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The Role of Chronic Inflammation in the Obesity-Diabetes-Cancer Axis

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ABSTRACT

The global rise in obesity and type 2 diabetes mellitus (T2DM) has triggered increased scientific attention toward their shared pathophysiological mechanisms and their connection with cancer. A growing body of evidence highlights chronic low-grade systemic inflammation as a central link in the obesity-diabetes-cancer axis. In obesity, hypertrophic adipocytes and immune cell infiltration contribute to the release of pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1, which not only perpetuate insulin resistance but also create a pro-tumorigenic microenvironment. In parallel, hyperinsulinemia and increased levels of insulin-like growth factor-1 (IGF-1) promote cellular proliferation and inhibit apoptosis, providing fertile ground for malignant transformation. This review explores the molecular and cellular mechanisms by which chronic inflammation serves as a bridge between obesity, diabetes, and cancer. It discusses the role of adipose tissue dysfunction, inflammatory signaling pathways, and metabolic reprogramming in cancer development and progression. Furthermore, it examines potential therapeutic interventions targeting inflammation to disrupt this triad and mitigate cancer risk in obese and diabetic individuals. Understanding the inflammatory underpinnings of this disease continuum offers valuable insights for the development of novel preventive and therapeutic strategies in the era of precision medicine.

Keywords: Chronic inflammation, Obesity, Type 2 diabetes, Cancer, Insulin resistance

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are chronic metabolic disorders that have emerged as major global health challenges, with their prevalence rising sharply over the past few decades[1–3]. According to the World Health Organization, over 1.9 billion adults are overweight, and of these, more than 650 million are obese. In parallel, more than 400 million individuals are currently living with diabetes, predominantly T2DM[4–6]. These conditions are closely interconnected through shared etiological and pathophysiological mechanisms, including insulin resistance, dysregulated glucose and lipid metabolism, and chronic low-grade inflammation[7, 8]. Notably, emerging evidence has highlighted that both obesity and T2DM not only predispose individuals to cardiovascular complications but also significantly increase the risk of developing various types of cancers, such as colorectal, breast, liver, pancreatic, endometrial, and kidney cancers[2, 9, 10].

The rising incidence of obesity-associated cancers has prompted a growing interest in unraveling the biological underpinnings that bridge metabolic diseases and tumorigenesis[11, 12]. A key overlapping mechanism that has gained considerable attention is chronic low-grade systemic inflammation, which is fundamentally distinct from the classical acute inflammatory response[13]. While acute inflammation serves as a protective, transient response to infection or injury, chronic inflammation is a prolonged, unresolved process that can create a pro-tumorigenic microenvironment[14, 15]. It is now well recognized that in obesity and T2DM, metabolic dysregulation leads to continuous immune activation and the production of inflammatory cytokines and chemokines, fostering an environment conducive to DNA damage, epigenetic modifications, and cellular transformation[16–18].

In obese individuals, this persistent inflammatory state largely stems from the dysfunction of adipose tissue, particularly visceral adipose depots, which undergo hypertrophy, hypoxia, and immune cell infiltration[16, 19, 20]. These alterations initiate a cascade of pro-inflammatory signaling events, resulting in the secretion of

adipokines and cytokines that not only exacerbate insulin resistance but also modulate oncogenic pathways[21, 22]. T2DM further compounds this risk through hyperinsulinemia, increased availability of insulin-like growth factors (IGFs), and oxidative stress, all of which have been shown to promote cell proliferation and inhibit apoptosis[23].

Importantly, the convergence of obesity, T2DM, and cancer is not merely coincidental but rather a consequence of interdependent pathophysiological events[12, 24]. Chronic inflammation functions as a central nexus, linking metabolic dysregulation to oncogenesis. Key inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) are frequently elevated in obese and diabetic individuals and play instrumental roles in shaping the tumor microenvironment[24, 25]. These molecules activate key intracellular signaling pathways such as nuclear factor-kappa B (NF-κB), c-Jun N-terminal kinase (JNK), and signal transducer and activator of transcription 3 (STAT3), which regulate gene expression patterns involved in cell survival, proliferation, angiogenesis, and immune evasion[26].

Moreover, obesity and T2DM are associated with immune dysregulation, including impaired natural killer (NK) cell function, altered T cell phenotypes, and macrophage polarization—all of which facilitate immune evasion by emerging tumor cells[27–29]. The metabolic reprogramming of immune cells in the inflamed adipose tissue further contributes to a pro-tumorigenic milieu, which favors malignant transformation and progression[30–32].

Given these intricate interconnections, it is imperative to consider chronic inflammation not just as a byproduct but as a driving force in the obesity-diabetes-cancer axis[33]. Understanding these mechanisms provides opportunities for identifying novel therapeutic targets, including anti-inflammatory interventions, metabolic modulators, and immunotherapeutic strategies. This review aims to provide an in-depth exploration of how obesity-induced inflammation and the resulting insulin resistance collectively fuel the development and progression of cancer. We will examine the cellular and molecular components of adipose tissue inflammation, dissect key signaling pathways implicated in metabolic and oncogenic crosstalk, and highlight emerging biomarkers and therapeutic targets that hold promise in mitigating cancer risk in obese and diabetic populations.

