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Immunotherapy targeting the obese white adipose tissue microenvironment: Focus on non-communicable diseases

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ABSTRACT

Obesity triggers inflammatory responses in the microenvironment of white adipose tissue, resulting in chronic systemic inflammation and the subsequent development of non-communicable diseases, including type 2 diabetes, coronary heart disease, and breast cancer. Current therapy approaches for obesity-induced non-communicable diseases persist in prioritizing symptom remission while frequently overlooking the criticality of targeting and alleviating inflammation at its source. Accordingly, this review highlights the importance of the microenvironment of obese white adipose tissue and the promising potential of employing immunotherapy to target it as an effective therapeutic approach for non-communicable diseases induced by obesity. Additionally, this review discusses the challenges and offers perspective about the immunotherapy targeting the microenvironment of obese white adipose tissue.

1. Introduction

Obesity, a chronic disease characterized by the excessive accumulation of adipose tissue, is frequently underestimated. Consequently, the prevalence of obesity has been continuously rising over the years, and it is projected that more than 1.5 billion adults will be categorized as obese by 2035 [1]. Furthermore, obesity is a multifactorial disease that arises from multiple factors of etiology and manifests in various pathological features. The etiology of obesity includes obesogenic environments, psycho-social factors, and genetic variants [2]. The pathological manifestations of obesity extend beyond the boundary of white adipose tissue (WAT) and include various other tissues, including bone, nerve, and intestinal epithelial tissues. Obesity has been found to promote the formation of osteoclasts, leading to a 37.5 % reduction in bone strength among obese patients [3,4]. Moreover, the brain of obese patients exhibits a significant alteration in the structure of the white matter due to the occurrence of obesity-induced demyelination [5]. Obesity not only affects the structure of neural tissue but also leads to alterations in the structure and permeability of the intestinal epithelial tissue. The observed phenomena may be attributed to the obesity-induced proliferation of intestinal stem cells and claudin-2-mediated restructuring of tight junctions [6,7].

The major pathological manifestation of obesity is most prominent in WAT, which defines obesity as a disease linked to the abundance of adipose tissue. Furthermore, the crucial role of WAT in determining the health consequences of obesity in an individual has demonstrated that the impact of obesity on WAT is more significant than its impact on other tissues [8]. A recent study has demonstrated that when WAT overcomes overnutrition by undergoing adipocyte hyperplasia, which involves an increase in the number of cells, it leads to obese patients exhibiting normal levels of inflammatory markers [9]. These patients are classified as having metabolically healthy obesity (MHO), a distinct phenotype observed in obese patients who do not exhibit the typical indications of dyslipidemia or hypertension [10]. Conversely, when WAT overcomes

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overnutrition by enlarging the size of adipocytes, these hypertrophic adipocytes trigger immune system responses by secreting pro-inflammatory factors [11]. As a consequence, the WAT microenvironment (WATME) undergoes a substantial alteration, shifting from an anti-inflammatory state, which is discernible in lean WATME, to a pro-inflammatory state, characteristic of obese WATME [12].

The strong correlation between inflammation occurring within obese WATME and the resulting impact on the development of obesity-related comorbidities, particularly non-communicable diseases (NCDs) has been extensively studied [13,14]. Empirical evidence unequivocally demonstrates that obesity significantly affects the development of NCDs. Obesity, at varying degrees of severity, decreases the number of NCD-free years by 3–9 years in persons aged 40 and above [15]. Furthermore, the 'WHO Acceleration Plan to Stop Obesity' received official endorsement from the World Health Organization (WHO) during the 75th World Health Assembly in 2022. The objective of this approach is to accomplish Sustainable Development Goal 3.4, which involves a 33 % reduction in premature deaths caused by NCDs by the year 2030 [16]. The proposition is supported by empirical data revealing that in 2019, obesity accounted for approximately 18 % of all preventable NCD-related mortalities and was the direct cause of the premature death of approximately five million individuals [17]. Additionally, obesity demonstrates a remarkable correlation with the development of type 2 diabetes (T2D), coronary heart disease (CHD), and breast cancer (BC), in comparison to other NCDs [18–20].

Accordingly, immunotherapy that works at the site of immune system response, referred to as "WATME-specific immunotherapy", offers outstanding potential as a therapeutic approach for treating obesity-induced T2D, CHD, and BC (Fig. 1). WATME-specific immunotherapy can be classified into two categories depending on how it affects the immune cell composition and inflammatory state of obese WATME. There is direct immunotherapy that works directly on cells or signaling pathways and indirect immunotherapy that works indirectly through targeting the secreted cytokines. Notwithstanding the encouraging prospects, there has been a notable absence of a comprehensive review focusing on the implementation of WATME-specific immunotherapy. Hence, in this review, we provide a concise summary of the mechanisms by which inflammation manifests in obese WATME, which eventually leads to the development of obesity-induced T2D, CHD, or BC. This review includes the status of WATME-specific immunotherapy and the implementation of this approach in clinical studies. Lastly, we discuss the existing challenges encountered in the field and the perspectives for WATME-specific immunotherapy.

2. Pathogenesis of obesity-induced NCDs

The strong correlation between obesity and the development of type 2 diabetes (T2D), coronary heart disease (CHD), or breast cancer (BC) is supported by statistical evidence indicating a significant majority, surpassing 80 % of individuals afflicted with T2D or CHD, also suffer from obesity [18,20]. Furthermore, empirical data indicates that premenopausal women who are obese face a significantly elevated risk of developing BC, with the risk being 80 % higher compared to non-obese women [19]. The primary reason for the development of these NCDs in obese patients is the direct involvement of obese WATME in facilitating insulin resistance, atherosclerosis, and upregulating estrogen levels through the secretion of pro-inflammatory factors [21–23].

2.1. Obese WATME

Obesity has been widely recognized as a significant contributor to the expansion of WAT as a result of the increased demand for storing excess nutrients [8]. In obesity, hypertrophic adipocytes experience mechanical stress as a consequence of persistent expansion of WAT via adipocyte hypertrophy, despite being constrained by the complex arrangement of adipocytes within a densely interconnected extracellular matrix (ECM) [12,24]. Furthermore, it has been observed that hypoxia frequently accompanies the expansion of WAT [25]. Hypoxia exerts significant impacts on hypertrophic adipocytes by inducing multiple cellular stresses. In addition to its well-known role in causing oxidative stress, hypoxia also leads to mechanical stress by increasing the cross-linking degree of collagen fibers in the ECM through the

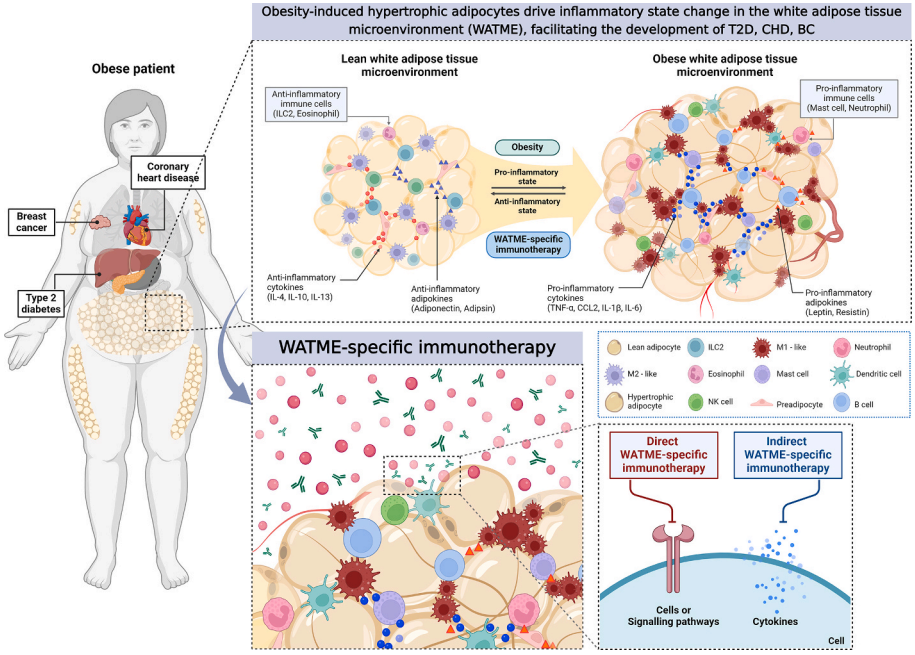

Fig. 1. Illustrative representation of WATME-specific immunotherapy for obesity-induced non-communicable diseases. Obesity changes the inflammatory state of the white adipose tissue microenvironment (WATME), leading to a pro-inflammatory state by triggering inflammatory responses mediated by hypertrophic adipocytes. This obese WATME facilitates the development of type 2 diabetes (T2D), coronary heart disease (CHD), and breast cancer (BC) in obese patients. Correspondingly, through the mitigation of inflammation in obese WATME, WATME-specific immunotherapy has the potential to treat obesity-induced non-communicable diseases. Direct immunotherapy: targeting cells or intracellular signaling pathway; Indirect immunotherapy: targeting secreted cytokines.

upregulation of lysyl oxidase enzyme [26]. The obesity-induced cellular stresses have been observed to cause notable alterations in the secretomes of hypertrophic adipocytes and subsequently lead to the death of these cells [12]. Adipocyte death initiates the inflammatory signaling cascades, which then induce the infiltration of immune cells and ultimately lead to alterations in the secretory profile of WAT [11]. The interrelated consequences of these chain reactions eventually culminate in inflammation, which is a distinctive characteristic of obese WATME (Fig. 2).

