



Adipokines Reframing the Obesity Paradox in Precision Oncology

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SUMMARY

The increasing coexistence of obesity, insulin resistance, and malignancy has intensified interest in adipokines as mechanistic links between metabolic disease and tumor progression. This review summarizes tumor-specific evidence in breast, colorectal, endometrial, ovarian, and hepatocellular cancers and discusses the biomarker and therapeutic value of circulating adipokines, receptor antagonists, pathway modulators, and metabolism-informed combination strategies. To date, adipokines are bioactive mediators released by adipocytes, stromal cells, and immune cells within adipose depots and tumor-adjacent fat. Rather than acting as isolated biomarkers, they form a dynamic signaling network that regulates proliferation, apoptosis resistance, angiogenesis, epithelial-mesenchymal transition, cancer stem-like behavior, and immune remodeling. Leptin, resistin, visfatin, and chemerin are predominantly associated with pro-tumorigenic effects, whereas adiponectin and omentin are more often linked to anti-inflammatory and anti-proliferative actions. Emerging adipokines such as apelin, vaspin, irislin, and RBP4 (Retinol-binding protein 4) display context-dependent behavior that varies with tumor type, receptor expression, and metabolic state. Mechanistically, adipokines converge on JAK(Janus kinase)/STAT, PI3K (Phosphoinositide 3-kinase)/Akt/mTOR (Mechanistic target of rapamycin), MAPK/ERK (Mitogen-activated protein kinase / Extracellular signal-regulated kinase), AMPK (AMP-activated protein kinase), NF- κ B, and insulin/IGF-1 pathways, thereby influencing both tumor cells and the surrounding microenvironment. The data suggest that precision oncology could be improved by integrating adipokine biology into patient stratification strategies, especially for metabolically dysregulated populations in whom tumor behavior and treatment response are shaped by the endocrine and immune state of adipose tissue.

Keywords: Adipokines; adiponectin; biomarkers; metabolic signaling; leptin; obesity-related cancer; precision oncology; therapeutic targeting; tumor microenvironment.

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INTRODUCTION

Obesity-associated malignancies are increasingly recognized as disorders of dysregulated systemic signaling rather than purely cell-autonomous genetic disease. The adipose tissue compartment is now understood as an active endocrine and immune organ capable of shaping tumor initiation, progression, immune escape, and treatment response.[1–3] It should be noted that

adipokines are secreted not only by mature adipocytes but also by stromal cells, macrophages, and fibroblasts. Their biological effects extend from energy balance and insulin sensitivity to angiogenesis, extracellular matrix (ECM) remodeling, endocrine cross-talk, and immune-cell metabolism.[4,5] In obesity, adipose tissue hypertrophy, hypoxia, inflammation, and fibrosis shift the secretory profile toward higher concentrations of pro-inflammatory and proliferative mediators and

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lower concentrations of protective molecules. Tumors developing in or near adipose-rich sites are thereby exposed to a complex microenvironment that can favor aggressive behavior. Precision oncology has traditionally focused on tumor genomics, targetable mutations, and histopathology. Two patients with the same tumor subtype may experience different disease trajectories because obesity, insulin resistance, body composition, and adipokine imbalance alter cancer cell signaling and the tumor microenvironment (TME).[6,7] It means that treatment response is also shaped by host metabolic context, and therefore, the adipokine biology offers an important framework for integrating tumor-intrinsic and host-derived determinants of outcome.

The available literature combines clinical, epidemiological, and mechanistic evidence and supports a consistent conceptual finding: Adipokines are neither passive obesity markers nor uniform actors. Instead, they function within a dynamic metabolic-immune signaling network whose consequences depend on receptor expression, tissue specificity, tumor stage, sex, and coexisting metabolic abnormalities.[7,8] This article retains that framework and extends its implications for translational practice. A useful conceptual distinction is to group adipokines as predominantly pro-tumorigenic, predominantly anti-tumorigenic, or context dependent. Leptin, resistin, visfatin, and many chemerin-associated signaling contexts fit the first category; adiponectin and omentin more often occupy the second; and apelin, vaspin, irisin, and RBP4 belong to the third because their biological behavior can vary considerably across tissues and disease states.[9–12] This classification is heuristic rather than absolute, but it remains helpful for organizing translational reasoning.

Another central concept is that adipokines operate across scales. They act systemically through endocrine circulation, locally by paracrine signaling, and within the tumor niche through reciprocal communication between cancer cells, adipocytes, endothelial cells, and immune cells.[2,13] Because of this multilevel action, adipokines can influence both cancer risk and treatment response.