2. Adipose Tissue Dysfunction and Inflammatory Signaling

Adipose tissue, long considered a passive reservoir for energy storage, is now recognized as an active endocrine and immunological organ[32, 34, 35]. In obesity, particularly visceral obesity, adipose tissue undergoes significant structural and functional remodeling that disrupts its homeostatic roles and contributes to systemic metabolic and inflammatory abnormalities. One of the earliest pathological changes in expanding adipose tissue is adipocyte hypertrophy, which results in local hypoxia and mechanical stress[34, 35]. These changes promote cell death and stimulate the recruitment of immune cells, thereby initiating and sustaining chronic inflammation within the tissue. Macrophages, which constitute a minor population in lean adipose tissue, become significantly more abundant in obesity, accounting for up to 40–50% of the total stromal vascular fraction[36]. Importantly, these macrophages shift in phenotype from the alternatively activated, anti-inflammatory M2 type to the classically activated, pro-inflammatory M1 type. M1 macrophages secrete high levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), which are key mediators of local and systemic inflammation[37, 38]. These cytokines, in turn, activate intracellular signaling cascades such as the NF-κB and JNK pathways, leading to the transcription of genes involved in inflammation, cell survival, and insulin resistance.

Adipocytes themselves contribute to the inflammatory milieu through the dysregulated secretion of adipokines, bioactive molecules that exert paracrine and endocrine effects. In obesity, levels of pro-inflammatory adipokines like leptin and resistin are elevated, while levels of the anti-inflammatory adiponectin are markedly reduced[39, 40]. Leptin, beyond its role in appetite regulation, has been implicated in promoting angiogenesis, cell proliferation, and cytokine production all features associated with tumor progression. Resistin has been shown to induce insulin resistance and stimulate the production of TNF-α and IL-6. In contrast, adiponectin exerts anti-inflammatory, insulin-sensitizing, and anti-proliferative effects, and its deficiency in obesity is considered a significant contributor to metabolic and oncogenic dysregulation[41].

The inflammatory changes in adipose tissue are not restricted to macrophages and adipocytes alone. T cells also play a critical role in orchestrating the immune landscape of obese adipose tissue. CD8+ cytotoxic T cells and pro-inflammatory Th1 CD4+ T cells are increased, whereas regulatory T cells (Tregs), which suppress inflammation, are decreased. Neutrophils, B cells, mast cells, and natural killer (NK) cells are also involved in shaping this inflammatory environment[42]. These immune cells produce various chemokines and cytokines that exacerbate inflammation and promote insulin resistance. The activation of NF-κB and JNK pathways in adipose tissue has systemic consequences. NF-κB activation leads to increased transcription of inflammatory genes, while JNK phosphorylates insulin receptor substrate-1 (IRS-1), impairing insulin signaling and promoting insulin resistance. This state of insulin resistance leads to compensatory hyperinsulinemia, which has been associated with increased bioavailability of insulin-like growth factors (IGFs). IGFs can bind to their

receptors on various cells, including pre-neoplastic and neoplastic cells, thereby stimulating mitogenic and anti-apoptotic pathways[43].

Collectively, the dysfunction of adipose tissue in obesity initiates a vicious cycle of inflammation and insulin resistance that spills over into systemic circulation. This chronic inflammatory state creates a tumor-promoting environment by supporting genomic instability, angiogenesis, evasion of apoptosis, and immune suppression[44]. Moreover, the crosstalk between adipokines and inflammatory cytokines enhances the expression of matrix metalloproteinases and adhesion molecules, facilitating tumor cell invasion and metastasis[44].

Given the centrality of adipose tissue dysfunction in linking obesity to insulin resistance and cancer, therapeutic strategies targeting inflammatory signaling pathways, adipokine modulation, and immune cell reprogramming hold promise for breaking this pathogenic triad[45]. Ongoing research is unraveling novel targets such as toll-like receptors (TLRs), inflammasomes, and chemokine receptors, which may serve as future therapeutic entry points. Understanding the complex cellular and molecular events within inflamed adipose tissue is thus crucial for devising effective interventions to prevent and treat obesity-associated malignancies[45].

3. Insulin Resistance, Hyperinsulinemia, and Cancer Risk

Insulin resistance is a hallmark of obesity and type 2 diabetes mellitus (T2DM), arising when cells in the body, particularly muscle, liver, and adipose tissue, fail to respond adequately to circulating insulin[44, 46]. To compensate for this diminished sensitivity, pancreatic β-cells increase insulin production, leading to a chronic state of hyperinsulinemia. While initially adaptive, prolonged hyperinsulinemia has significant downstream effects that can promote carcinogenesis.

One major oncogenic consequence of hyperinsulinemia is the alteration of insulin-like growth factor (IGF) signaling. Elevated insulin levels reduce the hepatic synthesis of insulin-like growth factor binding proteins (IGFBPs), especially IGFBP-1 and IGFBP-2, which are responsible for binding and sequestering IGF-1 in the circulation[44, 47]. The decline in IGFBPs increases the bioavailability of free IGF-1, which can then interact with its cognate receptor, IGF-1R, on various cell types, including epithelial and tumor cells. IGF-1R activation triggers potent mitogenic and anti-apoptotic pathways such as the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and the Ras/mitogen-activated protein kinase (MAPK) cascades. These pathways foster cellular proliferation, survival, angiogenesis, and metastasis while inhibiting programmed cell death, thereby enhancing tumorigenic potential[48, 49].

