1 differentiation and proliferation. M1 macrophages make up over 50% of WATs’ immune cells in individuals with obesity. They increase in number according to white adipocyte size and total adiposity and display a unique metabolically activated phenotype associated with inflammation and metabolic markers [50]. During obesity, ILC1 also accumulates in WAT depots, produces IFN-γ, and contributes to the occurrence of tissue and systemic inflammatory processes and impaired insulin signaling, as cell adoptive transfer led to exacerbated metabolic disorder and proinflammatory macrophage polarization [51].

The inflammatory processes that take place in the context of obesity can also be explained by the decreased number of anti-inflammatory cells. The protective roles against obesity presented by Treg cells, ILC2, iNKT, Breg, and δγ-T cells highlight the inflammatory nature of obesity [24]. The fact that inflammatory molecules inhibit noradrenergic signaling links obesity to decreased thermogenic capacity [52]. Obesity-associated BAT disruption copes with tissue ‘whitening’ due to elevated circulating IFN-γ levels [53]. During BAT

Figure 1. Immune cells from BAT and WAT of lean and obese phenotypes. While WAT of lean individuals tends to present mostly anti-inflammatory polarized immune cells (including Th2, Treg, and ILC2) WAT associated with obese phenotypes shows tissue inflammation due to an imbalance favoring proinflammatory immune cells, especially T lymphocytes (CD8+, Th1, Th17), B cells (B1) and macrophages (M1), which together form crown-like structures (CLS) and favors FFA release. Although BAT is less explored in the literature in this context and therefore is not as well characterized as WAT, T regulatory cells (Treg) and other anti-inflammatory immune cells have been identified in lean BAT. Obese BAT also presents inflammatory activity coped with massive infiltration of macrophages (MΦ), B cells, and T lymphocytes, although their polarization profile needs yet to be defined. The image emphasizes the most abundant cell types but is important to highlight that all AT types and phenotypes exhibit all cited immune cells.
whitening, the tissue shows increased inflammatory and lipogenic markers, displays diminished UCP1 expression and thermogenesis, and presents crown-like structure (CLS) formation [53].

CLS, considered histological hallmarks of AT inflammation, are also found in inflamed WAT and consists of M1 macrophages and proinflammatory B (B1) and T lymphocytes (Th1 and Th17) surrounding stressed and dying adipocytes [54]. During obesity-induced stress, white and brown adipocytes secrete unbalanced levels of adipokines (augmented proinflammatory and diminished anti-inflammatory mediators), including low levels of adiponectin and of BAT’s adipokines as Fibroblast growth factor 21 (FGF21) and C-terminal fragment of SLIT2 protein (SLIT2-C), also increased amounts of BAT mediators such as Chemerin and Endothelin-1 (ET-1), and WAT secreted leptin [53]. Peaking leptin levels and resistance correlate with AT’s mass and BMI, hence, stimulating systemic increased levels of inflammation mediators, such as a proinflammatory adipokine [56].

The obese state is also connected with brown and white adipocyte subcellular alterations, including mitochondrial dysfunction and endoplasmic reticulum (ER) stress, due to the harsh environment characteristic of obesity [57]. Nutrient overload favors reactive oxygen species (ROS) production, which leads to mitochondrial dysfunction, further exacerbating intracellular oxidative stress [58]. Excessive food intake induces ER stress as well, a process that also leads to ROS biogenesis [59]. The intracellular detrimental effects of oxidative stress are connected with damage-associated molecular patterns release, AT dysfunction, and inflammation [57]. Noteworthy, many food components often associated with obesogenic diets, such as saturated FAs and processed sugars, induce adipocyte ER stress and inflammation [60]. These intracellular disturbances favor cell death pathways leading to FA massive release and proinflammatory immune cell activation [61].

Another trigger for ER and systemic inflammation in ATs is the endotoxin lipopolysaccharide, a cell wall component of specific intestine-dwelling bacteria, that shows peaking amounts in the bloodstream of individuals affected by obesity [62]. Many studies inform that these augmented endotoxin levels are due to intestinal dysbiosis characterized by decreased microbiota diversity and outgrowth of pathobionts which results in increased intestinal permeability [63]. Endotoxemia exacerbates the inflammatory status of subjects with obesity, further impairing insulin signaling and systemic metabolism [64].

Nutrients obtained from diet not only impact intestinal microbiome composition and diversity but also may pose systemic immunomodulatory regulation [65]. In conjunction with cytokines and transcription factors expression, glycemic levels influence T-cell fate [66]. T cells present sensing systems that detect nutrient availability alterations, which influence cell function and differentiation status [67]. Hyperglycemia and TCR activation lead T cell to up-regulate glucose uptake through glucose receptor 1 (GLUT1) and reprogram its metabolism toward glycolysis and glutaminolysis [68]. However, current research points out that this metabolic reprogramming has effects on T lymphocyte differentiation. Increased glycolysis favors CD4+ T lymphocytes to differentiate to either Th1 or Th17 immune profiles, depending on the use and activation of hypoxia-inducible factor 1α (HIF1α) [69]. CD8+ expressing T cells are pictured according to a spectrum of glycolytic capacity, being CD8+ effector T (Teff) lymphocytes the cell that preferentially metabolizes glucose [70]. The adipokine leptin was shown to further enhance GLUT1 presence in the T-cell membrane, favoring T lymphocyte activation in hyperglycemic scenarios [71]. Studies inform that hyperglycemia drives activation and cytokine secretion by Th1, Th17, and CD8+ Teff [72]. These points help to explain why elevated glucose levels and hyperleptinemia are linked with higher levels of proinflammatory mediators in individuals affected by obesity.

In contrast, the anti-inflammatory Treg and Breg cells show a preferential requirement for FA oxidation and show higher resistance to lipotoxicity [73]. However, hyperinsulinemic environments impair IL-10 secretion by these cells and diminish their capacity of inhibiting TNF-α production by macrophages [74]. Therefore, hyperglycemic microenvironments rich in insulin, TCR ligands, and leptin, such as the ones associated with obesity and T2D, tend to result in inflammatory and metabolic diseases that impact the individual risk of developing other chronic co-morbidities.

The inflamed phenotype associated with obesity is also related to degrading effects on immunity. Diet-induced obesity and inflammation result in premature thymic involution, which leads to diminished production of T lymphocytes in the thymus, displaying decreased TCR diversity [75]. Obesity also favors adipocyte accumulation in the bone marrow, a process that disrupts hematopoiesis [76]. In addition, obesity is connected with disturbed secondary lymphoid organ function and less effective dendritic cell-mediated T-cell stimulation [77]. All these physiological consequences of obesity were reported to be linked with T lymphocyte senescence [78]. Human senescent (CD28−CD57+) CD8+ T lymphocytes occur in the obese and diabetic states and show ROS intracellular accumulation and cytokine secretion. Liver senescent CD8+ T lymphocytes are associated with mouse and human increased insulin resistance, inflammation, and adoptive transfer of senescent CD8+ T lymphocytes was shown to deteriorate systemic glucose homeostasis [78]. These dysfunctional T cells are related to impaired tumor surveillance, as indicated by Petrelli and other meta-analysis studies [79].

