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Review Article

Leptin Signaling and Its Relationship with Obesity-induced Insulin Resistance: A Bioinformatics-assisted Review

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Abstract

Obesity has become a global epidemic affecting diverse populations and leading to metabolic syndrome across different sexes and age groups. A significant aspect of obesity is the development of leptin resistance, primarily due to the inefficient transport of leptin across the blood-brain barrier and other mechanisms such as protein folding and dysregulation of leptin signaling in brain areas related to energy and adipose tissue metabolism. This hindrance in leptin delivery poses a challenge to using this adipokine as a potential therapy for obesity. Current research focuses on understanding the complex molecular pathways that link diet-induced obesity, characterized by increased levels of leptin, to the onset of metabolic syndrome. This syndrome encompasses various health issues, including type 2 diabetes mellitus, and involves intricate mechanisms primarily affecting pancreatic β-cells. This bioinformatics-assisted review describes key biological elements of known pathways, such as the forkhead box protein O1/leptin receptor and Janus kinase/signal transducer and activator of transcription 3, and discusses future directions that might contribute to understanding the relationship between obesity, leptin resistance, and metabolic complications (e.g., Rac1/cell division control protein 42 homolog), paving the way for future research on targeted therapeutic interventions.

Introduction

Obesity is recognized by the World Health Organization as the pandemic of the 21st century.[1] It is characterized by the excessive accumulation and dysfunction of adipose tissue, as well as systemic-grade inflammation with potentially negative health outcomes. This dysfunction involves imbalanced adipokine secretion and disrupted cellular communication mediated by extracellular vesicles like exosomes.[2] Continuous deviation of biological parameters (infra- or supraphysiological responses) due to prolonged stressors leads to wear and tear on the regulatory systems. This burden, or cost of adaptation, reflects the prevalence of the allostatic state, commonly known as allostatic load. If the over-activation of allostatic responses persists over time, it can result in illness and become life-threatening, a condition referred to as allostatic overload.[3] This leads to the onset and development of chronic diseases and increases mortality risk. In the context of this article, these disruptions detrimentally affect metabolic equilibrium and are closely tied to metabolic diseases, including chronic inflammation, insulin resistance (IR), lipid overload, organelle stress, and subsequent modulation of gene expression. Consequently, obesity increases susceptibility to cardiovascular diseases, type 2 diabetes mellitus (T2DM), chronic kidney disease, and various cancers.[4–7] Adipose tissue releases adipokines such as tumor necrosis factor-alpha, which drives cellular and systemic inflammation, and leptin, which regulates appetite and sympathetic nervous activity. Paradoxically, obese individuals exhibit leptin resistance, possibly due

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to blood-brain barrier (BBB) saturation, rendering exogenous leptin administration ineffective in treating obesity.[8]

Preliminary data show that reduced sensitivity to leptin leads to diet-induced obesity.[9] Hyperleptinemia serves as a marker of leptin resistance (LR); however, the precise diagnosis or explanation of LR remains elusive.[10] Despite this, LR is closely associated with obesity and is directly correlated with the amount of adipose tissue an individual possesses.[11] This, in turn, influences the development of metabolic diseases, whose pathophysiology converges in obesity and IR.[12,13] Thus, there is a correlation between genetics, dietary habits, and leptin deficiency in metabolic syndrome (MS).[14] This review aimed to discuss the intricate molecular relationships between leptin, obesity, and IR.

Procedure of the review

Protocol and registration

This bioinformatics-assisted review was conducted and reported according to previously published procedures.[15,16] The study is part of "The Project ATA", a multicenter study developed by the DBSS Research Division (ClinicalTrials.gov ID NCT05758311) in cooperation with several universities and research centers across America and Europe. Procedures were published and made freely available to avoid unnecessary duplication.[17]

Search strategy and information sources

The PubMed/MEDLINE, ScienceDirect, and Google Scholar databases were searched using the keywords "leptin", "insulin resistance", and "obesity".