In addition to IGF signaling, hyperinsulinemia influences sex hormone metabolism. Insulin suppresses the production of sex hormone-binding globulin (SHBG) in the liver, a protein that binds and inactivates circulating sex steroids such as estrogen and testosterone[50, 51]. Reduced SHBG levels lead to increased levels of free, bioactive estrogen, especially in postmenopausal women. Elevated estrogen levels are linked to heightened risks of hormone-sensitive cancers such as breast, endometrial, and ovarian cancers. Estrogen exerts mitogenic effects on mammary and endometrial tissues by activating estrogen receptors, which in turn stimulate DNA synthesis and cellular proliferation[52].

Moreover, insulin and IGF-1 can act directly on tumor cells and indirectly through the tumor microenvironment to promote malignancy. These hormones upregulate vascular endothelial growth factor (VEGF) expression, enhancing angiogenesis, and also stimulate inflammatory cytokines that contribute to a tumor-supportive milieu[53]. Importantly, the link between insulin resistance and cancer risk is further strengthened by chronic systemic inflammation associated with obesity and T2DM. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) can interfere with insulin signaling pathways, exacerbating insulin resistance and sustaining hyperinsulinemia. This creates a vicious cycle where inflammation and insulin dysregulation feed into one another, establishing a pro-tumorigenic internal environment[53]. Together, insulin resistance and hyperinsulinemia constitute a central mechanism by which metabolic disorders contribute to increased cancer risk. Their effects on growth factor signaling, hormone availability, cellular metabolism, and the immune microenvironment provide a multifaceted platform that promotes cancer initiation and progression in individuals with obesity and T2DM.

4. Metabolic Reprogramming and the Tumor Microenvironment

Metabolic reprogramming is a key hallmark of cancer, enabling tumor cells to adapt their bioenergetic and biosynthetic needs in response to environmental cues[54, 55]. One of the most well-characterized metabolic alterations in cancer is the Warburg effect, wherein tumor cells preferentially utilize aerobic glycolysis—converting glucose to lactate even in the presence of oxygen—rather than oxidative phosphorylation. This seemingly inefficient metabolic switch supports rapid ATP generation, provides intermediates for biosynthetic processes, and contributes to acidification of the tumor microenvironment (TME), which favors tumor invasion and immune evasion[54, 56].

In obesity, chronic low-grade inflammation exerts significant influence over both systemic and local metabolism, affecting not only cancer cells but also stromal components of the TME[57, 58]. Adipose tissue dysfunction leads to elevated secretion of pro-inflammatory cytokines, such as IL-6, TNF-α, and leptin, which modulate tumor cell behavior. These cytokines activate key transcription factors such as nuclear factor-kappa B (NF-κB)

and signal transducer and activator of transcription 3 (STAT3), which drive the expression of genes involved in glycolysis, lipid biosynthesis, and anti-apoptotic mechanisms [55, 59].

Furthermore, the altered metabolic state is not restricted to cancer cells alone; immune and stromal cells within the TME also undergo metabolic shifts. Tumor-associated macrophages (TAMs), for instance, differentiate toward an M2-like phenotype under the influence of IL-10 and lactic acid, promoting tissue remodeling, angiogenesis, and immune suppression[60]. Similarly, myeloid-derived suppressor cells (MDSCs) infiltrate tumors and inhibit T-cell activation through the depletion of arginine and production of reactive oxygen species. These immunosuppressive cells contribute to the creation of a permissive environment for tumor growth and dissemination[54, 61]. Lactate accumulation within the TME further exacerbates immune dysfunction by impairing dendritic cell maturation, reducing cytotoxic T lymphocyte activity, and enhancing regulatory T cell (Treg) function. These effects blunt anti-tumor immune responses and allow tumor cells to escape immune surveillance. Concurrently, elevated lipid biosynthesis supplies structural lipids for rapidly proliferating tumor cells and generates signaling molecules like prostaglandins, which support inflammation and angiogenesis[62].

Angiogenesis, stimulated by VEGF and other growth factors secreted by both cancer and stromal cells, is another defining feature of the TME in obesity-associated cancers. The new, often disorganized vasculature supplies nutrients to the growing tumor but also facilitates metastasis through leaky vessels and abnormal perfusion[63].

Fibrosis is another important component of the TME, resulting from the activation of cancer-associated fibroblasts (CAFs) and excessive extracellular matrix deposition[64]. This fibrotic stroma creates a physical barrier to drug delivery and immune cell infiltration, further complicating cancer treatment[65]. Altogether, metabolic reprogramming in both tumor and surrounding stromal cells driven by chronic inflammation and obesity, creates a hostile yet favorable environment for tumor progression. This remodeled TME not only supports tumor survival and growth but also shields it from immune detection and therapeutic intervention, making it a critical target for future anti-cancer strategies.