**Obesity and cancer**

As depicted in the previous section, the obese state copes with derangements in inflammation, metabolism, and immunity, including the immune responses against tumors. A special report conducted by the International Agency of Research on Cancer (IARC) based on over 1000 epidemiologic studies demonstrated that there is an increased risk of developing at least 13 types of cancer in individuals with excess body WAT, including breast, liver, pancreas, and ovaries malignancies [80]. According to the Centers for Disease Control and Prevention (CDC), overweight and obesity-related cancer represented about 40% of cancers diagnosed in the United States, which corresponds to 630,000 people diagnosed only in 2014. In counterpoint to overall cancer incidence, which declined since the 1990s, obesity-related cancers increased. That data does not include colorectal cancer, which, alone, increased by 7% between 2005 and 2014 [81]. Globally, a statistical data point out that 481,000 new cancer diagnoses were related to obesity, designating excessive body adiposity as a well-established risk factor for cancer development [82].

Considering the categorization of obesity as a pandemic and, in parallel, the increased incidence of obesity-related
cancers, studies on the influence of obesity on the outcomes of available antineoplastic therapies are increasing [83]. The world has experienced a decrease in cancer mortality rate due to early diagnosis and cancer treatments available and under development. Data from 2019 indicate that approximately 17 million Americans diagnosed with cancer were still alive by January 1st of that year. Fifty-six percent of these patients were diagnosed and properly treated within the previous 10 years. Several therapies are currently used, such as surgeries, radiotherapy, hormonal therapies, chemotherapies, and immunotherapies. These approaches can be sufficient alone or can be administered in combination depending on the clinical picture exhibited by the patient [84]. In the same way that the excess adiposity promotes differential prognoses depending on the tumor type and stage, the abnormal accumulation of body fat can promote differential results depending on the chosen therapeutic approach. Currently, it is known that obesity can affect treatments differently, however, there is no proper guidance for the management of oncologic patients with increased BMI under distinct therapies [85].

Patients with increased BMI have demonstrated a negative impact on the outcomes of conventional therapies such as cancer surgery, radiotherapy, and chemotherapy. Cancer surgery is a therapeutic approach that can act as a preventive measure or as a treatment. It is well known that obesity is a factor that predisposes the individual to wound complications, considering that adipose expansion is associated with less tissue vascularization, alteration of immune population, greater pressure under the tissue, and consequently a deficient wound healing process [86]. Furthermore, the impact of high adiposity on radiotherapy has indicated that an elevated BMI was positively related to lower efficiency of radiotherapy and clinical recurrence of prostate cancer, and overall mortality [87]. In breast cancer patients, a high BMI was associated with post-radiotherapy effects, such as dermatitis [88].

Chemotherapy is currently a standard cancer treatment, but the scenario is not so favorable for patients with obesity, since these individuals have poor outcomes for breast, prostate, endometrial, and colorectal tumors [89]. Besides that, it was reported that they may also experience greater toxicity from anticancer drugs. Patients with obesity who received the proper chemotherapy dose presented increased treatment-related toxicity, mainly high-grade hematological toxicities, and did not present any difference in overall survival (OS) [90]. More than that, it has been shown that adipocytes are capable of accumulating lipophilic chemotherapeutic agents, altering their distribution, and increasing enzymes that metabolize chemotherapeutic drugs. A profile that is intensified during obesity-related reduced pharmacological effectiveness, which in conjunction with greater susceptibility to tumor resistance, is associated with a worse outcome [91]. All these factors become preponderant for the therapeutic process. The increase in toxicity in the absence of positive results becomes an aggravating factor for the early discontinuation of the therapy.

Several studies have pointed to antagonistic roles that can be played by obesity across different neoplastic stages [92]. Obesity is a risk factor for tumor development, having a fundamental role in the maintenance of the inflammatory condition and also being reported as an essential factor for the onset of events such as metastasis and neoplastic recurrence [93]. However, in a contradictory and surprising way, patients impacted by obesity tend to present better prognosis for specific tumor types when compared with lean individuals [92]. Obesity-affected patients with lung cancer, renal cell carcinoma, nasopharyngeal carcinoma, and melanoma had better prognosis, including improved OS [79].

In contrast, cachexia-associated tumors tend to cope with worse disease outcome. Cancer-associated cachexia (CAC) is an irreversible metabolic syndrome characterized by loss of skeletal muscle (sarcopenia) that may or may not be associated with fat loss, and cannot be fully reversed nutritionally [94]. This syndrome is common in aggressive tumors in advanced stages and is associated with a worse prognosis, progressive functional impairment, high rates of complications, chemotherapy resistance, and high mortality in neoplastic patients [95].

An enhanced inflammatory profile is one of the main features of cachexia and it is well established that increased circulating levels of cytokines, such as TNF-α, IL-1β, IL-6, and IFNγ, secreted by both immune and non-immune cells, including tumor cells, modulate pathways related with severe catabolic processes in skeletal muscle and adipose tissue [96]. Although the role of immune cells in cachexia is complex and remains not fully understood, recent research has brought better enlightenment about the influence of specific immune cell types, such as macrophages, neutrophils, microglia, myeloid-derived suppressor cells, and T cells, in CAC progression [97].

Specifically, in AT, resident immune cells, such as macrophages, can perform paradoxical roles depending on the tumor type. Erdem and colleagues demonstrated a protective role of adipose tissue macrophages (ATM) in an intercrossed transgenic murine model that genetically induces hepatocellular carcinoma (HCC) and also presents a myeloid-specific deficiency in hypoxia-inducible factor 1α (HIF1α). It was observed that an impaired myeloid cell-mediated inflammation, due to the HIF-1α knockout, promoted augmented AT depletion in parallel to a decrease of ATM abundance, indicating that macrophages can play important roles in HCC-mediated AT loss in this context [98]. In contrast, Lu and others showed that ATM and tumor-associated macrophages (TAM) may contribute to the development of CAC in pancreatic ductal adenocarcinoma (PDAC). In this study, an antibody that neutralizes the proinflammatory cytokine IL-20 was used in a transgenic and orthotopic PDAC murine model. The authors observed that inhibition of IL-20 was able to reduce tumor size, attenuate CAC symptoms, and decrease tumor PD-L1 expression. In addition, treatment with anti-IL-20 induced a decrease of F4/80+IL-20+ macrophage infiltration in the epididymal AT in the transgenic PDAC model, and diminished M2-like polarization of TAM in vitro and in vivo orthotopic PDAC model. In this case, reduction of macrophage infiltration was associated with better prognosis and increased body weight and lean mass [99].