METHODS

Relevant literature was considered across three major evidence domains: Experimental studies describing adipokine-mediated signaling pathways, clinical and epidemiological studies evaluating adipokines as cancer-related biomarkers, and translational reports discussing adipokine-targeted or metabolism-informed

therapeutic strategies. Particular attention was given to adipokines with repeated relevance in cancer biology, including leptin, adiponectin, resistin, visfatin, chemerin, omentin, apelin, vaspin, irisin, and retinol-binding protein 4 (RBP4). Tumor types were selected based on their established association with obesity, adipose tissue dysfunction, or metabolic dysregulation. These included breast, colorectal, endometrial, ovarian, and hepatocellular cancers. The analysis aimed to identify recurring mechanistic patterns, areas of consistency, sources of conflicting evidence, and clinically relevant knowledge gaps. The final synthesis was used to propose a precision-oncology framework in which adipokine profiles, metabolic phenotype, receptor expression, and TME features may support improved patient stratification and treatment personalization.

PRO-TUMORIGENIC ADIPOKINES

Leptin is the prototypical adipokine linking excess adiposity to tumor-promoting biology. Originally characterized as a regulator of body weight and energy balance, leptin also signals through OB-R (Leptin receptor) and cytokine-like receptor mechanisms that can activate JAK/STAT3 (Signal transducer and activator of transcription 3), PI3K/Akt, and MAPK/ERK pathways.[14–16] These pathways stimulate cyclin expression, enhance cell-cycle progression, inhibit apoptosis, promote endothelial activation, and reinforce migratory and epithelial-mesenchymal phenotypes.[17–19] Leptin also interacts with estrogen receptor, EGFR (Epidermal growth factor receptor), IGF-1 (Insulin-like growth factor 1), reproductive, and immune signaling, generating amplification loops that may be particularly relevant in breast and gynecological malignancies.[20–24] Resistin and visfatin strengthen the inflammatory-metabolic component of tumor progression. Resistin has been associated with inflammatory signaling, angiogenesis, and VEGF (Vascular endothelial growth factor)-related processes, while visfatin supports proliferative and survival signaling through PI3K/Akt, MAPK/ERK, and STAT3/NF- κ B pathways.[6,7] These mediators exemplify how adipokines can connect insulin resistance, chronic inflammation, and oncogenic transcriptional programs. They are especially relevant in metabolically inflamed phenotypes where tumor cells and stromal cells are continuously exposed to pro-survival cytokine-like signals. Chemerin remains more complex. It can promote or restrain tumor progression depending on receptor usage, cellu-

lar context, and tumor type.[25–27] This duality illustrates an important principle for precision oncology: Adipokines should not be interpreted only by average effect direction. Their clinical meaning may depend on receptor expression patterns, local immune composition, and concurrent metabolic signals. Context dependence does not diminish translational value; it makes biomarker-guided stratification more necessary.

ANTI-TUMORIGENIC AND PROTECTIVE ADIPOKINES

Adiponectin is the best-characterized protective adipokine. Its actions include activation of AMPK, inhibition of PI3K/Akt/mTOR, suppression of NF- κ B signaling, promotion of apoptosis, and reduction of angiogenic drive.[8,28] These effects align with a less proliferative, less inflammatory, and more metabolically stable cellular state. In obesity, circulating adiponectin is typically reduced, suggesting that cancer-promoting conditions may arise not only from excess pro-tumor signals but also from loss of endogenous protective regulation. Adiponectin biology also has translational relevance at the receptor level. AdipoR1 (Adiponectin receptor 1), AdipoR2 (Adiponectin receptor 2), and T-cadherin help determine tissue-specific signaling output, and reduced receptor expression or receptor dysfunction in tumors may blunt the anti-proliferative influence of adiponectin even when circulating levels are measurable.[28] This means that future biomarker strategies may need to integrate ligand concentrations with receptor profiling rather than focusing on serum values alone. Omentin appears to share several anti-inflammatory and insulin-sensitizing characteristics, although the evidence base remains smaller and less consistent than for adiponectin. Vascular and metabolic studies indicate that omentin can oppose inflammation and vascular dysfunction, supporting its potential relevance in the broader obesity-cancer interface.[29–31] From a translational viewpoint, adiponectin and omentin represent a therapeutic logic: Restore or mimic protective adipokine signaling to counterbalance obesity-associated tumor promotion.