5. Evidence from Epidemiological and Experimental Studies

A substantial body of epidemiological and experimental evidence underscores the strong link between obesity, type 2 diabetes mellitus (T2DM), and cancer. Large-scale prospective cohort studies have consistently revealed that individuals with obesity and T2DM are at a significantly increased risk of developing various cancer types, including colorectal, pancreatic, liver, endometrial, and postmenopausal breast cancer[66]. For instance, data from the Nurses' Health Study and the Health Professionals Follow-Up Study have shown a positive association between elevated body mass index (BMI) and the incidence of several cancers[67]. Similarly, individuals with insulin resistance and elevated circulating insulin levels—a hallmark of T2DM—demonstrate a heightened cancer risk, likely due to increased levels of insulin-like growth factor 1 (IGF-1) and pro-inflammatory mediators[67].

Experimental studies using animal models further support these observations. Rodents fed a high-fat diet to induce obesity and insulin resistance exhibit increased rates of tumor initiation, growth, and metastasis compared to lean controls[68]. These effects are mediated, in part, by chronic low-grade inflammation and dysregulated insulin/IGF-1 signaling pathways. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) are elevated in obese animals and promote a tumor-permissive microenvironment by enhancing angiogenesis, cellular proliferation, and immune evasion. Genetically modified mouse models further confirm this mechanistic link. For example, mice deficient in TNF-α or components of the nuclear factor kappa B (NF-κB) pathway, both central to inflammation, exhibit significantly lower tumor burden even under obesogenic conditions[68].

Together, epidemiological and experimental findings support the notion that obesity- and diabetes-associated inflammation is not merely a consequence of disease but a driving force in carcinogenesis. These insights highlight the importance of targeting inflammatory processes to mitigate cancer risk in individuals with metabolic disorders.

6. Therapeutic Implications and Future Directions

The strong mechanistic and epidemiological links between chronic inflammation, obesity, T2DM, and cancer offer multiple therapeutic and preventive avenues. One promising strategy involves the use of anti-inflammatory pharmacologic agents to disrupt the progression of the obesity-diabetes-cancer axis. Metformin, a first-line drug for T2DM, has demonstrated significant anti-inflammatory effects and potential anticancer properties through AMPK activation and mTOR inhibition. Epidemiological studies suggest that metformin users have reduced incidence and mortality from several cancers. Similarly, low-dose aspirin, which inhibits cyclooxygenase enzymes and reduces prostaglandin-mediated inflammation, has been associated with decreased colorectal cancer risk. Statins, known for their lipid-lowering effects, also exhibit anti-inflammatory properties that may contribute to cancer prevention.

In addition to pharmacotherapy, lifestyle interventions remain a cornerstone in managing systemic inflammation and improving metabolic health. Weight reduction through caloric restriction, increased physical activity, and adherence to anti-inflammatory diets such as the Mediterranean or DASH diets have all been shown

to decrease inflammatory biomarkers and improve insulin sensitivity, thereby reducing cancer risk. Innovative therapeutic strategies are also emerging. These include biologics that neutralize pro-inflammatory cytokines such as IL-6 and TNF-α, and immune-modulatory therapies that reprogram adipose tissue macrophages or other immune cells to a more anti-inflammatory phenotype. Moreover, the integration of personalized medicine is on the horizon, with growing interest in utilizing individual inflammatory and metabolic profiles to stratify cancer risk and tailor preventive strategies accordingly.

However, despite these advances, large-scale randomized controlled trials are necessary to validate the long-term effectiveness and safety of these interventions. Future research should also explore the combined impact of anti-inflammatory agents with conventional cancer therapies and investigate novel molecular targets within the inflammatory signaling pathways. Such integrative approaches hold great promise in breaking the pathological cycle linking obesity, diabetes, and cancer.

CONCLUSION

Chronic inflammation serves as a central mechanistic bridge linking obesity, T2DM, and cancer. It fosters a pro-tumorigenic environment through adipose tissue dysfunction, immune cell activation, cytokine secretion, and insulin resistance. This persistent inflammatory state not only initiates but also supports tumor growth and metastasis. Addressing this inflammation through targeted therapies and lifestyle interventions holds promise for breaking the chain connecting these chronic diseases. A deeper understanding of the interplay between metabolic dysfunction and immune signaling will be instrumental in developing integrated strategies for cancer prevention and management in the context of metabolic syndrome.