**Immunotherapy: immune checkpoint blockade (ICB)**

The use of chemotherapy, as much effective as they are, induces non-specific cytotoxicity, a relevant clinical barrier to the patient’s physical and emotional well-being, and demonstrates the need for an improvement in oncological therapies [100]. Discoveries in the area of molecular biology
and cancer pathogenesis enabled the development of more effective approaches and technologies for cancer therapy [101]. Biological therapies arise from the deeper characterization of the molecular and physiological particularities of the tumor cell and its interaction with the environment in which it is inserted. The identification of tumor molecular targets (tumor-associated antigens or tumor-specific antigens), tumor mutations burden, neoantigens, defective DNA mismatch repair, microsatellite, and tumor-associated cells was essential for the development of molecular targeted therapies [102].

Immunotherapy is the class of molecular targeted therapy that aims to aid the host's defense cells to identify and eliminate tumor cells as well as induce the formation of immunological memory, which reduces the susceptibility of tumor recurrence. This therapy has gained prominence in the cancer treatment landscape due to the success observed in pre-clinical and clinical trials for melanoma, non-small-cell lung cancer, Hodgkin lymphoma, gastric cancer, bladder cancer, head, and neck, among others [103]. Immunotherapy can be categorized into four classes of treatments: anti-tumor vaccines, oncolytic virus, adoptive transfer of T cells, and therapy with monoclonal antibodies, with emphasis on immune checkpoint blockade (ICB) [104].

ICB is a class of antibody therapies that explores the expression of immune checkpoints (ICs). Although ICs are receptors that promote inhibitory or stimulatory signals, ICB therapy acts exclusively on inhibitory receptors, such as Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), Programmed death 1 (PD-1), Lymphocyte activation gene 3 protein (LAG3), T-cell immunoglobulin and mucin domain 3 (TIM-3). ICs activation does not occur spontaneously and depends on the interaction with their ligands, CD80/CD86, PD-L1, major histocompatibility complex (MHC) class II (MHCII), galectin-9, respectively [105]. These ligands can be expressed in antigen-presenting cells, mesenchymal stem cells, bone marrow-derived mast cells, and tumor cells in circumstances where prolonged activation and exacerbated activity of immune cells may pose a risk to the individual. In this scenario, these ICs are expressed and activated, inducing a negative regulation of the activity of immune cells, such as NK cells, T and B lymphocytes, favoring self-tolerance and preventing these cells from responding in a disorderly and indiscriminate way [106].

Some types of cancer can use the immune self-tolerance mechanism as an evasion tool, stimulating the expression of ICs and inhibiting the anti-tumor response of T cells. Antibodies, anti-ICs, and anti-IC ligands are administered to patients and selectively bind to the correspondent target, inhibiting their signaling activity. Therefore, the high expression of inhibitory IC and its ligand is essential for the proper performance of ICB therapies. The anergy phenotype is not necessarily associated with high IC expression. In contrast, the exhaustion phenotype is characterized by the increased expression of effective IC inhibitors such as PD-1 and CTLA-4, which makes this phenotype the ideal target in CD8+ T cells. Thus, neoplasia that presents a high expression of ligands in tumor cells, such as PD-L1, as well as a high rate of tumor-infiltrating CD8+ T cells with high expression of inhibitory ICs are linked with a better response to treatments with ICB [107].

Currently, ICB, especially anti-PD1 and anti-PDL1 antibodies, represent about 2/3 of cancer therapy trials, being applicable and obtaining optimistic results alone or in combination with conventional therapies for at least 50 types of cancer, in addition to having awarded its developers the Nobel Prize in 2018 [108]. There are only two classes of ICB-targeting therapies approved by the FDA: anti-CTLA-4, and anti-PD-1/PD-L1 (PD-1 ligand 1). In 2011, FDA approved the first ICB therapy: Ipilimumab, an anti-CTLA-4 drug, designated for melanoma metastatic treatment [109]. From this, in 2014, ICB gained a second class of target, PD-1/PD-L1, with the approval of pembrolizumab and nivolumab, also for melanoma treatment [110]. Until this present review, there are approximately seven FDA-approved anti-PD-1/PD-L1 drugs and one anti-CTLA-4 drug [111]. These drugs cover a variety of cancer types, such as melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, hepatocellular carcinoma, colorectal cancer, uterine cancer, head and neck cancer, among others, being mainly indicated for refractory tumors or in advanced and metastatic stages [112]. Clinical trials with the use of ICB administered alone or in association with other therapies have relevant results associated with improvement in parameters, such as progression-free survival (PFS) and OS, even when compared to conventional therapies such as chemotherapy [113]. However, despite great outcomes obtained from ICB therapy, this treatment has presented limitations, and a significant proportion of patients do not benefit from the positive results provided by ICB therapy [114]. Limitations include immune-related adverse events (irAEs) and resistance to the therapy by patients, which can occur initially or during the treatment. ICB responsiveness is associated with tumor relapse [115]. ICB resistance may be associated with the tumor profile that presents a low number of tumor-infiltrating T cells and the downregulation of immune checkpoints both in the tumor and in the T cells, a profile often exhibited by low-immunogenic tumors [116].

**Obesity and ICB: the obesity paradox**

Surprisingly, BMI-classified patients with overweight or obesity tend to experience a better response to ICB than lean patients (Fig. 2) [117, 118]. Recent studies have shown that a high BMI is associated with improved PFS and OS in ICB-treated patients with metastasis in more than 20 types of cancers. Maslov and others identified that subjects presenting overweight or obesity affected by major advanced-stage cancers submitted to ICB therapy had a median PFS of 287 and 479 days, respectively, while patients in the normal weight range had a median of 128 days. The same extends to the operating system, in which patients with clinical overweight and obesity exhibited a PFS median of 462 days and 751 days, respectively, while patients with normal weight exhibited 281 days in the context of ICB treatment. In addition, secondary obesity patients display 48% less risk of progression or death from the tumor compared to patients with normal BMI [119]. An observational study showed that patients with melanoma and high BMI treated with ipilimumab (anti-CTLA-4 antibody) had a greater response and less susceptibility to metastasis to the brain, in addition to having a longer OS [120]. A meta-analysis study investigated the correlation between BMI and response to ICB treatments of approximately 4090 patients with solid tumors, especially lung cancer and melanoma, from 16 retrospective studies. Higher PFS and OS of...
patients with high BMI compared to patients with low BMI was observed. In addition, a reduction in the risk of death by 3.6% was observed for every 1 kg/m² increase in BMI [121].