Manual curation and bioinformatics-assisted review

The bioinformatics-assisted review addresses the lack of systematization in reviews that aimed at updating and/or analyzing phenomena at the molecular level. To overcome the subjective and time-consuming manual extraction of information, this approach utilizes experimentally validated, high-level, manually curated, and reproducible data (open-source bioinformatics tools). The prioritization of biological elements was based on pathways and the regulation of leptin metabolism and signaling. In this study, several public databases and repositories were accessed to retrieve manually curated biological information, including UniProtKB (https://www.uniprot.org/),[18] PDB (https://www.rcsb.org/),[19] Ensembl (https://www.ensembl.org/index.html),[20] Gene Ontology Resource (http://geneontology.org/),[21] The Human Protein Atlas (https://www.proteinatlas.org/),[22] and BioGPS–Gene Portal System (http://biogps.org/).[23] Readers may refer to our recent article for a selection of widely used online bioinformatics databases and an accompanying website that includes additional information (https://sites.google.com/view/compgenomtools/).[24]

Findings presentation

The functional annotations were discussed within the literature review and expert clinical interpretation as follows: i) Obesity, leptin resistance, and metabolic syndrome; ii) Relevant molecular mechanisms of leptin resistance; iii) Convergence of molecular pathways between leptin and insulin resistance; and iv) Conclusions.

Obesity, leptin resistance, and metabolic syndrome

MS comprises a group of conditions that collectively increase the risk of cardiovascular diseases and T2DM.[25] In 2009, the International Diabetes Federation, in partnership with the American Heart Association and the National Heart, Lung, and Blood Institute, established the criteria for diagnosing MS. These criteria include abdominal girth (based on population/regional cut-off points), low levels of high-density lipoprotein cholesterol, elevated fasting glucose, elevated triglycerides, and increased blood pressure. A diagnosis requires the presence of at least three out of these five components, providing a comprehensive framework for identifying individuals at risk.[26]

Obesity emerges as a significant precursor to MS, resulting from complex interactions among genetic, behavioral, and environmental factors.[27] Unhealthy lifestyle habits, such as inadequate sleep, physical inactivity, and excessive food intake, contribute to weight gain,[28] leading to increased blood leptin levels. This elevation prompts IR, which aligns with oxidative stress and mitochondrial dysfunction, both central to the pathophysiology of T2DM.[29]

It is now clear that obesity contributes to MS, further exacerbated by LR.[30] Hyperleptinemia, which serves as a biomarker, is associated with MS due to the abundance of leptin receptors (LEPR, also known as OB-R) in pancreatic tissue. Dysfunction of these receptors can lead to diabetes.[31] Moreover, hyperleptinemia has been associated with various cardiac diseases, hypertension, and stroke, thereby exacerbating MS.[32] Although limited evidence initially reported promising results,[33,34] the treatment with exogenous leptin for weight management has proven ineffective.[35,36] Currently, the use of glucagon-like peptide-1 receptor agonists, such as Wegovy®, is a clinical option approved by the U.S. Food and Drug Administration, but further research is warranted to confirm its utility and identify side effects.[37] Available data suggest that increased visceral fat, rather than obesity *per se*, induces MS by triggering cytokine release from macrophages, activating inflammatory signaling cascades, and causing the accumulation of reactive oxygen species (ROS) resulting from endoplasmic reticulum (ER) dysfunction.[4,38,39] Interestingly, several studies have demonstrated positive results for MS management through physical activity, emphasizing exercise as a form of medicine.[40–42]

Relevant molecular mechanisms of leptin resistance

Table 1 summarizes the characteristics and expression patterns of all proteins discussed in this bioinformatics-assisted review for functional annotation and cross-referencing.

LR is depicted as a self-perpetuating cycle in which elevated leptin levels in the bloodstream contribute to heightened resistance, while an adequate amount of leptin is essential for its role as an anorexigenic hormone. In certain instances, diet-induced obesity is initiated by preexisting reductions in leptin sensitivity.[9] The secretion of adipokines, such as leptin, induces hyperleptinemia in the central nervous system, leading to insensitivity to LEPR, which favors LR and consequently promotes further obesity.[9,43]

Various underlying mechanisms of central and peripheral LR are known. Dysregulation of signaling in the hypothalamus can result from different causes, such as genetic mutations affecting not only the receptors but also protein complexes and secondary messengers, disrupting proper leptin signaling. For example, the SEL1L-HRD1 complex specific to proopiomelanocortin (POMC) neurons can trap LEPR in the ER by affecting its folding and maturation.[44] Additionally, increases in blood leptin concentration may