REFERENCES

1. Chandrasekaran, P., Weiskirchen, R.: The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. International Journal of Molecular Sciences. 25, 1882 (2024). https://doi.org/10.3390/ijms25031882
2. Fernandez, C.J., George, A.S., Subrahmanyan, N.A., Pappachan, J.M.: Epidemiological link between obesity, type 2 diabetes mellitus and cancer. World Journal of Methodology. 11, 23–45 (2021). https://doi.org/10.5662/wjm.v11.i3.23
3. Alum, E.U.: Metabolic memory in obesity: Can early-life interventions reverse lifelong risks? Obesity Medicine. 55, 100610 (2025). https://doi.org/10.1016/j.obmed.2025.100610
4. Westbury, S., Oyebode, O., van Rens, T., Barber, T.M.: Obesity Stigma: Causes, Consequences, and Potential Solutions. Curr Obes Rep. 12, 10–23 (2023). https://doi.org/10.1007/s13679-023-00495-3
5. Zubery, D., Kimiywe, J., Martin, H.D.: Prevalence of Overweight and Obesity, and Its Associated Factors Among Health-care Workers, Teachers, and Bankers in Arusha City, Tanzania. Diabetes Metab Syndr Obes. 14, 455–465 (2021). https://doi.org/10.2147/DMSO.S283595
6. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. Obesity Medicine. 56, 100623 (2025). https://doi.org/10.1016/j.obmed.2025.100623
7. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., Agwupuye, E.I., Obeten, U.N., Maitra, S., Subramaniyan, V., Wong, L.S., Aljarba, N.H., Kumarasamy, V.: Tetracarpidium conophorum nuts (African walnuts) up-regulated adiponectin and PPAR-γ expressions with reciprocal suppression of TNF-α gene in obesity. J Cell Mol Med. 28, e70086 (2024). https://doi.org/10.1111/jcmm.70086
8. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., De Campos, O.C., Udeozor, P.A., Nfona, S.O., Lawal, B., Alum, E.U.: Modulation of Lipogenesis by Tetracarpidium conophorum Nuts via SREBP-1/ACCA-1/FASN Inhibition in Monosodium-Glutamate-Induced Obesity in Rats. Natural Product Communications. 20, 1934578X251344035 (2025). https://doi.org/10.1177/1934578X251344035
9. Anand, S., Patel, T.N.: Integrating the metabolic and molecular circuits in diabetes, obesity and cancer: a comprehensive review. Discov Onc. 15, 779 (2024). https://doi.org/10.1007/s12672-024-01662-1
10. Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.Ak.: Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obesity Medicine. 100622 (2025). https://doi.org/10.1016/j.obmed.2025.100622
11. Abdulla, A., Sadida, H.Q., Jerobin, J., Elfaki, I., Mir, R., Mirza, S., Singh, M., Macha, M.A., Uddin, S., Fakhro, K., Bhat, A.A., Akil, A.S.A.-S.: Unraveling molecular interconnections and identifying potential therapeutic targets of significance in obesity-cancer link. J Natl Cancer Cent. 5, 8–27 (2024). https://doi.org/10.1016/j.jncc.2024.11.001
12. Gaskell, C., MacDonald, R., Aleem, E., Bendriss, G.: Obesity and cancer: unravelling the microbiome's hidden role. Front. Nutr. 12, (2025). https://doi.org/10.3389/fnut.2025.1602603
13. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
14. Alharbi, H.O.A., Alshebremi, M., Babiker, A.Y., Rahmani, A.H.: The Role of Quercetin, a Flavonoid in the Management of Pathogenesis Through Regulation of Oxidative Stress, Inflammation, and Biological Activities. Biomolecules. 15, 151 (2025). https://doi.org/10.3390/biom15010151