In obese WATME, hypertrophic adipocytes secrete pro-inflammatory factors including leptin, resistin, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and chemokine ligand 2 (CCL2) [11,27]. Simultaneously, there is an apparent reduction in the secretion of anti-inflammatory factors, such as adiponectin, adipsin, IL-4, IL-10, and IL-13, by hypertrophic adipocytes [28–30]. The alteration in the secretomes of hypertrophic adipocytes stimulates the proliferation of NK cells, infiltration of $CD8^+$ T cells, and recruitment of neutrophils and mast cells into obese WATME [31–33]. Concurrently, it reduces the abundance of anti-inflammatory immune cells, specifically eosinophils, T_{reg} cells, and innate lymphoid cells 2 (ILC2s) [34,35].

The death of hypertrophic adipocytes in obese WATME triggers metabolic activation of the nearby anti-inflammatory phenotype (M2-like) macrophages into the pro-inflammatory phenotype (M1-like) macrophages [36]. This polarization is facilitated through the toll-like receptor 4 (TLR4)/MyD88/IκB kinase (IKKβ)/NF-κB pathway, which are activated in response to damage-associated molecular patterns (DAMPs) and free fatty acids (FFAs) [37,38]. Furthermore, the dead hypertrophic adipocytes leave behind large lipid remnants that hamper efficient efferocytosis by a single M1-like macrophage [39], hence stimulating the recruitment of other immune cells. Circulating monocytes are recruited to the site through a complex interaction involving dead adipocytes, M1-like macrophages, and $CD8^+$ T cells, resulting in the formation of a crown-like structure (CLS) [33,40]. Additionally, obese WATME contains a substantial accumulation of M1-like macrophages, which comprise as much as 60 % of immune cells, compared to a mere 10 % in lean WATME [21,41]. The accumulation of M1-like macrophages is facilitated by neutrophil-derived elastase, interferon-gamma (IFN-γ) secreted by NK cells, the differentiation of recruited monocytes into M1-like macrophages, the proliferation of M1-like macrophages mediated by CCL2, as well as increased tissue retention of M1-like macrophages mediated by netrin-1 [33,42–44].

These inflammatory responses observed in obese WATME establish a positive feedback loop that ultimately contributes to the development of chronic systemic inflammation. The collaboration between M1-like macrophages and mast cells plays a significant role in the promotion of fibrosis, resulting in increased adipocyte death [45]. The rise in adipocyte death leads to the elevated secretion of DAMPs and FFAs, subsequently triggering the activation of the NF-κB pathway. The activated NF-κB upregulates the expression of CCL2, IL-6, IL-12, IL-1β, IL-18, and TNF-α [46]. These cytokines possess the capability to stimulate the NF-κB pathway, thereby leading to elevated secretion of pro-inflammatory cytokines. As a result, the initiation of the positive feedback loop occurs when these cytokines attract circulating monocytes, which subsequently undergo differentiation into M1-like macrophages. Consequently, M1-like macrophages facilitate the development of chronic inflammation in the obese WATME, promoting the infiltration of additional immune cells. These immune cells contribute to the development of chronic systemic inflammation through the secretion of pro-inflammatory factors, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM) [12,31,33,44,47,48].

2.2. Obese WATME-induced NCDs

Obese WATME-induced chronic systemic inflammation plays a crucial role in the development of obesity-induced type 2 diabetes (T2D), coronary heart disease (CHD), and breast cancer (BC) (Fig. 3).

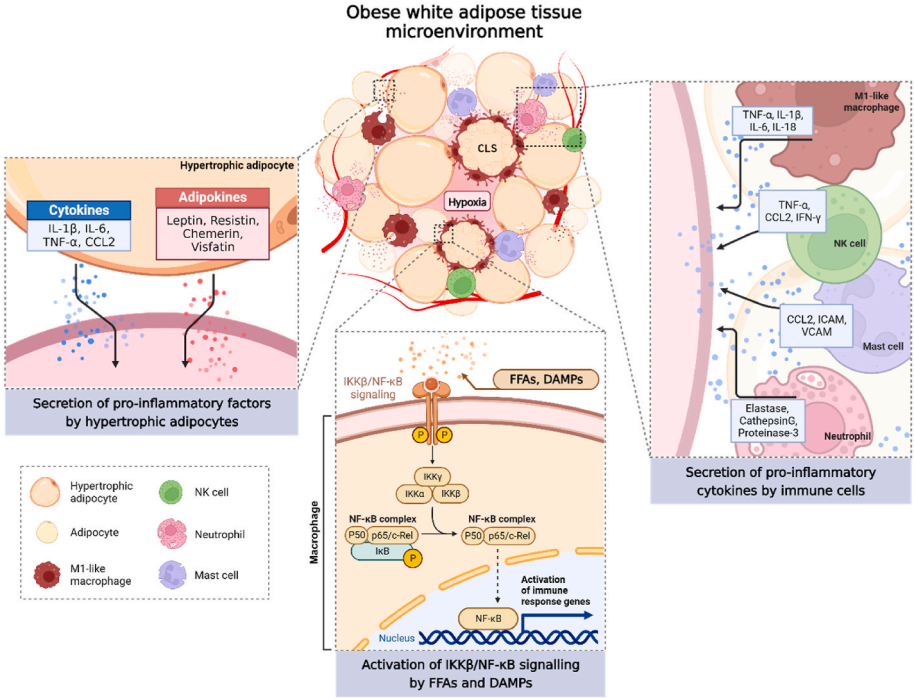

Fig. 2. Schematic illustration of obese WATME. Obesity induces cellular stress, leading to the secretion of pro-inflammatory factors by hypertrophic adipocytes. Prolonged cellular stress ultimately leads to the death of these cells, triggering the recruitment of immune cells surrounding the dead adipocytes, thereby resulting in the formation of crown-like structure (CLS). Moreover, the secretion of free fatty acids (FFA) and damage-associated molecular patterns (DAMPs) by these adipocytes initiate the activation of nuclear factor kappa B (NF-κB) signaling. The activation of the NF-κB downstream signaling pathway leads to the infiltration and stimulation of immune cells to secrete pro-inflammatory cytokines. These alterations in the cellular composition, secretory profile, and inflammatory state of WAT result in obese WATME.

The inflammatory responses within obese WATME significantly contribute to the development of insulin resistance, which in turn lead to the depletion of β-cells and ultimately results in chronic hyperglycemia and the onset of T2D [49]. Obesity-induced CHD typically occurs through the development of atherosclerosis, which is facilitated by chronic systemic inflammation induced by obese WATME [22,50]. In the context of obesity-induced BC, the pro-inflammatory factors secreted by obese WATME can upregulate the expression of aromatase enzyme [51,52]. Aromatase enzyme is responsible for the production of estrogen, a hormone closely associated with the development of estrogen receptor (ER)-positive breast cancer [53].