SIGNALING PATHWAYS AND NETWORK CONVERGENCE

Pathway convergence is one of the strongest mechanistic themes in adipokine research. JAK/STAT3, PI3K/Akt/mTOR, MAPK/ERK, NF- κ B, AMPK, and insulin/IGF-1 signaling are the major molecular hubs through

which metabolism communicates with growth and survival.[6,32] Leptin prominently activates JAK/STAT3 and PI3K/Akt; resistin and visfatin reinforce NF- κ B and MAPK-associated inflammatory proliferation; and adiponectin counterbalances through AMPK activation and downstream suppression of mTOR and inflammatory transcription. This convergence matters because adipokines can modify response to therapies that target the same pathways. For example, PI3K/Akt/mTOR inhibitors may behave differently in tumors embedded in leptin-rich or insulin-resistant environments.[33] Likewise, anti-angiogenic strategies might be influenced by adipokine-driven VEGF and endothelial signaling.[17] Experimental evidence also suggests that leptin-associated mitochondrial and survival signaling may contribute to drug resistance in selected malignancies.[34] Precision medicine that ignores host endocrine context may therefore underestimate one source of variability in response and resistance. The network perspective also helps resolve apparently contradictory findings. A single adipokine may not act identically across all settings because pathway dominance changes with receptor density, co-stimulating cytokines, oxygen tension, hormonal milieu, and metabolic state. Apparent inconsistency in observational studies may therefore reflect biological heterogeneity rather than simple noise.

TUMOR MICROENVIRONMENT (TME), CANCER-ASSOCIATED ADIPOCYTES (CAAS), AND IMMUNE REMODELING

Tumor progression in adipose-rich organs is heavily shaped by stromal ecology. Cancer-associated adipocytes (CAAs) are described as smaller, lipid-depleted, and secretory-active cells with elevated output of adipokines, cytokines, and ECM components.[35] These cells support tumor invasion by increasing matrix remodeling, lipid transfer, inflammatory signaling, and angiogenic potential. Their presence reinforces the idea that adipose tissue adjacent to tumors becomes functionally reprogrammed rather than merely displaced. Experimental and translational studies further show that adipocytes can support tumorigenesis, metastasis, radioresistance, and early mammary tumor progression through local matrix and metabolic effects.[13,36,37] These data link adipokine molecular signaling to tissue-level behavior that can be observed in clinical settings and directed toward experimental goals. Adipokines also regulate immune-cell metabo-

lism and composition within the TME. They can attract immunosuppressive myeloid populations, favor M2-like macrophage polarization, and impair effective cytotoxic T-cell activity, while leptin and adiponectin influence T-cell differentiation and metabolic fitness.[4,23,38] For precision oncology, this means that the biological behavior of obesity-associated cancers cannot be inferred from tumor genomics alone. The adipose compartment is therefore both a biomarker source and a therapeutic target.

TUMOR-SPECIFIC EVIDENCE

Breast cancer remains the most thoroughly studied model of adipokine-tumor interaction. Leptin can promote growth, invasion, angiogenesis, and epithelial-mesenchymal transition (EMT) in both hormone receptor-positive and triple-negative settings, whereas adiponectin is generally associated with lower risk or more favorable metabolic signaling.[18,39,40] Because mammary tissue is embedded in adipose tissue, adipokine effects are likely to be especially relevant in local microenvironmental signaling and endocrine crosstalk. Clinical cohort data have also examined circulating leptin, adiponectin, and resistin in relation to long-term breast cancer prognosis, underscoring the need to interpret biomarkers within patient phenotype and treatment context.[41] Colorectal cancer provides a second important model. Elevated leptin and lower adiponectin have been associated with colorectal adenoma and carcinoma risk in multiple analyses, although the strength of association can change after adjustment for body mass index (BMI) and metabolic covariates.[42,43] This heterogeneity is informative rather than merely contradictory: Adipokines likely participate in early neoplastic and inflammatory transitions, but their net predictive value depends on broader host context. Endometrial, ovarian, and hepatocellular cancers further illustrate the breadth of adipokine relevance. Endometrial cancer is strongly linked to obesity, altered estrogen metabolism, insulin signaling, and adipose inflammation.[44–47] Ovarian tumors interact closely with omental adipose tissue and CAAs.[48] Hepatocellular carcinoma often emerges in the setting of NAFLD (Non-alcoholic fatty liver disease), insulin resistance, fibrosis, and adipokine dysregulation.[49,50] Reproductive-endocrine literature further supports the view that adipokines link metabolic cues to hormonal and gonadal pathways relevant to gynecologic cancer biology.[21,51,52] Together, these examples support the

view that adipokines are particularly consequential in cancers embedded in metabolically altered organ ecosystems. Recent regional studies also emphasize that biochemical breast-cancer markers and lymph-node morphology can support recurrence and metastasis prediction, which is consistent with the need to combine circulating biomarkers, tissue features, and metabolic context in precision oncology.[53,54]