15. Bhat, A.A., Uppada, S., Achkar, I.W., Hashem, S., Yadav, S.K., Shanmugakonar, M., Al-Naemi, H.A., Haris, M., Uddin, S.: Tight Junction Proteins and Signaling Pathways in Cancer and Inflammation: A Functional Crosstalk. Front Physiol. 9, 1942 (2019). https://doi.org/10.3389/fphys.2018.01942
16. Bensussen, A., Torres-Magallanes, J.A., Roces De Álvarez-Buylla, E.: Molecular tracking of insulin resistance and inflammation development on visceral adipose tissue. Front. Immunol. 14, 1014778 (2023). https://doi.org/10.3389/fimmu.2023.1014778
17. Huang, S., Yan, F., Qiu, Y., Liu, T., Zhang, W., Yang, Y., Zhong, R., Yang, Y., Peng, X.: Exosomes in inflammation and cancer: from bench to bedside applications. Mol Biomed. 6, 41 (2025). https://doi.org/10.1186/s43556-025-00280-9
18. Ikpozu, E.N., Offor, C.E., Igwenyi, I.O., Obaroh, I.O., Ibiam, U.A., Ukaidi, C.U.A.: RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diabetes & Vascular Disease Research. 22, 14791641251334726 (2025). https://doi.org/10.1177/14791641251334726
19. Guerreiro, V.A., Carvalho, D., Freitas, P.: Obesity, Adipose Tissue, and Inflammation Answered in Questions. Journal of Obesity. 2022, 2252516 (2022). https://doi.org/10.1155/2022/2252516
20. Anguita-Ruiz, A., Bustos-Aibar, M., Plaza-Díaz, J., Mendez-Gutierrez, A., Alcalá-Fdez, J., Aguilera, C.M., Ruiz-Ojeda, F.J.: Omics Approaches in Adipose Tissue and Skeletal Muscle Addressing the Role of Extracellular Matrix in Obesity and Metabolic Dysfunction. International Journal of Molecular Sciences. 22, 2756 (2021). https://doi.org/10.3390/ijms22052756
21. Mittal, B.: Subcutaneous adipose tissue & visceral adipose tissue. Indian J Med Res. 149, 571–573 (2019). https://doi.org/10.4103/ijmr.IJMR_1910_18
22. Matsuura, N., Asano, C., Nagasawa, K., Ito, S., Sano, Y., Minagawa, Y., Yamada, Y., Hattori, T., Watanabe, S., Murohara, T., Nagata, K.: Effects of pioglitazone on cardiac and adipose tissue pathology in rats with metabolic syndrome. International Journal of Cardiology. 179, 360–369 (2015). https://doi.org/10.1016/j.ijcard.2014.11.099
23. Zhang, A.M.Y., Wellberg, E.A., Kopp, J.L., Johnson, J.D.: Hyperinsulinemia in Obesity, Inflammation, and Cancer. Diabetes Metab J. 45, 285–311 (2021). https://doi.org/10.4093/dmj.2020.0250
24. Ingram, Y., Olujide, O., Sheikh, N., Robinson, A., Ho, J.H., Syed, A.A., Adam, S.: The Relationship Between Obesity and Cancer: Epidemiology, Pathophysiology, and the Effect of Obesity Treatment on Cancer. Current Oncology. 32, 362 (2025). https://doi.org/10.3390/curroncol32060362
25. Bull, C.J., Hazelwood, E., Legge, D.N., Corbin, L.J., Richardson, T.G., Lee, M., Yarmolinsky, J., Smith-Byrne, K., Hughes, D.A., Johansson, M., Peters, U., Berndt, S.I., Brenner, H., Burnett-Hartman, A., Cheng, I., Kweon, S.-S., Marchand, L.L., Li, L., Newcomb, P.A., Pearlman, R., McConnachie, A., Welsh, P., Taylor, R., Lean, M.E.J., Sattar, N., Murphy, N., Gunter, M.J., Timpson, N.J., Vincent, E.E.: Impact of weight loss on cancer-related proteins in serum: results from a cluster randomised controlled trial of individuals with type 2 diabetes. eBioMedicine. 100, (2024). https://doi.org/10.1016/j.ebiom.2024.104977
26. Scully, T., Ettela, A., LeRoith, D., Gallagher, E.J.: Obesity, Type 2 Diabetes, and Cancer Risk. Front. Oncol. 10, (2021). https://doi.org/10.3389/fonc.2020.615375
27. Bhattacharya, S., Aggarwal, P., Bera, O.P., Saleem, S.M., Shikha, D., Vallabh, V., Juyal, R., Singh, A.: Covid-19 and Childhood Obesity (Co-Besity) in the Era of New Normal Life: A Need for a Policy Research. Journal of Public Health Research. 10, jphr.2021.2673 (2021). https://doi.org/10.4081/jphr.2021.2673
28. Andò, S., Gelsomino, L., Panza, S., Giordano, C., Bonofiglio, D., Barone, I., Catalano, S.: Obesity, Leptin and Breast Cancer: Epidemiological Evidence and Proposed Mechanisms. Cancers (Basel). 11, 62 (2019). https://doi.org/10.3390/cancers11010062
29. Barber, T.M., Kyrou, I., Randeva, H.S., Weickert, M.O.: Mechanisms of Insulin Resistance at the Crossroad of Obesity with Associated Metabolic Abnormalities and Cognitive Dysfunction. Int J Mol Sci. 22, 546 (2021). https://doi.org/10.3390/ijms22020546
30. Sun, K., Li, X., Scherer, P.E.: Extracellular Matrix (ECM) and Fibrosis in Adipose Tissue: Overview and Perspectives. Compr Physiol. 13, 4387–4407 (2023). https://doi.org/10.1002/cphy.c220020
31. Guria, S., Hoory, A., Das, S., Chattopadhyay, D., Mukherjee, S.: Adipose tissue macrophages and their role in obesity-associated insulin resistance: an overview of the complex dynamics at play. Biosci Rep. 43, BSR20220200 (2023). https://doi.org/10.1042/BSR20220200
32. Magro, B.S., Dias, D.P.M.: Brown and beige adipose tissue: New therapeutic targets for metabolic disorders. Health Sciences Review. 10, 100148 (2024). https://doi.org/10.1016/j.hsr.2024.100148
33. Gkrinia, E.M.M., Belančić, A.: The Mechanisms of Chronic Inflammation in Obesity and Potential Therapeutic Strategies: A Narrative Review. Current Issues in Molecular Biology. 47, 357 (2025). https://doi.org/10.3390/cimb47050357
34. Daley, A.D., Bénézech, C.: Fat-associated lymphoid clusters: Supporting visceral adipose tissue B cell function in immunity and metabolism. Immunological Reviews. 324, 78–94 (2024). https://doi.org/10.1111/imr.13339