A multicohort analysis aimed to evaluate the correlation between BMI and therapeutic outcomes of targeted therapy, immunotherapy, and chemotherapy in patients with metastatic melanoma. The cohort included 538 patients treated with ipilimumab or pembrolizumab, nivolumab, or atezolizumab (anti-PD-1/PD-L1 antibodies) and, corroborating with other studies, suggested a better response associated with increased PFS and OS of patients with high BMI compared to lean patients. On the other hand, the same association between high BMI and improved response to treatment was not observed for other treatments [122]. In a clinical trial that compared the impact of BMI on the prognosis of patients treated with ICB or chemotherapy, 1,434 male patients with NSCLC were treated with atezolizumab (anti-PD-1/PD-L1) or docetaxel, a chemotherapy agent. Obesity was observed to substantially improve PFS and OS in patients treated with atezolizumab, an outcome associated with increased PD-L1 expression in these patients’ tumors. But the same was not observed for patients who received docetaxel. In this study, the side effects observed were not related to BMI [83].

The obese phenotype copes with T lymphocyte dysfunction, a state characterized by a hyporesponsive profile, associated with loss of effector, proliferative capacity, and reduced production of cytokines, TNF-α and IFN-γ, in conditions that can be classified as anergy or exhaustion [123]. Anergy is a profile characterized by an inadequate activation of CD8+ T cells due to low co-stimulatory signaling, mediated by stimulatory IC, such as CD-28 and OX-40, associated or not with an increase of inhibitory signal mediated by inhibitory IC expression. Anergy phenotype is frequently observed in the early stages of the tumor progression [124]. In contrast, exhaustion is a profile exhibited by CD8+ T cells after chronic and persistent exposure to antigens, which in a self-tolerance mechanism, triggers a remarkable increase of inhibitory IC expression, including PD-1 and CTLA-4, to suppress their activity. Exhausted CD8+ T cells are frequently seen in more advanced tumors and can be divided into two populations: progenitor exhausted or terminally exhausted [125]. Miller and colleagues suggest that the efficacy of therapies with PD-1 blockade is associated with different subpopulations and functionalities of exhausted CD8+ T cells, since progenitor exhausted CD8+ T lymphocytes can recover their effector activity, unlike terminally exhausted ones [126].

The excess adiposity may promote a greater expression of PD-1 in effector CD8+ T lymphocytes, promoting a better response to ICB therapies. Zhang and others informed that obesity was related to a decrease in the effector activity of CD8+ T cells in PyMT mice, which is a rodent model that spontaneously develops breast tumors, through a metabolic change consisting of increased oxidative phosphorylation (FA oxidation) and reduced glycolysis [127]. Moreover, Kado and colleagues demonstrated that the high-fat diet was able to induce a shift in the CD8+ T cell profile to an exhausted CD8+PD-1+ T cell profile in animals with breast cancer. In the same line, obese mice impacted by melanoma have been observed to have better responses to ICB therapies. These findings extended to clinical data associated with other tumors, such as NSCLC, RCC, ovarian cancer, and others [118]. The impact of obesity on PD-1 T lymphocyte levels may explain the increased effectiveness of ICB therapy against certain tumors displayed by this population.

A paradoxical predictor for anti-tumoral response and response to ICB therapy is a high rate of glycolytic activity exhibited by tumor cells. The Warburg effect is an adaptive mechanism acquired by tumor cells that gives them
a selective advantage over other cells in the environment. Healthy cells use glucose as the substrate to obtain energy, adenosine triphosphate (ATP), through the Citric Acid Cycle (TCA) pathways and oxidative phosphorylation (OXPHOS). However, in the 1920s, Otto Warburg observed an excessive consumption of glucose by tumor cells compared to healthy cells. Moreover, he observed that consumed glucose was converted to lactate even in the presence of oxygen in a phenomenon that became known as the Warburg effect or aerobic glycolysis [128]. Several hypotheses have been developed since that to explain the metabolic shift to another pathway. Recent studies have demonstrated that the Warburg effect appears to provide advantages that support the growth, proliferation, and evasion of tumor cells [129].

The Warburg effect has direct and indirect roles on the immune system that favor tumor progression. Colegio and colleagues demonstrated that tumor-derived lactate acts to polarize tumor-associated macrophages in an M2 profile by impacting the expression of HIF1-α [130]. In addition, the high consumption of glucose by tumor cells diminishes their bioavailability in the environment, which has a direct impact on activation and effector activity, such as the production of IFN-γ from tumor-infiltrating lymphocytes (TIL) [131]. High glycolytic activity can be considered a good predictor of the response to anti-PD-1/ PD-L1 immunotherapy since the increase in aerobic glycolysis is associated with the increased expression of PD-L1 in the tumor [132].

In addition, estrogen circulating amounts activity can also be placed as a possible mechanism for the obesity paradox, especially for melanoma patients. The female gender has long been associated with favorable melanoma outcomes when compared to males. Although melanoma is recognized as non-hormone cancer, several studies have indicated that sex hormone signaling, more specifically estrogen, is responsible for better prognosis and improved therapies responses of this tumor [133]. Estrogen is a sex steroid hormone more abundant in females. This hormone directly promotes melanocyte differentiation, increases the production of melanin, and decreases proliferative capacity through a non-classical Gs-coupled G protein-coupled receptor (GPCR) called G-protein coupled estrogen receptor (GPER). Moreover, GPER activation depletes c-Myc protein, a transcription factor that regulates several genes involved in essential cellular pathways, including cell growth, proliferation, survival, differentiation, and immune checkpoint expression, such as PD-L1, on the tumor [134]. Natale and colleagues demonstrated that GPER activation of B16-F10 melanoma cells inhibits growth and favors higher susceptibility of these cells to immunotherapy anti-PD-1 antibody in vitro. A similar phenomenon was observed in melanoma-bearing mice that received GPER agonists associated with anti-PD-1 antibody. G-1 pre-treatment of human melanoma cells inhibited tumor growth in mice and increased the innate and adaptive anti-tumor immune cells infiltration, such as NK and T CD8+ cells within the tumor, demonstrating a great potential of GPER agonist as a cancer immunotherapy adjuvant [135].

In the same way, it is hypothesized that these same biological phenomena arising from estrogens are responsible for the successful response of immunotherapy in obese male patients with melanoma. Obese men present higher expression of aromatase, an enzyme that irreversibly converts androgens, such as testosterone, into estrogen. Aromatase expression is proportional to body fat mass and promotes a significant increase of circulating estrogen in obese individuals [136]. However, it is still not possible to state that the activation of GPER, which has been shown to play a central role in the prognosis of female melanoma patients, is responsible for the efficacy of ICB observed in obese men. To this end, further investigation is required to obtain more concrete explanations.