Obese WATME facilitates the development of obesity-induced T2D

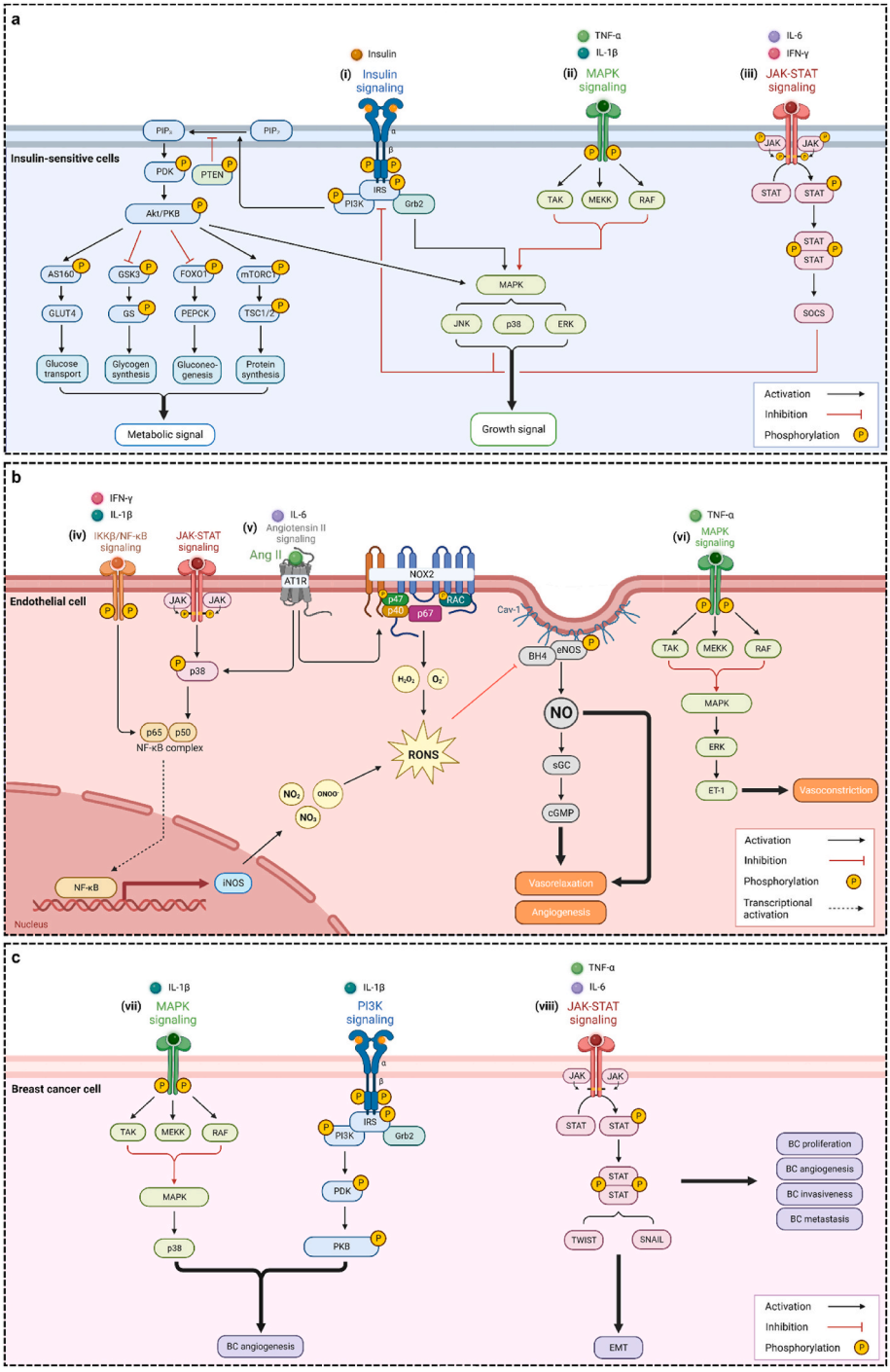

Fig. 3. Illustrative representation of molecular mechanisms of obesity-induced non-communicable diseases. a, obesity-induced type 2 diabetes. (i) The insulin signaling pathway begins with phosphorylated IRS1/2 activates the PI3K-Akt/PKB and MAPK signaling pathways which regulate metabolic processes and growth signaling. Pro-inflammatory factors secreted by obese WATME trigger the activation of (ii) the MAPK and (iii) the JAK/STAT signaling pathways, which subsequently inhibit insulin signaling, impair insulin sensitivity, and ultimately result in insulin resistance. **b, obesity-induced coronary heart disease.** Pro-inflammatory factors secreted by obese WATME exert atherogenic effects by generating RONS through the activation of (iv) the IKK/NF-κB, JAK/STAT/NF-κB, and (v) the Ang II signaling pathways. Additionally, the pro-inflammatory factors generate vasoconstrictors through activating (vi) the MAPK/ERK signaling pathway. **c, obesity-induced breast cancer.** Obese WATME facilitates the progression and metastasis of breast cancer by activating (vii) the MAPK/p38, the PI3K/PKB, and (viii) the JAK/STAT3 signaling pathways.

by reducing insulin sensitivity of adipocytes, liver, and skeletal muscle by activating mitogen-activated protein kinase (MAPK) and Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway (Fig. 3a) [54,55]. Both TNF-α and IL-1β secreted by obese WATME have been shown to activate the MAPK pathway, but their inhibition of the insulin signaling pathway operates through distinct molecular mechanisms. TNF-α inhibits the insulin signaling pathways by affecting phosphoinositide-3 kinase (PI3K)/protein kinase B (PKB) signaling through the activation of MAPK/c-Jun N-terminal kinase (JNK) [56,57]. The inhibitory effects of IL-1β on the insulin signaling pathways have been observed to be mediated by downregulating the expression of insulin receptor substrate-1 (IRS-1) through the MAPK/extracellular-signal-regulated kinase (ERK) signaling pathway [58]. Meanwhile, the JAK/STAT signaling pathway is activated by IL-6 and IFN-γ. IL-6 activates the JAK/STAT3 pathway, which causes an upregulation of the expression of suppressor of cytokine signaling-3 (SOCS3) [59,60]. On the other hand, IFN-γ activates the JAK1/JAK2/-STAT1 pathway, resulting in the increased expression of SOCS1 [61,62]. These SOCS proteins promote the degradation of IRS and inhibit the insulin signaling pathway [63]. The reduced insulin sensitivity by obese WATME leads β-cells to secrete elevated levels of insulin to counteract the insulin resistance [64]. However, persistent insulin resistance due to obese WATME-induced chronic systemic inflammation ultimately results in the exhaustion of β-cells and the development of T2D caused by obesity [49].

The pathogenesis of obesity-induced CHD is a complex process involving multiple mechanisms facilitated by obese WATME that ultimately lead to the development and progression of atherosclerosis. Obese WATME induces chronic systemic inflammation that triggers endothelial cells (ECs) to secrete leukocyte adhesion molecules such as ICAM1 and VCAM1. These leukocyte adhesion molecules can facilitate circulating monocytes, T cells, and B cells to adhere and migrate into the intima layer of the blood vessel wall [65–67], thereby initiating the formation of atheroma. Additionally, obese WATME contributes to the progression of atherosclerosis by inducing ECs dysfunction and vasoconstriction through the secretion of pro-inflammatory factors (Fig. 3b). IL-6 is discovered to substantially contribute to obese WATME-induced ECs dysfunction by promoting the production of reactive oxygen and nitrogen species (RONS). IL-6, IL-1β, and IFN-γ stimulate reactive nitrogen species (RNS) production by activating the NF-κB pathway, which leads to the upregulation of inducible nitric oxide synthase (iNOS) enzyme expression [68]. Moreover, IL-6 along with angiotensin II (Ang II) promotes reactive oxygen species (ROS) production by increasing the expression of NADPH oxidase 2 (NOX2) enzyme [69]. These RONS inhibit the function of endothelial NOS (eNOS) enzyme to produce nitric oxide (NO), resulting in the inhibition of vasorelaxation and angiogenesis [70]. In the context of obese WATME-induced vasoconstriction, it is discovered that vasoconstriction is facilitated by TNF-α, which promotes the synthesis of a strong vasoconstrictor called endothelin-1 (ET-1) through the MAPK/ERK pathway [71,72].