35. Chen, S., Huang, X.: Cytosolic lipolysis in non-adipose tissues: energy provision and beyond. The FEBS Journal. 289, 7385–7398 (2022). https://doi.org/10.1111/febs.16161
36. Joffin, N., Gliniak, C.M., Funcke, J.-B., Paschoal, V.A., Crewe, C., Chen, S., Gordillo, R., Kusminski, C.M., Oh, D.Y., Geldenhuys, W.J., Scherer, P.E.: Adipose tissue macrophages exert systemic metabolic control by manipulating local iron concentrations. Nat Metab. 4, 1474–1494 (2022). https://doi.org/10.1038/s42255-022-00664-z
37. Strizova, Z., Benesova, I., Bartolini, R., Novysedlak, R., Cecrdlova, E., Foley, L.K., Striz, I.: M1/M2 macrophages and their overlaps – myth or reality? Clin Sci (Lond). 137, 1067–1093 (2023). https://doi.org/10.1042/CS20220531
38. Deng, Z., Yang, W., Zhao, B., Yang, Z., Li, D., Yang, F.: Advances in research on M1/M2 macrophage polarization in the pathogenesis and treatment of osteoarthritis. Heliyon. 11, e42881 (2025). https://doi.org/10.1016/j.heliyon.2025.e42881
39. Kirichenko, T.V., Markina, Y.V., Bogatyreva, A.I., Tolstik, T.V., Varaeva, Y.R., Starodubova, A.V.: The Role of Adipokines in Inflammatory Mechanisms of Obesity. Int J Mol Sci. 23, 14982 (2022). https://doi.org/10.3390/ijms232314982
40. Chait, A., den Hartigh, L.J.: Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. Front. Cardiovasc. Med. 7, (2020). https://doi.org/10.3389/fcvm.2020.00022
41. de Candia, P., Prattichizzo, F., Garavelli, S., Alviggi, C., La Cava, A., Matarese, G.: The pleiotropic roles of leptin in metabolism, immunity, and cancer. J Exp Med. 218, e20191593 (2021). https://doi.org/10.1084/jem.20191593
42. Khan, S., Chan, Y.T., Revelo, X.S., Winer, D.A.: The Immune Landscape of Visceral Adipose Tissue During Obesity and Aging. Front Endocrinol (Lausanne). 11, 267 (2020). https://doi.org/10.3389/fendo.2020.00267
43. Zatterale, F., Longo, M., Naderi, J., Raciti, G.A., Desiderio, A., Miele, C., Beguinot, F.: Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. Front Physiol. 10, 1607 (2020). https://doi.org/10.3389/fphys.2019.01607
44. Dobre, M.-Z., Virgolici, B., Timnea, O.: Key Roles of Brown, Subcutaneous, and Visceral Adipose Tissues in Obesity and Insulin Resistance. Current Issues in Molecular Biology. 47, 343 (2025). https://doi.org/10.3390/cimb47050343
45. Fei, Q., Huang, J., He, Y., Zhang, Y., Zhang, X., Wang, J., Fu, Q.: Immunometabolic Interactions in Obesity: Implications for Therapeutic Strategies. Biomedicines. 13, 1429 (2025). https://doi.org/10.3390/biomedicines13061429
46. Krishnamoorthy, R., Gatasheh, M.K., Subbarayan, S., Vijayalakshmi, P., Uti, D.E.: Protective Role of Jimson Weed in Mitigating Dyslipidemia, Cardiovascular, and Renal Dysfunction in Diabetic Rat Models: In Vivo and in Silico Evidence. Natural Product Communications. 19, 1934578X241299279 (2024). https://doi.org/10.1177/1934578X241299279
47. Gómez, W.A., Humeres, G., Orozco-Castaño, C.A., Cannataro, R., Muñoz-Contreras, A.M., Gómez-Miranda, L.M., Petro, J.L., Bonilla, D.A.: Leptin Signaling and Its Relationship with Obesity-induced Insulin Resistance: A Bioinformatics-assisted Review. Gene Expression. 24, 56–63 (2025). https://doi.org/10.14218/GE.2024.00039
48. Li, M., Chi, X., Wang, Y., Setrerrahmane, S., Xie, W., Xu, H.: Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Sig Transduct Target Ther. 7, 216 (2022). https://doi.org/10.1038/s41392-022-01073-0
49. Odeniyi, I.A., Ahmed, B., Anbiah, B., Hester, G., Abraham, P.T., Lipke, E.A., Greene, M.W.: An improved in vitro 3T3-L1 adipocyte model of inflammation and insulin resistance. Adipocyte. 13, 2414919. https://doi.org/10.1080/21623945.2024.2414919
50. Xing, C., Zhang, J., Zhao, H., He, B.: Effect of Sex Hormone-Binding Globulin on Polycystic Ovary Syndrome: Mechanisms, Manifestations, Genetics, and Treatment. Int J Womens Health. 14, 91–105 (2022). https://doi.org/10.2147/IJWH.S344542
51. Song, M.J., Choi, J.Y.: Androgen dysfunction in non-alcoholic fatty liver disease: Role of sex hormone binding globulin. Front. Endocrinol. 13, (2022). https://doi.org/10.3389/fendo.2022.1053709
52. Martinez, D.: Hyperinsulinemia does not reduce plasma sex hormone-binding globulin levels in obesity. In: Endocrine Abstracts. Bioscientifica (2020)
53. Sharma, D., Arora, S., Banerjee, A., Singh, J.: Improved insulin sensitivity in obese-diabetic mice via chitosan Nanomicelles mediated silencing of pro-inflammatory Adipocytokines. Nanomedicine: Nanotechnology, Biology and Medicine. 33, 102357 (2021). https://doi.org/10.1016/j.nano.2020.102357
54. Badoiu, S.C., Greabu, M., Miricescu, D., Stanescu-Spinu, I.-I., Ilinca, R., Balan, D.G., Balcangiu-Stroescu, A.-E., Mihai, D.-A., Vacaroiu, I.A., Stefani, C., Jinga, V.: PI3K/AKT/mTOR Dysregulation and