Nevertheless, recent studies have brought a new perspective to the obesity paradox in ICB antibody treatments. Similarly, it has been shown that overweight or obese phenotypes are also linked with an increased likelihood of experiencing different degrees of irAEs [137]. Cortellini and others investigated 1070 patients with NSCLC, melanoma, RCC, or other advanced-stage cancers who received anti-PD-1/PD-L1 treatments and observed a correlation between high BMI and the development of irAEs that included cutaneous, endocrine, gastrointestinal, liver, among others, adverse events. Particularly, obese patients experienced a high incidence of rheumatic and pulmonary irAEs compared to patients with normal BMI. Such complications are often followed by discontinuation of treatment and therefore further investigations are needed to characterize the benefits and risks associated with BMI and treatment with ICB [138]. Taken all together, the need for better characterizing other parameters that may influence the different results regarding efficacy versus adverse events obtained in high BMI neoplastic patients treated with ICB is evident.

Body composition is a large spectrum that presents several intermediate phenotypes between these extremes. Among them, there is a phenotype called sarcopenic obesity (SO). SO is characterized by a significant loss of lean mass camouflaged by little or no change in adiposity. This phenotype poses a great challenge regarding cancer therapy [139]. Studies revealed that about 20% of obese patients with advanced or metastatic cancer presented SO [140]. Nonetheless, little is known about the impact of SO in immunotherapy. Until the present review, no clinical trials have been published about the relation between SO and immunotherapy efficacy or toxicity. However, Heidelberger and colleagues performed a preclinical study with 77 patients with advanced melanoma, including 13 (19%) sarcoleptic overweight patients treated with the anti-PD1 checkpoint inhibitors nivolumab or pembrolizumab in doses of 3 mg/kg every 2 weeks and 2 mg/kg-dose every 3 weeks, respectively. It was observed that sarcoleptic female patients presented 6.5-fold more anti-PD1-related early acute limiting toxicity and did not present any improvement in the anti-tumor response. The authors hypothesized that it could be related to weight-based dosing, which indicates a high drug dose administration, once it is assumed that pharmacokinetic parameters are altered in patients with high BMI and drug distribution may be impaired due to loss of lean mass in sarcoleptic patients [141].

**Conclusion**

It is undeniable that ATs play fundamental roles in the individual’s immune and inflammatory modulations. The recognition of ATs as immune organs, in addition to continuous discoveries that reinforce the intrinsic relationship of this issue with the immune system, has brought new perspectives to the investigation of AT’s role in several metabolic, infectious and neoplastic diseases. ATs’ composition and their plastic phenotype give these tissues the ability to substantially modulate aspects such as onset progression and prognosis of
various pathologies. Therefore, the increase in observational studies using the ATs’ profile as a scalable factor in favor of promoting the improvement of local and systemic conditions is not surprising.

As we showed in the present review, WAT and BAT functions and their impact on system physiology are intimately dependent on their immune cell components. The proinflammatory characteristics of ATs derived from individuals affected by obesity contribute to metabolic and immune systemic disturbances that associate this group with a scenario of a greater propensity for the development of, in general, a worse prognosis of fatal diseases, including cancer. Recent data have clearly shown the increase in obesity-related tumors, contrary to what has been observed about the incidence of tumors in general, which has shown a downward trend in the world. Tumor progression and mortality rate are also positively associated with high BMI. However, with the use of technologies and innovations in the development of new cancer treatments, and an antagonistic phenomenon called ‘The obesity paradox’ was observed. In a specific strand of immunotherapy, antibodies blocking immune checkpoints, obesity appeared to be related to better prognosis with increased PFS and OS. The main hypothesis associated with this phenomenon is the ability of adipose tissue to modulate the phenotype of immune cells, especially CD8+ PD-1+ T cells, in a dysfunctional profile, but responsive to treatment due to a higher expression of the PD-1 target molecule.

The phenomenon is intriguing but not homogeneous. Some clinical studies have shown that in parallel to the greater efficacy of ICB therapy in overweight and obese patients, higher incidences of adverse events related to the therapy have also been observed. All these findings highlight the need for further investigation and characterization of adjacent processes that may be influencing this phenomenon observed in neoplastic patients with high BMI.

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**Conflict of interest**

The authors declare that they have no competing interests.

**Data availability**

Not applicable.

**References**

1. Lu Y, Hajifathalian K, Ezzati M et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet* 2014; 383(9921):970–83. https://doi.org/10.1016/S0140-6736(13)61836-X

2. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol* 2019; 15(5):288–98. https://doi.org/10.1038/s41574-019-0176-8

3. WHO. *World Health Statistics 2021: monitoring health for SDGs, sustainable development goals*. 2021:1–121. ISBN: 978-92-4-002705-3.

4. Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. *Nature* 2000; 404(6778):652–60. https://doi.org/10.1038/35007527

5. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004; 89(6):2548–56. https://doi.org/10.1210/jc.2004-0395

6. Page MM, Johnson JD. Mild suppression of hyperinsulinemia to treat obesity and insulin resistance. *Trends Endocrinol Metab* 2018; 29(6):389–99. https://doi.org/10.1016/j.tem.2018.03.018

7. Huh JY, Park YJ, Ham M et al. Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. *Mol Cells* 2014; 37(5):365–71. https://doi.org/10.14348/molcells.2014.0074

8. Corrêa LH, Heyn GS, Magalhães KG. The impact of the adipose organ plasticity on inflammation and cancer progression. *Cells* 2019; 8(7):662. https://doi.org/10.3390/cells8070662

9. Cinti S. The adipose organ: morphological perspectives of adipose tissues. *Proc Nutr Soc* 2001; 60(3):319–28. https://doi.org/10.1079/pns200192

10. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. *Nat Med* 2013; 19(10):1252–63. https://doi.org/10.1038/nm.3361

11. Wolf G. Brown adipose tissue: the molecular mechanism of its formation. *Nutr Rev* 2009; 67(3):167–71. https://doi.org/10.1111/j.1753-4887.2009.00184.x

12. Gilsanz V, Smith ML, Goodarzian F et al. Changes in brown adipose tissue in boys and girls during childhood and puberty. *J Pediatr* 2012; 160(4):604–609.e1. https://doi.org/10.1016/j.jpeds.2011.09.035

13. Symonds ME, Pope M, Budge H. The ontogeny of brown adipose tissue. *Annu Rev Nutr* 2015; 35(1):295–320. https://doi.org/10.1146/annurev-nut-071813-105330

14. Heaton JM. The distribution of brown adipose tissue in the human. *J Anat* 1972; 112(Pt 1):35–9.

15. Cinti S. Adipose organ development and remodeling. *Compr Physiol* 2018; 8(4):1357–431. https://doi.org/10.1002/cphy.c170042

16. Bostrom P, Wu J, Jedrychowski MP et al. A PGC1α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012; 481(7382):463–8. https://doi.org/10.1038/nature10777.