In obesity-induced BC, obese WATME secretes IL-6 and TNF-α, which work through distinct cellular pathways to upregulate the expression of aromatase enzymes. IL-6 triggers BC cells to secrete prostaglandin E2 (PGE2), which subsequently leads to the upregulation of aromatase enzyme expression in breast adipose stromal cells (ASCs) [51,73,74]. On the other hand, TNF-α directly affects breast ASCs by activating the MAPK/ERK1/2 signaling pathway [52,75]. This obese WATME-induced upregulation of estrogen levels facilitates the development of estrogen receptor (ER)-positive BC through both genomic and non-genomic mechanisms [76]. Furthermore, pro-inflammatory factors secreted by obese WATME not only stimulate the development of BC but also facilitate the progression and metastasis of BC (Fig. 3c). It is discovered that when IL-1β binds to its receptor, it facilitates angiogenesis by inducing BC cells to secrete vascular endothelial growth factor (VEGF) through the activation of MAPK/p38 and phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) signaling pathways [77,78]. Moreover, TNF-α and IL-6 promote the progression and epithelial-to-mesenchymal transition (EMT) of BC cells by activating the JAK/STAT3 signaling pathway [79,80]. The activated STAT3 pathway induces the expression of target genes associated with apoptosis, proliferation, angiogenesis, invasiveness, and metastasis [81,82]. Furthermore, upon phosphorylation, STAT3 translocates to the nucleus and elicits the transcriptional upregulation of TWIST and SNAIL genes, which are recognized as key regulators of the EMT in cancer cells [83,84].

Taken together, the inflammatory responses that occur in obese WATME play a crucial role in the development of obesity-induced T2D, CHD, or BC. The interrelationships between this inflammation and obesity-induced NCDs emphasize the potential of targeting the obese WATME as a promising immunotherapy target for treating these diseases.

3. WATME-specific immunotherapy for obesity-induced NCDs

WATME-specific immunotherapy, which modulates the inflammatory responses in obese WATME to alleviate the chronic systemic inflammation, demonstrates therapeutic efficacy for obesity-induced type 2 diabetes (T2D), coronary heart disease (CHD), and breast cancer (BC) (Table 1). The efficacy of WATME-specific immunotherapy in targeting obese WATME is readily apparent based on the reduction in body weight (BW) or fat mass, as well as alterations in the secretomes, cellular composition, and signaling pathway cascades of obese WATME. Here, recent advances in WATME-specific immunotherapy for the treatment of obesity-induced NCDs are reviewed.

PAI-1: plasminogen activator inhibitor-1, GIP: gastric inhibitory polypeptide, GLP-: glucagon-like peptide-1, SREBP-1c: sterol regulatory element-binding protein-1c, FAS: fatty acid synthase, ACC: acetyl-CoA carboxylase, LC3-II: microtubule-associated protein 2 light chain 3, CXCL: chemokine ligand, PPAR: peroxisome proliferator-activated receptor, TG: triglyceride, NLRP3: NLR family pyrin domain containing 3, LV: left ventricular, Nrf2: nuclear factor erythroid 2–related factor 2, HO-1: heme oxygenase-1, IRF3: interferon regulatory factor 3, IL-1R: IL-1 receptor, PCSK9: proprotein convertase subtilisin/kexin type 9, LDLR: low-density lipoprotein receptor, mAb: monoclonal antibody, ApoB100: apolipoprotein B100, FAK: focal adhesion kinase, pPAX: phosphorylated paxillin, PP2A: protein phosphatase 2A, C/EBPα: CCAAT/enhancer-binding protein alpha GRO: growth related oncogene, OCT4: octamer-binding transcription factor 4, KLF4: Krüppel-like factor 4, SOX2: SRY-box transcription factor 2, NLRC4: NLR family CARD domain-containing protein 4, FABP2: fatty acid-binding protein 2, MMP: Matrix metalloproteinase, PDGF-C: platelet-derived growth factor C.

3.1. WATME-specific immunotherapy for obesity-induced type 2 diabetes (T2D)

In order to effectively treat obesity-induced type 2 diabetes (T2D), it is essential to suppress the secretion of pro-inflammatory cytokines including TNF-α, IL-6, IL-1β, and IFN-γ by obese WATME. These pro-inflammatory cytokines facilitate the development of insulin resistance, subsequently resulting in the occurrence of hyperinsulinemia. The prolonged hyperinsulinemia because of chronic systemic inflammation induced by obese WATME leads to β-cell dysfunction and ultimately to the development of T2D. Therefore, the inhibition of the secretion of pro-inflammatory cytokines by employing WATME-specific immunotherapy, which involves inhibiting inflammatory signaling pathways, enzymes, receptors, and senescent cells, has emerged as an effective approach for treating obesity-induced T2D (Fig. 4, Table 1).

3.1.1. Sulforaphane (SFN)

Sulforaphane (SFN), a phytochemical present in cruciferous vegetables, demonstrates promising therapeutic potential of direct WATME-specific immunotherapy for obesity-induced T2D. Observations have shown that the SFN treatment effectively reduces insulin resistance, as

Table 1
Summary of WATME-specific immunotherapy for obesity-induced NCDs.

Disease	Drug	Direct/ Indirect	Description	Ref.
T2D	Formononetin	Direct	- Inhibition of JAK2/ STAT3 - Activation of AMPK/ β-catenin pathway - IL-6, IL-1β, ICAM-1, NO ↓ - BW (−18 %), blood glucose (−15.73 mmol/dL) ↓	[85–87]
	Coffee silver skin and husk	Direct	- Inhibition of ERK1/2, MAPK, JNK - Activation of insulin/ PI3K/AKT - Serine IRS-1, TNF-α, CCL2, NF-κB, IL-6 ↓ - Lipid accumulation (−20 %) ↓	[88]
	SZ-A	Direct	- Inhibition of p38 MAPK/ERK/JNK - TNF-α, IL-6, PAI-1, Ang-II, leptin ↓ - IL-4, IL-10, IL-13 ↑ - BW (−25 %), blood glucose↓	[89]
	Baricitinib	Direct	- Inhibition of JAK2/ STAT2 - Leptin, resistin, IL-1β, TNF-α, IFN-γ, IL-6↓ - Ghrelin, GIP, GLP-1 ↑ - BW (−33 %), blood glucose (−25 mg/dL) ↓	[90]
	Sulforaphane	Direct	- Inhibition of JAK2/ STAT3/SOCS3 - SREBP-1c, FAS, ACC, NF-κB, IL-22 ↓ - Beclin-1, LC3-II ↑ - BW (−60 %), blood glucose (−37.83 mg/ dL) ↓	[91]
	mAb-ATR/ ATRQβ-001	Direct	- Inhibition of Ang II type 1 receptor (AT1R) - JAK2/STAT3↓ - BW, fasting serum insulin (−6 mg/ml) ↓	[92]
	Dasatinib and Quercetin	Direct	- Senolytic agents → elimination of senescent cells - IL-6, PAI-1, CCL2, CXCL1, NF-κB ↓ - BW, blood glucose ↓	[93]
	AdipoRon	Direct	- Adiponectin receptor (AdipoR) agonist - Activation of AMPK, PPAR-α - TNF-α, IL-6, CCL2, M1-like macrophages ↓ - FFA, TG ↓ - Blood glucose (−30 mg/dL) ↓	[94]
	Vildagliptin	Indirect	- Inhibition of dipeptidyl peptidase-4 (DPP-4) - CCL5, CXCL2, CXCL11 and CXCL12 ↓ - GLP-1, GIP ↑ - BW ↓, insulin secretion (>30 %) ↑	[95,96]
	Dapagliflozin	Indirect	- Inhibition of sodium–glucose co-transporter 2 (SGLT2) - TNF- α, IL-6, CCL2 ↓ - BW, blood glucose (−1.33 mmol/L) ↓	[96,97]
CHD	INF200	Direct	- Inhibition of NLRP3 - IL-1β, TNF-α↓ - Fat mass (−25 %), cardiac dysfunction ↓	[98]
	MCC950	Direct	- Inhibition of AKT/ AMPK/NLRP3 - IL-1β, IL-10, M1-like macrophages ↓ - M2-like macrophages ↑ - LV hypertrophy (−18 %) ↓	[99]
	Salidroside	Direct	- Activate Nrf2/HO-1 → inhibition of NLRP3 - Macrophage infiltration, CCL2 ↓ - Lipid profile, thermogenesis ↑ - Fat mass, Plaque area (−25 %) ↓	[100–102]
	Statin	Direct	- Inhibition of TLR4/ Trif/IRF3/IFN-β - CCL2, IL-6, TNF-α ↓ - Lipid profile, adiponectin ↑ - Plaque area (−27 %) ↓	[103,104]
	Empagliflozin	Direct	- Activation of AMPK → WAT browning - Leptin, CCL2, M1-like macrophages ↓ - Adiponectin, cardiac function ↑ - Fat mass, LV thickness (−22 %) ↓	[105,106]
	Bindarit	Direct	- Inhibition of P-p65/p-IκBα→inhibit NF-κB - TNF-α, IFN-γ, IL-1β, CCL2 ↓ - Hypertrophic adipocyte ↓ - Plaque (−70 %) ↓	[107,108]
	Anakinra	Direct	- IL-1R antagonist - CCL2, TG, CLS, IL-6, IL-1β ↓ - Plaque area (−30.6 %) ↓	[109]
	Canagliflozin	Direct	- Activation of PPAR-α → WAT browning - IL-1β, CCL2, VCAM1 ↓ - Fat mass, adipocyte hypertrophy (−33 %) ↓ - Plaque area (−25 %) ↓	[110,111]
	Etanercept	Indirect	- Inhibition of TNF-α - IL-1β, IL-6, cardiac hypertrophy ↓ - Lipid profile, adiponectin ↑ - Adipocyte hypertrophy (−42 %) ↓	[112,113]
	AT04A vaccine (PCSK9 mAb)	Indirect	- Inhibition of LDLR degradation - ICAM-1, NLRP3, WAT thickness ↓ - Lipid profile ↑ - Plaque area (−60 %) ↓	[114–116]
	ApoB-based vaccination	Indirect	- Inhibition of ApoB100 → LDL ↓ - IL-6, VCAM-1, TNF ↓ - Fat mass, plaque (−58 %) ↓	[117,118]
BC	Lunasin	Direct	- Inhibition of FAK/Akt/ ERK and NF-κB - IL-6, IL-1β, TNF-α, CCL2, leptin ↓ - Adiponectin ↑	[119,120]