Reprogramming Metabolic Pathways in Renal Cancer: Crosstalk with the VHL/HIF Axis. International Journal of Molecular Sciences. 24, 8391 (2023). https://doi.org/10.3390/ijms24098391
55. Hua, W., ten Dijke, P., Kostidis, S., Giera, M., Hornsveld, M.: TGFβ-induced metabolic reprogramming during epithelial-to-mesenchymal transition in cancer. Cell. Mol. Life Sci. 77, 2103–2123 (2020). https://doi.org/10.1007/s00018-019-03398-6
56. Alum, E.U., Uti, D.E., Ugwu, O.P.-C., Alum, B.N., Edeh, F.O., Ainebyoona, C.: Unveiling the microbial orchestra: exploring the role of microbiota in cancer development and treatment. Discov Onc. 16, 646 (2025). https://doi.org/10.1007/s12672-025-02352-2
57. Jiang, C., Tang, M., Su, Y., Xie, J., Shang, Q., Guo, M., An, X., Lin, L., Wang, R., Huang, Q., Zhang, G., Li, H., Wang, F.: Nanomedicine-driven tumor glucose metabolic reprogramming for enhanced cancer immunotherapy. Acta Pharmaceutica Sinica B. 15, 2845–2866 (2025). https://doi.org/10.1016/j.apsb.2025.04.002
58. Jiang, J., Yan, Y., Yang, C., Cai, H.: Immunogenic Cell Death and Metabolic Reprogramming in Cancer: Mechanisms, Synergies, and Innovative Therapeutic Strategies. Biomedicines. 13, 950 (2025). https://doi.org/10.3390/biomedicines13040950
59. Wei, X., Hou, Y., Long, M., Jiang, L., Du, Y.: Molecular mechanisms underlying the role of hypoxia-inducible factor-1 α in metabolic reprogramming in renal fibrosis. Front. Endocrinol. 13, (2022). https://doi.org/10.3389/fendo.2022.927329
60. Obisi, J.N., Abimbola, A.N.J., Babaleye, O.A., Atidoglo, P.K., Usin, S.G., Nwanaforo, E.O., Patrick-Inezi, F.S., Fasogbon, I.V., Chimezie, J., Dare, C.A., Kuti, O.O., Uti, D.E., Omeoga, H.C.: Unveiling the future of cancer stem cell therapy: a narrative exploration of emerging innovations. Discov Onc. 16, 373 (2025). https://doi.org/10.1007/s12672-025-02102-4
61. Wang, Q., Liu, J., Chen, Z., Zheng, J., Wang, Y., Dong, J.: Targeting metabolic reprogramming in hepatocellular carcinoma to overcome therapeutic resistance: A comprehensive review. Biomedicine & Pharmacotherapy. 170, 116021 (2024). https://doi.org/10.1016/j.biopha.2023.116021
62. Gu, X.-Y., Yang, J.-L., Lai, R., Zhou, Z.-J., Tang, D., Hu, L., Zhao, L.-J.: Impact of lactate on immune cell function in the tumor microenvironment: mechanisms and therapeutic perspectives. Front Immunol. 16, 1563303 (2025). https://doi.org/10.3389/fimmu.2025.1563303
63. Patel, S.A., Nilsson, M.B., Le, X., Cascone, T., Jain, R.K., Heymach, J.V.: Molecular Mechanisms and Future Implications of VEGF/VEGFR in Cancer Therapy. Clin Cancer Res. 29, 30–39 (2023). https://doi.org/10.1158/1078-0432.CCR-22-1366
64. Yang, D., Liu, J., Qian, H., Zhuang, Q.: Cancer-associated fibroblasts: from basic science to anticancer therapy. Exp Mol Med. 55, 1322–1332 (2023). https://doi.org/10.1038/s12276-023-01013-0
65. Zhou, S., Zhao, Z., Wang, Z., Xu, H., Li, Y., Xu, K., Li, W., Yang, J.: Cancer-associated fibroblasts in carcinogenesis. Journal of Translational Medicine. 23, 50 (2025). https://doi.org/10.1186/s12967-025-06071-8
66. Fernandez, C.J., George, A.S., Subrahmanyan, N.A., Pappachan, J.M.: Epidemiological link between obesity, type 2 diabetes mellitus and cancer. World J Methodol. 11, 23–45 (2021). https://doi.org/10.5662/wjm.v11.i3.23
67. Asad, S., Damicis, A., Heng, Y.J., Kananen, K., Collier, K.A., Adams, E.J., Kensler, K.H., Baker, G.M., Wesolowski, R., Sardesai, S., Gatti-Mays, M., Ramaswamy, B., Eliassen, A.H., Hankinson, S.E., Tabung, F.K., Tamimi, R.M., Stover, D.G.: Association of body mass index and inflammatory dietary pattern with breast cancer pathologic and genomic immunophenotype in the nurses' health study. Breast Cancer Res. 24, 78 (2022). https://doi.org/10.1186/s13058-022-01573-5
68. de Moura e Dias, M., dos Reis, S.A., da Conceição, L.L., Sediyama, C.M.N. de O., Pereira, S.S., de Oliveira, L.L., Gouveia Peluzio, M. do C., Martinez, J.A., Milagro, F.I.: Diet-induced obesity in animal models: points to consider and influence on metabolic markers. Diabetology & Metabolic Syndrome. 13, 32 (2021). https://doi.org/10.1186/s13098-021-00647-2

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