17. Bartelt A, Heeren J. Adipose tissue browning and metabolic health. *Nat Rev Endocrinol* 2014; 10(1):24–36. https://doi.org/10.1038/nrendo.2013.204

18. Kurylowicz A, Puzianowska-Kuźnicka M. Induction of adipose tissue browning as a strategy to combat obesity. *Int J Mol Sci* 2020; 21(17):1–28. https://doi.org/10.3390/ijms21176241

19. Corvera S. Cellular heterogeneity in adipose tissues. *Annu Rev Physiol* 2021; 83(1):257–78. https://doi.org/10.1146/annurev-physiol-031620-095446

20. Lu J, Zhao J, Meng H et al. Adipose tissue-resident immune cells in obesity and type 2 diabetes. *Front Immunol* 2019; 10:1173. https://doi.org/10.3389/fimmu.2019.01173

21. Iynegar NM, Arthur R, Manson JE et al. Association of body fat and risk of breast cancer in postmenopausal women with normal body mass index: a secondary analysis of a randomized clinical trial and observational study. *JAMA Oncol* 2019; 5(2):155–63. https://doi.org/10.1001/jamaoncol.2018.5327

22. Brestoff JR, Kim BS, Saenz SA et al. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature* 2015; 519(7542):242–6. https://doi.org/10.1038/nature14115

23. Lynch L, Nowak M, Varghese B et al. Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic
disorder through regulatory cytokine production. *Immunity* 2012; 37(3):574–87. https://doi.org/10.1016/j.immuni.2012.06.016

24. Costanze AE, Taylor KR, Dutt S et al. Obesity impairs γδ T cell homeostasis and antiviral function in humans. Varga SM, editor. *PLoS One* 2015; 10(3):e0120918. https://doi.org/10.1371/journal.pone.0120918

25. Donnelly D, Bajaj S, Yu J et al. The complex relationship between body mass index and response to immune checkpoint inhibition in metastatic melanoma patients. *J Immunother Cancer* 2019; 7(1):222. https://doi.org/10.1186/s40425-019-0699-5

26. Vohralik EJ, Psaila AM, Knights AJ et al. EoTHiNophils: eosinophils as key players in adipose tissue homeostasis. *Clin Exp Pharmacol Physiol* 2020; 47(8):1495–505. https://doi.org/10.1111/1440-1681.13304

27. Peterson KR, Flaherty DK, Hasty AH. Obesity alters B cell and macrophage populations in brown adipose tissue. *Obesity* 2017; 25(11):1881–4. https://doi.org/10.1002/oby.21982

28. Sanders VM. The beta2-adrenergic receptor on T and B lymphocytes: do we understand it yet? *Brain Behav Immun* 2012; 26(2):195–200. https://doi.org/10.1016/j.bbi.2011.08.001

29. Medriкова D, Sijmonsma TP, Sowodniok K et al. Brown adipose tissue harbors a distinct sub-population of regulatory T cells. Unutmaz D, editor. *PLoS One* 2015; 10(2):e0118534. https://doi.org/10.1371/journal.pone.0118534

30. Feuerer M, Herrero L, Cipolletta D et al. Lean, but not obese, fat tissue harbors a distinct sub-population of regulatory T cells. *J Immunol* 2010; 183(3):1836–45. https://doi.org/10.4049/jimmunol.1000021

31. Winer DA, Winer S, Shen L et al. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. *Nat Med* 2011; 17(5):610–7. https://doi.org/10.1038/nm.2353

32. Milner JJ, Rebeles J, Dhungan S et al. Obesity increases mortality and modulates the lung metabolome during pandemic H1N1 influenza virus infection in mice. *Physiol Behav* 2016; 176(1):139–48. https://doi.org/10.4049/jimmunol.1402295

33. Nishimura S, Manabe I, Nagasaki M et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* 2009; 15(8):914–20. https://doi.org/10.1038/nm.1964

34. Strissel KJ, DeFuria J, Shaul ME et al. T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice. *Obesity*. 2010; 18(10):1918–23. https://doi.org/10.1038/oby.2010.1

35. Shirakawa K, Yan X, Shimura K et al. Obesity accelerates T cell senescence in murine visceral adipose tissue. *J Clin Invest* 2016; 126(12):4626–39. https://doi.org/10.1172/JCI88606

36. Stentz FB, Kitabchi AE. Palmitech acid-induced activation of human T-lymphocytes and aortic endothelial cells with production of insulin receptors, reactive oxygen species, cytokines, and lipid peroxidation. *Biochem Biophys Res Commun* 2006; 346(3):721–6. https://doi.org/10.1016/j.bbrc.2006.05.159

37. Yang H, Youm Y-H, Vandanmagar B et al. Obesity increases the production of proinflammatory mediators from adipose tissue T cells and compromises TCR repertoire diversity: implications for systemic inflammation and insulin resistance. *J Immunol* 2010; 183(3):1836–45. https://doi.org/10.4049/jimmunol.1000021

38. Winer S, Chan Y, Palser G et al. Normalization of obesity-associated insulin resistance through immunotherapy. *Nat Med* 2009; 15(8):921–9. https://doi.org/10.1038/nm.2001

39. Sam S, Mazzone T. Adipose tissue changes in obesity and the impact on metabolic function. *Transl Res* 2014; 164(4):284–92. https://doi.org/10.1016/j.trsl.2014.05.008

40. Boulenouar S, Michelet X, Duquette D et al. Adipose type one innate lymphoid cells regulate macrophage homeostasis through targeted cytotoxicity. *Immunity* 2017; 46(2):273–86. https://doi.org/10.1016/j.immunity.2017.01.008

41. Villarroya F, Cereijo R, Villarroya J et al. Toward an understanding of how immune cells control brown and beige adipobiology. *Cell Metab* 2018; 27(5):954–61. https://doi.org/10.1016/j.cmet.2018.04.006

42. Pan X-K, Yao K-L., Yang Y-F et al. Senescent T cell induces brown adipose tissue “whitening” via secreting IFN-γ. *Front Cell Dev Biol* 2021; 9:637424. https://doi.org/10.3389/fcell.2021.637424

43. Wang L, Zhao R, Song X et al. Targeting ERK1 in macrophage reduces crown-like structures in adipose tissue by inhibiting miR-175 and HIF-1α. *Sci Rep* 2019; 9(1):15762. https://doi.org/10.1038/s41598-019-52265-8

44. Kowalczyk A, Kliewierska P, Kolodziejczyk M et al. The role of endothelin-1 and endothelin receptor antagonists in inflammatory response and sepsis. *Arch Immunol Ther Exp (Warsz)* 2015; 63(1):41–52. https://doi.org/10.1007/s00005-014-0310-1

45. Carbone F, La Rocca C, Matarese G. Immunological functions of leptin and adiponectin. *Biochimie* 2012; 94(10):2082–8. https://doi.org/10.1016/j.biochi.2012.05.018