(*continued on next page*)

Table 1 (*continued*)

Disease	Drug	Direct/ Indirect	Description	Ref.
	Niclosamide	Direct	- Breast cancer cell metastasis, VEGF ↓ - Inhibition of IL-6/ STAT - IL-6, FAK, pPAX ↓ - p53, PP2A, AMPK ↑ - Lipid accumulation, tumor volume (−400 mm^3) ↓	[121]
	Sulforaphane	Direct	- Inhibition of JAK2/ STAT3/SOCS3 - C/EBPα, IL-6, CCL2, GRO, IL-8 ↓ - OCT4, KLF4, SOX2 ↑ - Lipid accumulation, tumor volume (−330 mm^3) ↓	[122]
	BZ26	Direct	- Inhibition of PPAR-γ - IL-1β, IL-6, CCL2, TNF-α, PAI-1, FFA ↓ - FABP2, adiponectin ↑ - Tumor metastasis, tumor volume (−1.7 cm^3) ↓	[123]
	Reparixin	Indirect	- Inhibition of IL-8 - IL-8, NF-κB, CXCL8, STAT3, leptin ↓ - IL-6/NF-κB/Lin28B epigenetic feedback loop ↓ - Tumor volume (−400 mm^3) ↓	[124]
	ANGPLT4 Ab	Indirect	- Inhibition of Angiopoietin-like 4 (ANGPTL4) - ANGPTL4 ↓→ NF-κB/ MAPK ↓→ IL-1β ↓ - IL-1β, NLRC4 inflammasome ↓ - BW (−15 g), tumor volume (−2.2 cm^3) ↓	[125]
	pCCL2 trap	Indirect	- Inhibition of CCL2 - MMP2, MMP9, MMP13, PDGF-C ↓ - CXCL9, CXCL10, IFN-γ, IL-12 ↑ - Tumor volume (−650 mm^3) ↓	[126]

indicated by a decrease in fasting blood glucose levels in the SFN group [127]. SFN enhances insulin sensitivity through working directly on adipocytes in obese WATME through the inhibition of JAK2/-STAT3/SOCS3 signaling pathway. Additionally, SFN inhibits the expression of sterol regulatory element-binding protein-1c (SREBP-1c), a transcription factor responsible for lipid and cholesterol synthesis [128]. This inhibition results in the suppression of adipocyte hypertrophy, improvement of lipid profile, and reduction in body weight. SFN also ameliorates the inflammatory responses in obese WATME by inhibiting NF-κB signaling pathway, therefore decreasing the secretion of pro-inflammatory factors such as IL-22, IL-6, and leptin [129,130].

3.1.2. Formononetin (FNT)

Formononetin (FNT), an estrogen-resembling compound derived from plants, inhibits adipogenesis by inhibiting the activity of various adipogenic genes such as PPAR and CCAAT/enhancer-binding protein alpha (C/EBP-α). Also, it inhibits adipocyte hypertrophy by suppressing intracellular triglyceride accumulation [85]. Furthermore, FNT treatment is found to downregulate the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ, while upregulating the secretion of anti-inflammatory cytokine IL-10 from obese WATME. This effect is achieved by inhibiting the MyD88 or TRIF/MAPK/ERK and MAPK/JNK pathways. Accordingly, the effects of FNT on obese WATME lead to weight loss, increased energy consumption, and improved lipid profile [131]. In addition, it stimulates upregulation of SIRT1 expression in the pancreas organ, resulting in a synergistic effect on the treatment of obesity-induced T2D through mitigating insulin resistance and hyperglycemia [86]. These findings demonstrate that FNT is an efficacious direct WATME-specific immunotherapy for the treatment of obesity-induced T2D.

3.1.3. Coffee silverskin (CSE) and husk (CHE)

Coffee silverskin (CSE) and husk (CHE) aqueous extracts demonstrate anti-inflammatory properties in obese WATME by inhibiting the crosstalk between M1-like macrophages and hypertrophic adipocytes. Both cells in obese WATME secrete less pro-inflammatory cytokines, like TNF-α and CCL2, because the crosstalk is suppressed through the NF-κB and JNK pathways [88]. Moreover, treatment with CSE and CHE extracts inhibit the formation of hypertrophic adipocytes in obese WATME by upregulating the expression of PPARG coactivator 1 alpha (PGC1α) and uncoupling protein 1 (UCP1) genes, which promote browning and increase thermogenesis [132]. Furthermore, these extracts directly enhance insulin sensitivity in adipocytes by stimulating the PI3K/AKT signaling pathway [88]. The promising therapeutic potential of direct WATME-specific immunotherapy for the treatment of obesity-induced T2D is demonstrated by the ability of phenolic compounds found in CSE and CHE extract to mitigate insulin resistance in obese WATME by alleviating the inflammatory responses in obese WATME.

3.1.4. Ramulus mori (Sangzhi) alkaloids (SZ-A)

Sangzhi alkaloids (SZ-A) can inhibit the formation of hypertrophic adipocytes in obese WATME by upregulating the expression of lipolysis-related enzymes such as adipose triglyceride lipase (ATGL) and hormone-sensitive triglyceride lipase (HSL) [89]. Also, SZ-A treatment inhibits the p38 MAPK, ERK, JNK, and TLR signaling pathways of M1-like macrophages, leading to an alleviation in inflammation in obese WATME. SZ-A treatment can induce improvements in the lipid profile, decreases in body weight, and reductions in levels of inflammatory biomarkers such as plasminogen activator inhibitor-1 (PAI-1), angiotensin II (Ang-II), and leptin. In addition, SZ-A treatment increases the levels of anti-inflammatory factors including IL-4, IL-10, IL-13, and adiponectin. Accordingly, SZ-A has been demonstrated to be an effective direct WATME-specific immunotherapy, leading to the amelioration of inflammation in obese WATME and the treatment of obesity-induced T2D.

3.2. WATME-specific immunotherapy for obesity-induced coronary heart disease (CHD)

Obese WATME-induced chronic systemic inflammation plays an important role in the development of obesity-induced coronary heart disease (CHD). WATME-specific immunotherapy that targets obese WATME to alleviate chronic systemic inflammation by directly affecting cells or indirectly by working on the secreted pro-inflammatory cytokines has emerged as a promising therapeutic approach for obesity-induced CHD (Table 1). Direct WATME-specific immunotherapy demonstrates efficacy in the treatment of obesity-induced CHD by targeting the inflammasome, inflammatory signaling pathways, and receptors. Conversely, indirect WATME-specific immunotherapy exhibits favorable outcomes through targeting pro-inflammatory factors, including TNF-α, proprotein convertase subtilisin/kexin type 9 (PCSK9), and apolipoprotein B100 (ApoB100) (Fig. 5).