Table 1. Functional annotation of the prioritized proteins

Protein name	Gene name	Ensembl ID†	Gene location	Uni-ProtKB	Subunit structure	PDB entry or AlphaFold ID	Cellular location	Expression*	ID BioGPS
Leptin	*LEP*	ENSG00000174697	Chromosome 7: 128,241,278-128,257,629 forward strand	P41159	Monomer	1AX8	Cytosol, extracellular region, and extracellular space	Adipose tissue	LEP-3952
Tumor necrosis factor (TNF-α)	*TNF*	ENSG00000232810	Chromosome 6: 31,575,565-31,578,336 forward strand	P01375	Dimer of identical or non-identical chains	1TNF	Cell surface, external side of the plasma membrane, extracellular region, extracellular space, membrane raft, neuronal cell body, phagocytic cup, plasma membrane, recycling, and endosome	Mainly immune system and bone barrow	TNF-7124
Cell division control protein 42 homolog (rho GTPase Cdc42)	*CDC42*	ENSG00000070831	Chromosome 1: 22,052,627-22,101,360 forward strand	P60953	Dimer of identical or non-identical chains	1AJE	Centrosome, cytoplasm, cytoplasmic ribonucleoprotein granule, cytosol, dendritic spine, endoplasmic reticulum membrane, filopodium, focal adhesion, Golgi membrane, Golgi transport complex, mitotic spindle neuron projection, neuronal cell body, phagocytic vesicle, plasma membrane, and spindle midzone	Bone marrow, brain, and adipose tissue, among several others	CDC42-998
Tyrosine-protein kinase JAK2 (janus kinase 2)	*JAK2*	ENSG00000096968	Chromosome 9: 4,984,390-5,129,948 forward strand	O60674	Dimer of identical or non-identical chains	4BBE	Caveola, cytoplasm, cytoskeleton, cytosol, endosome lumen, extrinsic component of the plasma membrane, focal adhesion, nucleus, nucleoplasm, and plasma membrane	Mainly adipose tissue, but also in, bone marrow, immune system, brain, and hematopoietic tissues, among several others	JAK2-3717
Signal transducer and activator of transcription 3 (STAT3)	*STAT3*	ENSG00000168610	Chromosome 17: 42,313,324-42,388,568 reverse strand	P40763	Dimer of identical or non-identical chains	6TLC	Cytoplasm, cytosol, nucleus, nucleoplasm, and plasma membrane	Mainly liver and lung, but also in the immune system, and hematopoietic tissues, among several others	STAT3-6774
Forkhead box protein O1 (FoxO1)	*FOXO1*	ENSG00000150907	Chromosome 13: 40,555,667-40,666,641 reverse strand	Q12778	Monomer	6QVW	Cytoplasm, cytosol, mitochondrion, nucleoplasm, and nucleus	Mainly immune system and adipose tissue, but also in the ovary, thyroid, adipocyte, among several others	FoxO1-2308
Leptin receptor (LEPR)	*LEPR*	ENSG00000116678	Chromosome 1: 65,420,652-65,641,559 forward strand	P48357	3V6O	Dimer of identical or non-identical chains	The basolateral plasma membrane, external side of the plasma membrane, and extracellular region	Mainly liver and brain, but also in adipose tissue, among several others	LEPR-3953
Suppressor of cytokine signaling (SOCS3)	*SOCS3*	ENSG00000184557	Chromosome 17: 78,356,778-78,360,077 reverse strand	O14543	AF-O14543-F1	Monomer	Cytoplasmic side of plasma membrane and cytosol	Mainly adipose tissue and skeletal muscle but also in the liver, among several others.	SOCS3-9021

Information retrieved from PDB, Ensembl, UniProtKB, and the Gene Ontology databases. *For more details on how expression varies in different tissues or under pathological conditions, see the Human Protein Atlas (https://www.proteinatlas.org/) and BioGPS (http://biogps.org/). †Databases/repositories were accessed on January 22, 2024.

trigger downregulation and desensitization through the degradation of LEPR.[8] Indeed, the primary determinant of LR is impaired responsiveness or reduced sensitivity of the brain to leptin, which is attributed to altered function in BBB transport mediated by short isoforms of LEPR (i.e., LEPR-a, LEPR-b, LEPR-c). These isoforms are involved in the cerebral uptake of leptin, mainly in brain areas related to energy and adipose tissue metabolism, thereby contributing to the development of obesity.[45] Elevated blood triglyceride levels from the diet may also influence the low permeability of the BBB, hindering proper leptin transport to the brain and thus impeding its anorexigenic effect.[46,47] However, leptin transport to the brain can be modulated. Evidence shows that high dietary salt intake and fasting can induce obesity by promoting hyperphagia and endogenous fructose production, which in turn trigger LR.[48] Although LR via the BBB is widely acknowledged, Harrison *et al*.[49] demonstrated through fluorescence labeling of leptin in obese rats that leptin passage through the BBB remains intact.