46. Qiürós PM, Langer T, López-Otín C. New roles for mitochondrial proteases in health, ageing and disease. *Nat Rev Mol Cell Biol* 2015; 16(6):345–59. https://doi.org/10.1038/nrm3984

47. Cunarro J, Casado S, Lugilde J et al. Hypothalamic mitochondrial proteases in health, ageing and disease. *Nature* 2020; 578(7796):610–619. https://doi.org/10.1038/s41598-020-7598-5

48. Molosky AB, Nusbaum JC, Liang H-E et al. Inmate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J Exp Med* 2013; 210(3):535–49. https://doi.org/10.1084/jem.20121964

49. Hu B, Jin C, Zeng X et al. γδ T cells and adipocyte IL-17RC control fat innervation and thermogenesis. *Nature* 2020; 578(7796):610–4. https://doi.org/10.1038/s41586-020-2288-z

50. Liu R, Nikolajczyk BS. Tissue immune cells fuel obesity-associated inflammation in adipose tissue and beyond. *Front Immunol* 2019; 10:1587. https://doi.org/10.3389/fimmu.2019.01587

51. Dyck L, Mills KGH. Immune checkpoints and their inhibition in cancer and infectious diseases. *Eur J Immunol* 2017; 47(5):765–79. https://doi.org/10.1002/eji.201646875

52. Alcalá M, Calderón-Domínguez M, Bustos E et al. Increased inflammation, oxidative stress and mitochondrial respiration in brown adipose tissue from obese mice. *Sci Rep* 2017; 7(1):1–12. https://doi.org/10.1038/s41598-017-1646-5

53. Winer DA, Winer S, Shen L et al. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. *Nat Med* 2011; 17(5):610–7. https://doi.org/10.1038/nm.2353
61. Ioan-Facsinay A, Kwekkeboom JC, Westhoff S et al. Adipocyte-derived lipids modulate CD4 + T-cell function. Eur J Immunol 2013; 43(6):1578–87. https://doi.org/10.1002/eji.201243096

62. Alhusaini S, McGee K, Schisano B et al. Lipopolysaccharide, high glucose and saturated fatty acids induce endoplasmic reticulum stress in cultured primary human adipocytes: Salicylate alleviates this stress. Biochem Biophys Res Commun 2010; 397(3):472–8. https://doi.org/10.1016/j.bbrc.2010.03.138

63. Muscogiuri G, Cantone E, Cassarano S et al. Gut microbiota: a new path to treat obesity. Int J Obes Suppl 2019; 9(1):10–9. https://doi.org/10.1038/s41367-019-0011-7

64. de La Serre CB, Ellis CL, Lee J et al. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am J Physiol Liver Physiol 2010; 299(2):G440–8. https://doi.org/10.1152/ajpregm.00098.2010

65. Esser N, Legrand-Poels S, Pieter J et al. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabet Res Clin Pract 2014; 105(2):141–50. https://doi.org/10.1016/j.diarres.2014.04.006

66. Pan Y, Tian T, Park CO et al. Survival of tissue-resident memory T cells requires exogenous lipid uptake and metabolism. Nature 2017; 543(7644):252–6. https://doi.org/10.1038/nature21379

67. Wei J, Raynor J, Nguyen T-LM et al. Nutrient and metabolic sensing in T cell responses. Front Immunol 2017; 8:247. https://doi.org/10.3389/fimmu.2017.00247

68. Procaccini C, Carbone F, Di Silvestre D et al. The proteomic landscape of human ex vivo regulatory and conventional T cells reveals specific metabolic requirements. Immunity 2016; 44(2):406–21. https://doi.org/10.1016/j.immuni.2016.01.028

69. Michalek RD, Gerriets VA, Jacobs SR et al. Cutting edge: distinct metabolic components of the hematopoietic stem cell niche. J Immunol 2014; 192(2):623–9. https://doi.org/10.4049/jimmunol.1302181

70. Kumar P, Natarajan K, Shanmugam N. High glucose driven expression of pro-inflammatory cytokine and chemokine genes in lymphocytes: Molecular mechanisms of IL-17 family gene expression. Cell Signal 2014; 26(3):528–39. https://doi.org/10.1016/j.cellsig.2013.11.031

71. Howie D, Ten Bokum A, Cobbold SP et al. A novel role for triglyceride metabolism supports CD8 + T cell effector memory differentiation. J Immunol 2016; 197(5):1024–37. https://doi.org/10.1016/j.immuni.2016.10.017

72. Sauceillo DC, Gerriets VA, Sheng J et al. Cutting edge: distinct leptin metabolically licenses T cells for activation to link nutrition and immunity. J Immunol 2014; 192(1):136–44. https://doi.org/10.4049/jimmunol.1301158

73. Hu C, Zhang Q, Jin X et al. A paradox between preoperative malnutrition and postoperative wound healing: a current review. J Surg Oncol 2014; 26(3):528–39. https://doi.org/10.1002/jso.22755

74. Li Y, Chen Y, Song Y et al. Higher rate of severe toxicities in obese patients receiving dose-dense (dd) chemotherapy according to unadjusted body surface area: results of the prospectively randomized GAIN study. Ann Oncol 2016; 27(11):2053–9. https://doi.org/10.1093/annonc/mdw315

75. Bore Y, Markov SD, Attri KS et al. Differential benefit of adjuvant docetaxel-based chemotherapy in patients with early breast cancer according to baseline body mass index. J Clin Oncol 2020; 38(25):2883–91. https://doi.org/10.1200/JCO.19.01771

76. Wang LS, Murphy CT, Ruth K et al. Impact of obesity on outcomes after definitive dose-escalated intensity-modulated radiotherapy for localized prostate cancer. Cancer 2015; 121(17):3010–7. https://doi.org/10.1002/cncr.29472

77. Furlanetto J, Eiermann W, Marmé F et al. Higher rate of severe toxicities in obese patients receiving dose-dense (dd) chemotherapy according to adjusted body surface area: results of the prospectively randomized GAIN study. Ann Oncol 2016; 27(11):2053–9. https://doi.org/10.1093/annonc/mdw315

78. Eiermann W, Marmé F et al. Higher rate of severe toxicities in obese patients receiving dose-dense (dd) chemotherapy according to adjusted body surface area: results of the prospectively randomized GAIN study. Ann Oncol 2016; 27(11):2053–9. https://doi.org/10.1093/annonc/mdw315

79. Jayson MMG, Stepleton M, Williams IR et al. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am J Physiol Liver Physiol 2010; 299(2):G440–8. https://doi.org/10.1152/ajpregm.00098.2010

80. Lauby-Secretan B, Scoccianti C, Loomis D et al. Body fatness and cancer — viewpoint of the IARC working group. N Engl J Med 2016; 375(8):794–8. https://doi.org/10.1056/NEJMr1606602