3.2.1. Bazedoxifene

Bazedoxifene, a selective estrogen receptor modulator, has the potential to improve insulin sensitivity [133,134]. Bazedoxifene enhances insulin sensitivity and prevents abnormal lipid buildup in the liver and

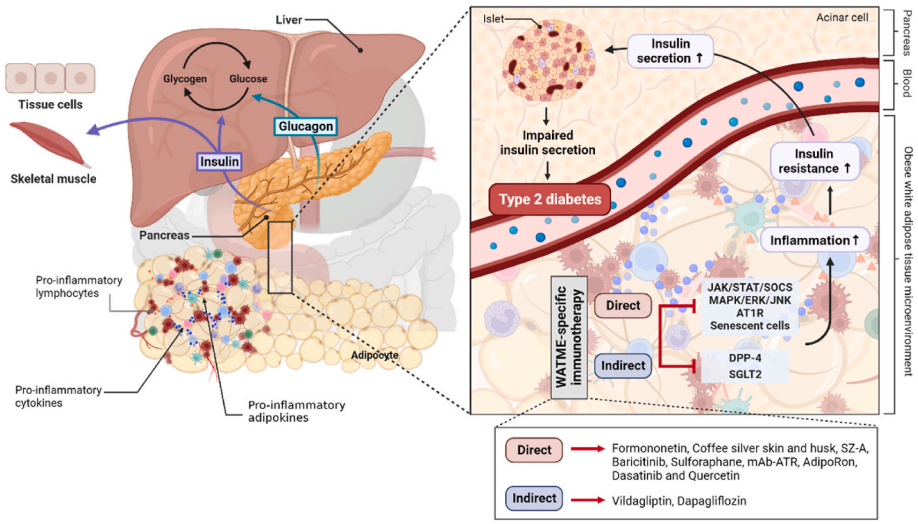

Fig. 4. Schematic diagram of WATME-specific immunotherapy for obesity-induced type 2 diabetes (T2D). Inflammation in obese WATME plays a crucial role in the development of insulin resistance which leads to the development of obesity-induced T2D. These are mediated by the inflammatory signaling pathways, enzymes, and senescent cells. Several WATME-specific immunotherapies targeting those have been discovered. Some examples of these WATME-specific immunotherapies are Sulforaphane, Formononetin, SZ-A, coffee silver skin and husk.

skeletal muscle by attaching to the estrogen receptor found on enlarged fat cells, which leads to increased fat oxidation and energy expenditure [135]. These results are achieved through the downregulation of lipogenesis-related genes such as fatty acid synthase, lipoprotein lipase, acetyl-coenzyme A (CoA) carboxylate-α and -β, stearoyl-CoA desaturase, fatty acid desaturase and PPAR-γ [136]. Additionally, a recent investigation reveals that Bazedoxifene inhibits the IL-6/IL-6R/STAT3 signaling pathway in obese WATME, hence disrupting the progression of atherosclerosis in HFD-induced mouse models [137]. It is worth mentioning that Bazedoxifene treatment significantly reduces the concentrations of IL-6 and TNF-α as well as the atherosclerotic plaque. Therefore, Bazedoxifene as direct WATME-specific immunotherapy demonstrates significant therapeutic potential in treating obesity-induced CHD.

3.2.2. *Etanercept (Enbrel®)*

Etanercept is a biologically engineered human soluble TNF-α receptor protein that efficiently inhibits the action of TNF-α [138]. Administering Etanercept through subcutaneous injection in a model of diet-induced obesity (DIO) rats effectively alleviates cardiac fibrosis [112]. This is accomplished by inhibiting the activation of JAK/STAT3, a crucial signaling pathway in fibrosis, which is stimulated by TNF-α in obese WATME [139]. Also, Etanercept inhibits the upregulation of the secretion of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and NF-kB from obese WATME in high-fat diet (HFD)-fed rodents [140]. Therefore, the alleviation of inflammation in obese WATME through the suppression of TNF-α by Etanercept demonstrates the effectiveness of indirect WATME-specific immunotherapy for treating obesity-induced CHD.

3.3. *WATME-specific immunotherapy for obesity-induced breast cancer (BC)*

It has become increasingly evident that inflammation in obese WATME plays a crucial role in the progression and metastasis of obesity-induced breast cancer (BC). Obese WATME secretes pro-inflammatory cytokines, including IL-6 and TNF-α, which have significant implications in the development, advancement, and metastasis of obesity-induced BC. WATME-specific immunotherapy that aims to mitigate inflammatory responses in obese WATME through targeting inflammatory signaling pathways (NF-κB and STAT) and pro-inflammatory factors (IL-8 and CCL2) has emerged as a potentially effective therapeutic approach in the treatment of obesity-induced BC (Fig. 6). WATME-specific immunotherapy has made notable advancements in the treatment of obesity-induced BC (Table 1).

3.3.1. *Niclosamide*

Niclosamide, an anthelminthic drug approved by the FDA, inhibits the epithelial-mesenchymal transition (EMT) induced by adipocytes, thereby exerting its anti-breast cancer effects [141]. STAT3 is activated in the tumor microenvironment in response to increased IL-6 secretion. This process contributes to the formation of tumors by regulating important genes that are crucial for apoptosis, survival, proliferation, and metastasis. Therefore, therapeutic approaches encompass the inhibition of the IL-6/STAT3 signaling pathway and STAT3 phosphorylation in breast cancer cells, such as Niclosamide can inhibit the adipocyte-induced EMT [142]. Also, it inhibits adipogenesis of pre-adipocytes present in obese WATME through stimulating AMPK, leading to an elevation in fat oxidation and inhibition of adipocyte hypertrophy [143]. Niclosamide, as a direct WATME-specific immunotherapy, has the potential to effectively treat obesity-induced BC by suppressing EMT and inhibiting the formation of hypertrophic adipocytes.

3.3.2. *BZ26*

BZ26, a specific antagonist of PPAR-γ, reduces the proliferation and invasion of obesity-induced BC by inhibiting the transformation of mature adipocytes into cancer-associated adipocyte (CAA) cells [144]. Delipidated and reprogramed CAAs secrete an excess of inflammatory cytokines and proteases to promote tumor survival and growth, thereby fostering an environment that enhances the invasiveness and hostility of cancer cells. Mature adipocytes in HFD-fed mice exhibit the same phenotype as an intriguing CAA [145]. However, PPAR-β inhibition of BZ26 can prevent the differentiation of mature adipocytes into CAAs, thus impeding the progression of obesity-induced breast cancer as well as their metastasis. Also, BZ26 can significantly decrease the levels of inflammatory factors such as IL-1β, IL-6, and CCL2, as well as an inhibition of NF-κB activity. These effects collectively diminish the inflammatory response in obese WATME [146]. In addition, BZ26 has a regulatory effect on the browning of WAT via alterations in PPAR-γ activity. When BZ26 is administered to HFD-fed rodents, brown adipose-related genes (PPARα, Cidea, and Otop1) are gradually

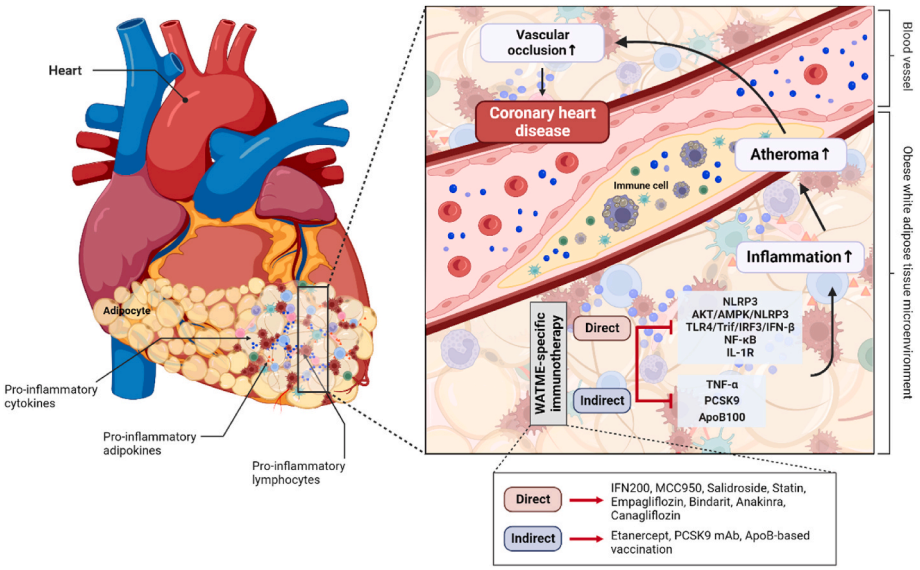

Fig. 5. Schematic diagram of WATME-specific immunotherapy for obesity-induced coronary heart disease (CHD). Obesity is associated with increased secretion of pro-inflammatory cytokines, especially IL-1β, TNF-α, and IL-6, by obese WATME. There is established evidence linking these cytokines to the occurrence of atherosclerosis. Several WATME-specific immunotherapies have been identified for the treatment of atherosclerosis-mediated development of obesity-induced CHD. These WATME-specific immunotherapies target the NLRP3 inflammasome, TNF-α, and inflammatory signaling pathways. Some examples are Bazedoxifene and Etanercept.

upregulated. Therefore, BZ26 demonstrates the therapeutic efficacy of direct WATME-specific immunotherapy for obesity-induced BC.