Upon binding to LEPR, leptin initiates a signaling cascade by activating the Janus kinase (JAK) 2 tyrosine kinase family, leading to physical interaction with Rho-kinase 1. This interaction promotes the phosphorylation of tyrosine residues Y985, Y1077, and Y1138.[50] Subsequently, tyrosine Y1138 binds to the Src homology 2 domain of signal transducer and activator of transcription (STAT) 3, initiating STAT3 phosphorylation. This phosphorylation induces the dimerization of STAT3 and STAT5, facilitating their translocation to the nucleus, where they act as gene regulators for neuropeptides such as POMC, agouti-related protein, and neuropeptide Y. Furthermore, to regulate LEPR signaling, STAT3 phosphorylation establishes a negative feedback mechanism by promoting the transcription of suppressor of cytokine signaling 3.[50]

The presence of LR in obese individuals can also be attributed to other factors, including the direct inhibition of leptin binding to its receptors by C-reactive protein. This phenomenon is directly correlated with increased leptin bioavailability in obese individuals, leading to heightened C-reactive protein binding to LEPR at multiple sites, thereby modifying the pleiotropic effects of leptin.[6–16,18–29] Additionally, overexpression of cytosolic suppressor of cytokine signaling 3 may block the downstream signaling pathway of LEPR, potentially induced by obesity-induced hyperleptinemia.[51,52] In LR, ER stress also affects leptin signaling, blocking the JAK2/STAT3 pathway triggered by leptin present in POMC neurons, potentially contributing to metabolic disturbances in the peripheral tissues of obese phenotypes (Fig. 1a).[53,54]

Convergence of molecular pathways between leptin and insulin resistance

LEPR proteins are localized in pancreatic β cells, where leptin directly influences insulin gene expression, leading to a reduction in insulin secretion. This inhibitory effect operates through various pathways, including the blockade of glucose transport, reorganization of the actin cytoskeleton, and activation of phosphodiesterase 3B via the phosphatidylinositol 3-kinase pathway. The activation of phosphodiesterase 3B results in decreased cAMP levels, which affects the protein kinase A pathway, a crucial regulator of calcium channels and exocytosis. These intricate mechanisms collectively limit insulin release.[31] However, recent studies by Zhang *et al*.[55] have revealed a novel aspect of this regulatory network. *In vitro* experiments conducted on pancreatic β-cells (INS-1E) demonstrated that tumor necrosis factor-alpha, in conjunction with leptin, reduces the phosphorylation level of forkhead box protein O1 (FoxO1). FoxO1 is a pivotal player in insulin regulation and may function as a transcriptional regulator of *LEPR* expression. This regulatory action affects insulin stimulation by glucose and promotes hyperinsulinemia (Fig. 2).[56]

In the brain, elevated levels of circulating leptin can lead to dysregulation by overactivation of the LEPR receptor, inducing ER stress and generating high levels of ROS.[53] This surge in ROS may, in turn, trigger overactivation of the GTPase cell division control protein 42 homolog (Cdc42). Recent studies have linked dysregulation of the Rho GTPase Cdc42 to various diseases, including cancer and IR. Under physiological conditions, Cdc42 toggles between its inactive GDP-bound form and its active GTP-bound form, regulating signaling pathways involved in cellular functions such as cell morphology, cell cycle control, actin cytoskeleton dynamics, vesicle trafficking, and cell polarity.[57] Additionally, Cdc42 participates in the second phase of glucose-stimulated insulin secretion in the pancreas via the serine/threonine-protein kinase PAK 1/RAF proto-oncogene serine/threonine-protein kinase, Mitogen-activated protein kinase kinase 1/extracellular signal-regulated kinase (MEK/ERK) axis,[58,59] potentially enhancing insulin expression through ERK1/2-mediated promotion of NeuroD1 nuclear translocation.[60] In this bioinformatics-assisted review, a plausible molecular pathway is suggested whereby ROS-induced activation of Cdc42, in conjunction with Rac1 protein, initiates inflammatory signaling pathways, particularly RAC-alpha serine/threonine-protein kinase (Akt), and serine/threonine-protein kinase PAK 1/mitogen-activated protein kinases (MAPKs) such as ERK1/2, MAPK 8 (JNK), and p38 MAPK. Upon activation, LEP/LEPR signaling upregulates 72 kDa type IV collagenase (*MMP2)* expression through the activation of JNK within the MAPK pathway mediated by Cdc42. This dysregulation inhibits LEPR's signal transduction ability by cleaving its extracellular domain via MMP2.[61] This potential signaling pathway provides insights into the impact of adipokines originating from adipose tissue on pancreatic β cells, offering a possible explanation for the development of T2DM. However, experimental validation of this proposed pathway is required. Xie *et al*.[62] observed activation of pMEK, pERK, pSTAT3, Rac1/Cdc42, pFAK, and vinculin in Sca-1+ progenitor cells. Additional research in neuronal cells is warranted to elucidate other molecular pathways (Fig. 1b).