81. Centers for Disease Control and Prevention (CDC). Cancer associated with Overweight and Obesity Make up 40 percent of Cancers Diagnosed in the United States | CDC Online Newsroom | CDC [Internet]. 2017 [cited 2021 Oct 24]. https://www.cdc.gov/media/releases/2017/p1003-vs-cancer-obesity.html

82. Porporato PE. Understanding cachexia as a cancer metabolism syndrome. Oncogenesis 2016; 5(2):e200–200. https://doi.org/10.3389/oncsci.2016.3

83. Shukla SK, Markov SD, Attri KS et al. Macrophages potentiate STAT3 signaling in skeletal muscles and regulate pancreatic...
cancer cachexia. Cancer Lett 2020; 484(2020):29–39. https://doi.org/10.1016/j.canlet.2020.04.017

98. Erdem M, Möckel D, Jumpertz S et al. Macrophages protect against loss of adipose tissue during cancer cachexia. J Cachexia Sarcopenia Muscle 2019; 10(5):1128–42. https://doi.org/10.1002/jscm.12450

99. Lu S-W, Pan H-C, Hsu Y-H et al. IL-20 antagonist suppresses PD-L1 expression and prolongs survival in pancreatic cancer models. Nat Commun 2020; 11(1):4611. https://doi.org/10.1038/s41467-020-18244-8

100. Schirrmacher V. From chemotherapy to biological therapy: a review of novel concepts to reduce the side effects of systemic cancer treatment (Review). Int J Oncol 2019; 54(2):407–19. https://doi.org/10.3892/ijo.2018.4661

101. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immuno-therapy: from T cell basic science to clinical practice. Nat Rev Immunol 2020; 20(11):651–68. https://doi.org/10.1038/s41577-020-0306-5

102. Cohen R, Rousseau B, Vidal J et al. Immune checkpoint inhibition in colorectal cancer: microsatellite instability and beyond. Target Oncol 2020; 15(1):11–24. https://doi.org/10.1007/s11523-019-00690-0

103. Vaddeparty RK, Kharel P, Pandey R et al. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. Cancers (Basel) 2020; 12(3):738. https://doi.org/10.3390/cancers12030738

104. Yousef H, Yuan J, Keshavarz-Fathi M et al. Immuno-therapy of cancers comes of age. Expert Rev Clin Immunol 2017; 13(10):1001–15. https://doi.org/10.1080/1744666X.2017.1366315

105. Graydon CG, Mohideen S, Fowke KR. LAG3's enigmatic mechanism of action. Front Immunol 2021; 11(615317):1–5. https://doi.org/10.3389/fimmu.2020.615317

106. Heinzerling L, de Toni E, Schett G et al. Checkpoint inhibitors. Dtsch Arztebl Int 2019; 116(8):119. https://doi.org/10.3238/arztebl.2019.0119

107. Han HS, Jeong S, Kim H et al. TOX-expressing terminally exhausted tumor-infiltrating CD8+ T cells are reinvigorated by co-blockade of PD-1 and TIGIT in bladder cancer. Cancer Lett 2021; 499(2021):137–47. https://doi.org/10.1016/j.canlet.2020.11.033

108. Xin Yu J, Hubbard-Lucey VM, Tang J. Immuno-oncology drug development goes global. Nat Rev Drug Discov 2019; 18(12):899–900. https://doi.org/10.1038/s41573-019-00167-9

109. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363(8):711–23. https://doi.org/10.1056/NEJMoa1003466

110. Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372(26):2521–32. https://doi.org/10.1056/NEJMoa1503093

111. Cancer Research Institute. Immunomodulators: Checkpoint Inhibitors, Cytokines, Agonists, Adjuvants – Cancer Research Institute (CRI) [Internet]. 2021 [cited 2021 Nov 3]. https://www.cancerresearch.org/en-us/immunotherapy/treatment-types/immunomodulators-checkpoint-inhibitors

112. Topalian SL, Hodi FS, Brahmer JR et al. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non–small-cell lung cancer treated with nivolumab. JAMA Oncol 2019; 5(10):1411–20. https://doi.org/10.1001/jamaoncol.2019.2187

113. Baas P, Scherperel A, Nowak AK et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021; 397(10272):375–86. https://doi.org/10.1016/S0140-6736(20)32714-8

114. World Health organization. Global Health Sector Strategy on HIV 2016-2021 towards ending AIDS. World Health Organization, 2018, 60.
EBioMedicine 2019; 42(2019):431–42. https://doi.org/10.1016/j.ebiom.2019.03.068

133. Joosse A, de Vries E, Eckel R et al. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. J Invest Dermatol 2011; 131(3):719–26. https://doi.org/10.1038/jid.2010.354

134. Natale CA, Duperret EK, Zhang J et al. Sex steroids regulate skin pigmentation through nonclassical membrane-bound receptors. Elife 2016; 5(e15104):1–16. https://doi.org/10.7554/eLife.15104

135. Natale CA, Li J, Zhang J et al. Activation of G protein-coupled estrogen receptor signaling inhibits melanoma and improves response to immune checkpoint blockade. Elife 2018; 7(e31770):1–19. https://doi.org/10.7554/eLife.31770

136. Xu X, Sun M, Ye J et al. The effect of aromatase on the reproductive function of obese males. Horm Metab Res 2017; 49(08):572–9. https://doi.org/10.1055/s-0043-107835

137. Gülave B, Hew MN, de Groot JS et al. High body mass index and pre-existing autoimmune disease are associated with an increased risk of immune-related adverse events in cancer patients treated with PD-(L)1 inhibitors across different solid tumors. ESMO Open 2021; 6(3):100107. https://doi.org/10.1016/j.esmoop.2021.100107

138. Cortellini A, Bersanelli M, Santini D et al. Another side of the association between body mass index (BMI) and clinical outcomes of cancer patients receiving programmed cell death protein-1 (PD-1)/ Programmed cell death-ligand 1 (PD-L1) checkpoint inhibitors: a multicentre analysis of immune-related. Eur J Cancer 2020; 128(2020):17–26. https://doi.org/10.1016/j.ejca.2019.12.031

139. Anandavadivelan P, Brismar TB, Nilsson M et al. Sarcopenic obesity: a probable risk factor for dose limiting toxicity during neoadjuvant chemotherapy in oesophageal cancer patients. Clin Nutr 2016; 35(3):724–30. https://doi.org/10.1016/j.clnu.2015.05.011

140. Dalal S, Hui D, Bidaut L et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manage 2012; 44(2):181–91. https://doi.org/10.1016/j.jpainsymman.2011.09.010

141. Heidelberger V, Goldwasser F, Kramkimel N et al. Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. Invest New Drugs 2017; 35(4):436–41. https://doi.org/10.1007/s10637-017-0464-x