4. Clinical trials employing WATME-specific immunotherapy for obesity-induced NCDs

Clinical applications of WATME-specific immunotherapy have not yet been explored extensively despite the encouraging outcomes observed in the animal models (Table 2). Numerous clinical trials investigating obesity-induced NCDs do not consider the interrelationship between obesity, inflammation, and those diseases. These are clear from the fact that many of these trials only simply evaluate the pathological condition of the diseases and do not incorporate adiposity measurement or assessment of inflammatory biomarkers. Consequently, our approach is to focus on clinical trials that provide substantial evidence of the efficacy of WATME-specific immunotherapy when treating obesity-induced T2D, CHD, and BC. Also, the efficacy of WATME-specific immunotherapy in treating multiple obesity-induced NCDs is investigated.

4.1. Type 2 diabetes (T2D)

NCT02964572 trial demonstrates that direct WATME-specific immunotherapy shows a positive outcome in the treatment of T2D in humans [147]. Empagliflozin, a sodium-glucose transport protein 2 (SGLT2) inhibitor, is administered to 29 T2D patients for 60 days. This treatment leads to an improvement in insulin sensitivity, as evidenced by a decrease in fasting serum insulin levels and a reduction in the

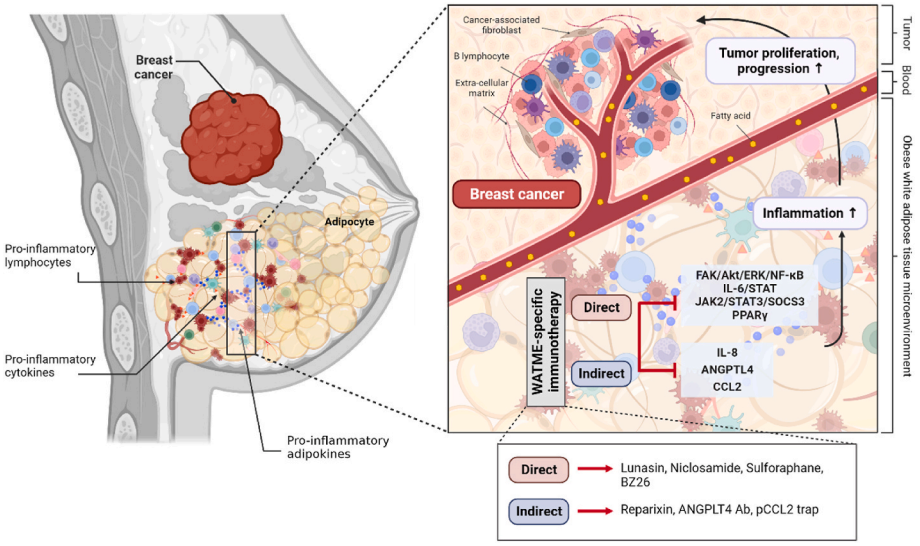

Fig. 6. Schematic diagram of WATME-specific immunotherapy for obesity-induced breast cancer (BC). Obese WATME secretes pro-inflammatory cytokines, such as IL-6, IL-1β, and TNFα, which contribute to the progression, metastasis, and development of obesity-induced BC through distinct cellular mechanisms. Niclosamide and BZ26 are examples of WATME-specific immunotherapies that have demonstrated efficacy in the treatment of obesity-induced BC.

Table 2
Clinical trials employing WATME-specific immunotherapy.

Disease	NCT number	Drug	Phase	Summary	Ref.
T2D	NCT02964572	Empagliflozin	N.A.	- Inhibition of SGLT2 → NLRP3, IL-1β ↓ - Participant: 29/61 - AE: 2 (6.9 %) - Discontinued due to AE: 1 (3.45 %) - HOMA-IR: −0.8, P < 0.001 - Body weight: −2.5 %, P < 0.001 - Serum IL-1β: −0.03 pg/ml, P = 0.29 - Serum IL-18: −1.6 pg/ml, P = 0.57	[147]
CHD	NCT01327846	Canakinumab	3	- IL-1β human mAb → inflammation ↓ - Group: 50mg/150mg/300mg/placebo - Participant: 2144/2252/2235/3311 - AE: 1872/1970/1987/2915 - Serious AE: 741/812/836/1204 - Discontinued due to AE: 254/304/308/446 - HR of revascularization: 0.72/0.68/0.70/1.00 - HR of ASCVD death: 0.80/0.88/0.93/1.00 - hsCRP: −47.5 %/-57.1 %/-62.8 %/-18.4 % - IL-6: −19.1 %/-33.8 %/-37.7 %/+3.49 % - LDL: +1.53 %/+0.81 %/0.00 %/0.00 % - HDL: +1.06 %/+2.67 %/+2.75 %/0.00 %	[148]
BC	NCT06150898	Ketorolac	2	- Estimated completion date: 2026-12 - Inhibition of COX-2 → inflammation ↓ - Group: Control/Ketorolac/Pregabalin/Ketorolac and Pregabalin - Estimated participant: 28/28/28/28	[150]
CHD, T2D	NCT01131676	Empagliflozin	3	- Inhibition of SGLT2 - Group: 10mg/25mg/placebo - Participant: 1790/1800/1650 - AE: 1556/1551/1690 - Serious AE: 876/913/988 - Discontinued due to AE: 416/397/453 - Body weight: −2.5kg/-3kg/-1.5 kg - HbA1c: −0.24 %/-0.36 %/0.00 % - HR of revascularization: 0.81/0.92/1.00 - HR of ASCVD death: 0.65/0.59/1.00	[149]

N.A: Not applicable, AE: adverse event, HR: hazard ratio.

homeostasis model assessment-IR (HOMA-IR) index. In comparison, 32 patients with T2D who receive sulfonylurea do not experience the same improvements. Although administered systemically, Empagliflozin effectively targets obese WATME, as evidenced by the weight loss observed in the Empagliflozin group. Empagliflozin is found to improve the inflammation in obese WATME by suppressing the NLR family pyrin domain containing 3 (NLRP3) inflammasome, hence reducing the secretion of IL-1β and IL-18 from obese WATME. Although the decrease in circulating cytokine levels in the Empagliflozin-treated group does not reach statistical significance, it can significantly inhibit IL-1β secretion by primary macrophages isolated from the group exposed to the NLRP3 inflammasome agonist.

4.2. Coronary heart disease (CHD)

The Canakinumab anti-inflammatory thrombosis outcome study (CANTOS) trial (NCT01327846) demonstrates the efficacy of indirect WATME-specific immunotherapy in the treatment of atherosclerosis [148]. In this trial, patients diagnosed with CHD and experiencing a prior myocardial infarction receive a therapeutic intervention with subcutaneous administration of Canakinumab, a completely humanized monoclonal antibody (mAb) that specifically targets IL-1β. The purpose of this trial is to evaluate the efficacy of Canakinumab in reducing the incidence of revascularization due to atherosclerosis compared with placebo. As a result, when Canakinumab is administered at all doses, the annual incidence of revascularization per 100 people is 2.53, which is significantly reduced compared to 3.61 in the placebo group. Additionally, IL-1β inhibition leads to a decrease in the levels of inflammatory biomarkers in all groups receiving Canakinumab. Higher doses of Canakinumab result in greater reductions in high-sensitivity C-reactive protein (hsCRP) and IL-6 levels. The impact of canakinumab on obese WATME can be observed through an improvement in the lipid profile, characterized by a greater increase in high-density lipoprotein (HDL) levels compared to low-density lipoprotein (LDL) levels.