Conclusions

Obesity, a widespread condition affecting individuals across diverse demographics, primarily results from an imbalance between calorie intake and energy expenditure. However, its development is multifactorial, involving complex interactions between genetic predisposition, environmental factors, and lifestyle habits. In this bioinformatics-assisted review, we summarize the close relationship between obesity and metabolic disorders, with IR serving as an early indicator of potential MS. This link operates through complex molecular pathways, prominently featuring FoxO1/LEPR and JAK/STAT3 signaling, and possibly involving Cdc42. Nevertheless, a comprehensive understanding of LR requires further experimental validation to uncover the intricately associated molecular pathways. Such insights are crucial for devising novel therapeutic strategies for obesity management, such as glucagon-like peptide-1 receptor agonists, beyond conventional approaches like leptin administration, which has proven challenging and ineffective. This review provides researchers and practitioners

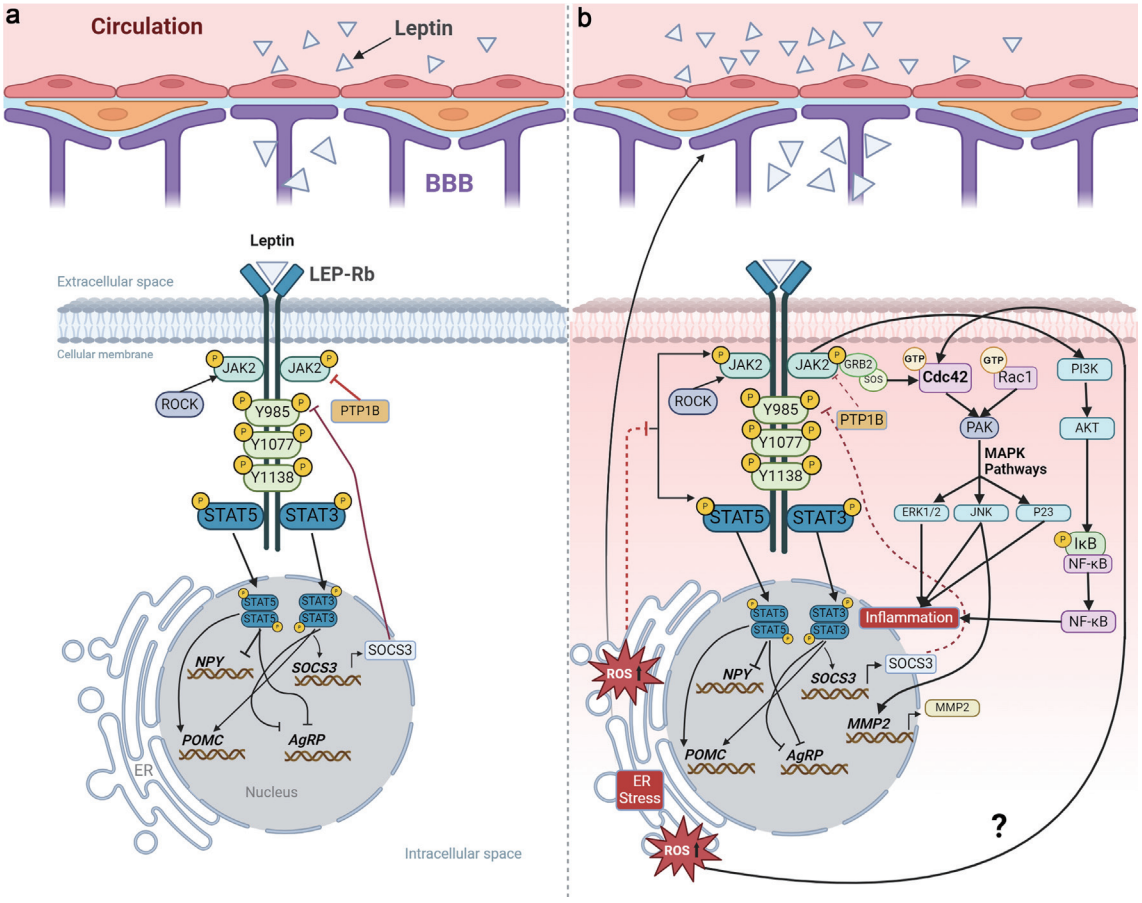

Fig. 1. Molecular mechanisms of leptin resistance-mediated endoplasmic reticulum stress in the hypothalamus. (a) In mammals without excess adiposity, leptin binds normally to LEPR, initiating the phosphorylation cascade of JAK2 and tyrosine residues within the intracellular domain of LEPR (Y985, Y1077, and Y1138). This phosphorylation event further leads to STAT3/5 activation. Negative feedback mechanisms from SOCS3 and PTP1B act to inhibit the receptor, ensuring that LEPR is not excessively activated. (b) In obese mammals, increased circulating leptin results in reduced LEPR expression across the blood-brain barrier. This overactivation of LEPR initiates an inflammatory signaling cascade that promotes LR possibly via the activation of the PI3K/Akt/IκB/NF-κB pathway and the plausible activation of Cdc42, which in turn activates MAPKs like ERK1/2, JNK, and p38. The activation of JNK promotes the overexpression of MMP2. Created by the authors with BioRender (https://biorender.com/). AgRP, agouti-related protein; Akt, RAC-alpha serine/threonine-protein kinase; BBB, blood-brain barrier; Cdc42, cell division control protein 42 homolog; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinase 1/2; GRB2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; IκB, inhibitor of nuclear factor kappa-B kinase; JAK2, janus kinase 2; JNK, mitogen-activated protein kinase 8 (also known as c-Jun N-terminal kinase); LEPR, leptin receptor; LR, leptin resistance; MAPK, mitogen-activated protein kinase; MMP2, 72 kDa type IV collagenase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NPY, neuropeptide Y; PAK, serine/threonine-protein kinase PAK 1; PI3K, phosphatidylinositol 3-kinase; POMC, proopiomelanocortin; PTP1B, tyrosine-protein phosphatase non-receptor type 1; Rac1, Ras-related C3 botulinum toxin substrate 1; ROCK, Rho-associated protein kinase 1; ROS, reactive oxygen species; SOCS3, suppressor of cytokine signaling 3; SOS, son of sevenless homolog; STAT 3/5, signal transducer and activator of transcription 3/5.

with an up-to-date perspective and outlines future directions that will aid in refining our understanding and exploring innovative interventions for combating obesity.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Conceptualization (WAG, GH, DAB), original draft preparation (WAG, DAB), visualization (WAG), critical review and editing (CAO-C, RC, AMM-C, GH, LMG-M, JLP, DAB), and supervision (DAB). All authors have read and agreed to the published version of the manuscript.