4.3. Breast cancer (BC)

Results from the upcoming NCT06150898 trial are anticipated to provide valuable insights into the effectiveness of direct WATME-specific immunotherapy as a potential treatment for breast cancer. Ketorolac, a non-steroidal anti-inflammatory drug (NSAID) that inhibits the cyclooxygenase-2 (COX-2) enzyme, will be administered orally to 28 breast cancer patients (14 of them being obese) five days before their surgery. The primary objective of this trial is to evaluate the potential effectiveness of ketorolac in lowering systemic inflammation, metastasis-related biomarkers, and immune cell recruitment in BC. Furthermore, the effect of Ketorolac on obese WATME can be evaluated by assessing adiposity measurement, including body mass index, fat percentage, and waist-to-hip ratio, regardless of the systemic administration of Ketorolac.

4.4. WATME-specific immunotherapy for multiple obesity-induced NCDs

Empagliflozin can be used as a multi-target WATME-specific immunotherapy in the treatment of patients with T2D and high risk of atherosclerotic cardiovascular disease (ASCVD) [149]. NCT01131676 trial shows that oral Empagliflozin is effective in reducing the risk of ASCVD outcomes and ASCVD mortality compared with placebo. Empagliflozin can reduce the incidence rate of 3-point major adverse cardiovascular events (3-point MACE) per 1000 patients-years by 6.5 %. Furthermore, all dosages of Empagliflozin can reduce glycosylated hemoglobin (HbA1c) levels, which may be due to the improved insulin sensitivity. The effect of Empagliflozin on obese WATME can be observed through greater weight loss in the Empagliflozin groups

compared to the placebo group. Although this trial does not evaluate the effect of Empagliflozin on alleviating inflammatory responses, recent evidence from the NCT02964572 trial can support the effectiveness of Empagliflozin in the treatment of both CHD and T2D due to its ability to alleviate the inflammation in obese WATME.

5. Challenges

The employment of WATME-specific immunotherapy for treating obesity-induced NCDs is a relatively new and developing field. Recent studies have demonstrated the promising therapeutic potential of WATME-specific immunotherapy for obesity-induced T2D, CHD, and BC. However, the efficacy of WATME-specific immunotherapy is impacted by immunological toxicities, which involve multiple organs and exhibit variability [151]. Although WATME-specific immunotherapy targets specific cytokines, inappropriate inhibition of cytokines can disrupt essential immune responses, thereby elevating the susceptibility to infection or exacerbating certain diseases such as cancers, skin lesions, and influenza-like symptoms (e.g., shivering, fever, headache, lethargy, anorexia, nausea, and vomiting) [152,153]. Also, more than 30 % of patients treated with immunotherapy suffer from skin toxicities such as rash and mucositis [154]. Moreover, cytokine inhibition can result in unforeseen consequences on the immune system, including the induction of autoimmune responses or immune deficiencies [155]. As immunotherapy causes a significant number of adverse events, it has been essential to continuously improve treatment approaches to reduce the incidence of adverse effects and optimize treatment effectiveness. Immunomodulators have often been used alongside immunotherapy to mitigate these adverse effects. Immunomodulators alter the immune system to enhance the functionality of the immune response to treat diseases [156]. Additionally, the severity of side effects and the suitability of immunotherapy may vary from person to person. To adapt immunotherapy to the distinctive features of everyone, personalized immunotherapy can be employed by exploiting sequencing technology, metagenomics, and metabolomics [157–159].

Although WATME-specific immunotherapy is witnessing a tremendous pace in the testing and approval of new medicines along with the continuous discovery of innovative strategies to effectively engage the immune system [160,161], WATME-specific immunotherapy is still in its early stage with limited clinical evidence supporting safety, efficacy, and long-term benefits. Therefore, it is essential to increase understanding and knowledge about the clinical manifestations, diagnostic approaches, and treatment strategies used to manage the adverse effects of WATME-specific immunotherapy. Also, designing clinical trials for WATME-specific immunotherapy presents a unique set of challenges, including selecting appropriate endpoints, accurately defining response criteria, and carefully considering the inherent variability within patient populations.

6. Perspectives

Traditional obesity treatment generally consists of a variety of treatments aimed at preventing, maintaining, or treating obesity through lifestyle changes, behavioral adjustments, medicines, or surgical procedures [162]. However, obesity is a complicated condition with numerous causes and variables contributing to its development. Moreover, the immune system plays important role in regulating metabolism, inflammation, and fat accumulation in obesity [163]. As previously shown, many epidemiological investigations have demonstrated a strong association between obese WATME and the development of non-communicable diseases (NCDs), including type 2 diabetes, coronary heart disease, and breast cancer. As a result, WATME-specific immunotherapy is a premised therapeutic approach for obesity-induced NCDs through alleviating inflammation in obese WATME by targeting cells, signaling pathways, and secreted cytokines.

Studies of pharmacotherapy for obesity-induced NCD have provided valuable insights into successful immunotherapy. Moreover, obesity and obesity-induced NCDs may be treated concurrently through a synergistic effect when pharmacotherapy and WATME-specific immunotherapy are combined. Concurrent administration of pharmacotherapy aimed at regulating appetite, adipogenesis, or fat metabolism, as well as immunotherapy that specifically targets pathways or cells implicated in inflammation or metabolic dysregulation associated with obesity, could be performed [164]. Integrating immunotherapy and pharmaceuticals in the management of obesity addresses multiple aspects of the condition, including metabolic dysregulation, inflammation, adipose tissue function, and potential obesity-related comorbidities that are affected by obesity-related inflammation.

In addition to NCDs, obesity also affects various metabolic processes in the liver. It is associated with the progression of various liver diseases, including alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) as well as the development of associated inflammation and steatosis [165]. Chronic liver disease is often attributed to NAFLD, which has also become a major cause of hepatocellular carcinoma (HCC) with the highest growth rate [166]. The development of NAFLD includes the accumulation of TG in the liver [167]. Obesity-related insulin resistance compromises adipose tissue fat storage, resulting in an accumulation of FFAs in the liver and the development of obese liver [168]. Hypoxia induced by the obese liver results in the apoptosis of adipocytes, an augmentation of M1-like macrophages infiltration, and the secretion of pro-inflammatory cytokines, including TNF-α, IL-6, and CCL2 [169]. These pro-inflammatory cytokines induce activation of inflammatory pathways such as NF-κB and JAK/STAT, thereby expediting the progression of liver injury and the disease [170].

In some pharmacotherapies, therapeutic agents that improve insulin sensitivity, including thiazolidinediones (TZDs) such as pioglitazone, have been applied to treat NAFLD [171]. Additionally, bile acid regulation drugs such as obeticholic acid (OCA) and farnesoid X receptor (FXR) agonists have been investigated together with glucagon-like peptide-1 (GLP-1) receptor agonists [172]. Although a variety of treatment options exist, efficacy endpoints may not always be appropriate for the treatment of this multisystem disease affecting multiple extrahepatic organs and diseases. Also, despite the high global prevalence and detrimental effects of NAFLD on life expectancy, there is currently no licensed pharmacotherapy for this liver disease. Therefore, given the intricate and diverse nature of these diseases, the primary goal should be to develop a treatment that efficiently targets distinct aspects of the disease. We suggest that this can be achieved through the design of WATME-specific immunotherapies that can specifically target inflammatory cytokines, cells, or pathways associated with obese WATME, as we have done in this review.

7. Conclusion

Obesity, which is a prevalent condition in modern society, can be recognized as a chronic systemic inflammatory disease that may give rise to the development of NCDs. The increase in the prevalence of obesity has greatly increased vulnerability to NCDs around the world. As an important connection between obesity and NCDs, the perception of inflammation of obese WATME is a survivable treatment approach to obesity-induced NCDs, thereby opening the door for the exploration of WATME-specific immunotherapy. Considering the remarkable progress achieved in WATME-specific immunotherapy, other areas require additional investigation and development.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must include a statement on ethics approval: Not applicable.

Studies involving animals must include a statement on ethics approval: Not applicable.

CRediT authorship contribution statement

Lia Priscilla: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Chaerim Yoo:** Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Seonmi Jang:** Formal analysis, Visualization, Writing – original draft. **Sewon Park:** Formal analysis, Visualization, Writing – original draft. **Gayoung Lim:** Formal analysis, Visualization, Writing – original draft. **Taekyun Kim:** Formal analysis, Visualization, Writing – original draft. **Dong Yun Lee:** Conceptualization, Formal analysis, Funding acquisition, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing – review & editing.

Declaration of competing interest

D.Y.L. is CEO & Funder of Elixir Pharmatech Inc., no of whom contributed or was involved in this research. All other authors declare no conflict of interest.

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