Data sharing statement

The curated data supporting the statements discussed in this article

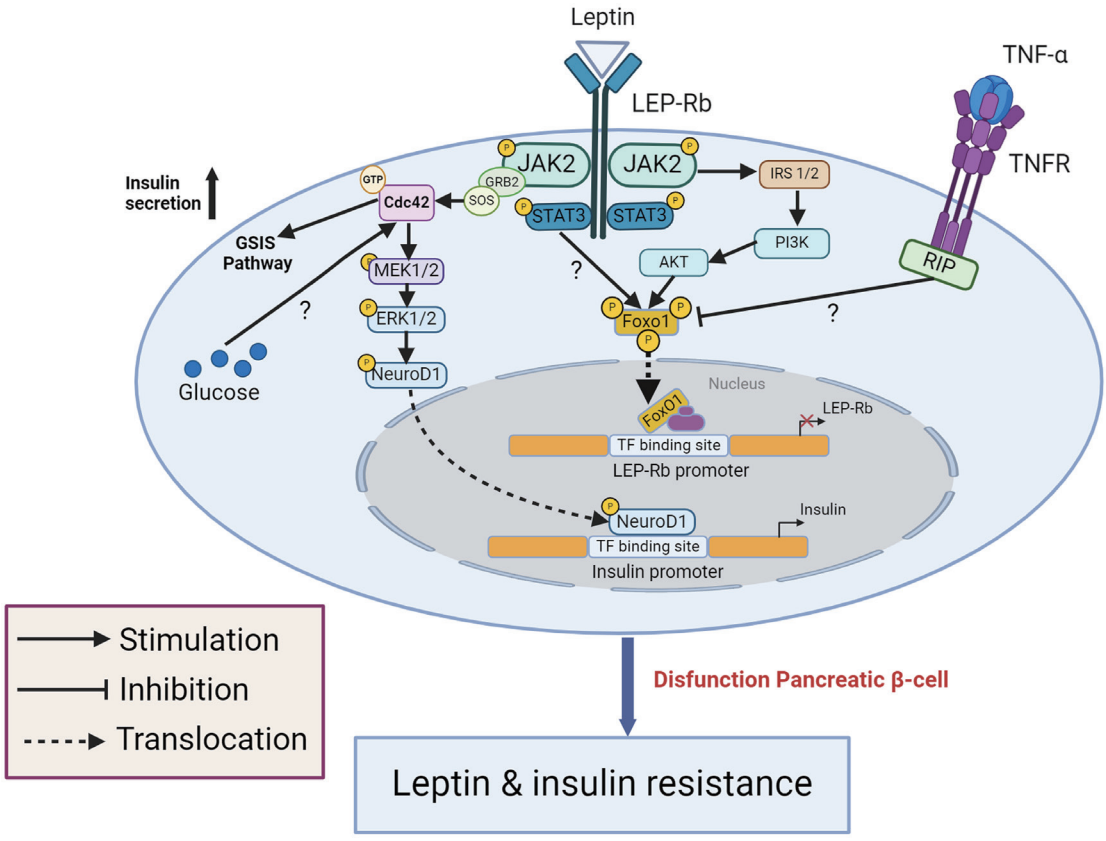

Fig. 2. β-cell dysfunction through the FOXO1/LEPR signaling pathway. Under normal conditions, leptin effectively regulates insulin metabolism in pancreatic β-cells through the JAK2/STAT3 and Akt/FoxO1 signaling pathways. However, in obese mammals, pancreatic β-cell dysregulation occurs. When the cell receives combined stimuli of TNF-α and leptin, it might stimulate the GSIS pathway, interfering with leptin-mediated negative regulation. TNF dephosphorylates FoxO1, which is then translocated directly to the nucleus, negatively inhibiting the *LEPR* promoter and inducing leptin resistance. Overactivation of LEPR might increase the levels of Cdc42, which is directly related to the secretion of insulin granules, as well as the activation of Cdc42 through the MEK/ERK/NeuroD1 axis, which induces insulin expression. This mechanism could promote leptin and insulin resistance. Created by the authors with BioRender (https://biorender.com/) based on artwork published by Casado *et al*.[56] – Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). Akt, RAC-alpha serine/threonine-protein kinase; Cdc42, cell division control protein 42 homolog; ERK1/2, extracellular signal-regulated kinase 1/2; FoxO1, forkhead box protein O1; GRB2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; GSIS, glucose-stimulated insulin secretion; IRS 1/2, insulin receptor substrate 1/2; JAK2, janus kinase 2; LEPR, leptin receptor; MEK 1/2, Mitogen-activated protein kinase kinase 1/2; NeuroD1, neurogenic differentiation factor 1; PI3K, phosphatidylinositol 3-kinase; PTP1B, tyrosine-protein phosphatase non-receptor type 1; Rac1, Ras-related C3 botulinum toxin substrate 1; RIP, Receptor-interacting serine/threonine-protein kinase 1; ROCK, Rho-associated protein kinase 1; ROS, reactive oxygen species; SOCS3, suppressor of cytokine signaling 3; SOS, son of sevenless homolog; STAT 3/5, signal transducer and activator of transcription 3/5; TF, transcription factor; TNF-α, tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor.

are available in the bioinformatics repositories. All identifier numbers are listed in Table 1.

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