BIOMARKERS, CLINICAL HETEROGENEITY, AND THE OBESITY PARADOX

Circulating adipokines have been studied as diagnostic, prognostic, and predictive biomarkers. Repeated interest has focused on leptin, adiponectin, resistin, visfatin, chemerin, and especially the leptin-to-adiponectin ratio, because these markers are biologically plausible and relatively accessible.[6,7,55] A blood-based marker that reflects tumor-promoting metabolic context would be valuable for both risk stratification and treatment planning. Clinical translation remains limited by heterogeneity, and this problem should be treated as a design challenge rather than a reason to abandon the field. Assay differences, population characteristics, timing of measurement, tumor stage, sex, comorbid diabetes, medication use, and body composition all influence results. Two individuals with the same BMI may differ markedly in visceral fat, ectopic fat, muscle mass, NAFLD status, and inflammatory burden.[50] Therefore, future models should combine serum adipokines with imaging-based body composition, metabolic phenotyping, and tissue-level receptor data. Another challenge is that serum adipokines are systemic markers whereas many decisive interactions occur locally within the TME. High circulating leptin may indicate generalized adipose dysfunction, but local receptor density or paracrine signaling at the tumor-fat interface may better predict biological effect. This transition from systemic measurement to local interpretation is essential for aligning adipokine research with precision-oncology standards. Without multidimensional approaches, clinically promising adipokines may continue to appear inconsistent simply because they are being measured too narrowly. The so-called obesity paradox does not necessarily invalidate adipokine biology. Rather, it indicates that cancer outcomes are shaped by body composition, treatment type, immune contexture, metabolic reserve, and possibly treatment tolerance. Leptin, for example, may be pro-tumorigenic in some settings while correlating

with better immunotherapy outcomes in others. The translational lesson is clear: Biomarker interpretation must be context specific and integrated with clinical phenotype. Because metabolic and inflammatory signals extend beyond classical adipokines, complementary markers such as homocysteine metabolism, MTHFR polymorphism, and oxidative DNA damage may help define high-risk or therapy-sensitive phenotypes in selected cancer contexts.[56–58]

THERAPEUTIC AND PRECISION-ONCOLOGY IMPLICATIONS

Several therapeutic strategies have translational promise. One is direct interference with pro-tumor adipokine signaling, such as leptin receptor antagonists, neutralizing antibodies, or small-molecule pathway inhibitors. Another is restoration of protective signaling through adiponectin receptor agonists, AMPK-activating agents, or metabolic interventions that improve insulin sensitivity.[8,28] A third is reprogramming CAAs to reduce inflammatory output and lipid transfer. These strategies reflect complementary ways of disrupting the metabolic support system of tumors. Combination treatment is likely to be the most realistic path forward. Adipokine-targeted interventions may sensitize tumors to endocrine therapy, chemotherapy, targeted agents, or immunotherapy rather than replacing existing modalities. Precision oncology could use adipokine profiles, receptor expression, pathway activation, and metabolic phenotype to identify patients most likely to benefit from such combinations.[7,59] This would be especially relevant in obesity-associated malignancies or tumors arising in adipose-rich microenvironments.

Lifestyle and metabolic interventions should also be viewed as translational therapies, not merely supportive care. Weight loss, physical activity, improvement of insulin sensitivity, and correction of NAFLD-related metabolic dysfunction can alter adipokine balance and may thereby modify tumor biology.[3,50] Integrating these measures into oncology care could strengthen outcomes, particularly for patients whose disease is strongly shaped by host metabolic state. A practical translational roadmap follows from this evidence. The first step is phenotyping: Patients should be characterized not only by tumor subtype but also by body composition, visceral adiposity, insulin resistance, NAFLD status, and baseline inflammatory-metabolic profile. The second step is biomarker layering, where circulating adipokines and selected receptor or pathway mark-

ers are interpreted alongside this phenotype. The third step is intervention matching: Some patients may be candidates for lifestyle-based metabolic correction, some for adipokine-informed combination therapy, and others for exploratory pathway-directed trials. The fourth step is longitudinal monitoring, because adipokine biology is dynamic and may change with treatment, weight loss, sarcopenia, or disease progression. This roadmap is especially relevant for health systems facing parallel increases in obesity, type 2 diabetes, and cancer burden. Multidisciplinary management linking oncology, endocrinology, nutrition, rehabilitation, and laboratory medicine could help operationalize adipokine-informed care. Several research priorities follow directly from this approach: Prospective studies should evaluate whether adipokine panels improve prediction of recurrence, treatment toxicity, or survival when added to standard clinicopathologic models; biomarker studies should distinguish total adipokine abundance from biologically active isoforms; tissue-based investigations should clarify receptor patterns in tumors adjacent to adipose depots; and interventional trials should test whether metabolic optimization changes adipokine profiles in ways that translate into measurable oncologic benefit. Future studies should prioritize standardized biomarker measurement, longitudinal designs, receptor-aware interpretation, and trials that test adipokine-informed intervention strategies. Such work could move the field from associative evidence toward metabolically informed personalized oncology. This broader biomarker-layering approach is particularly relevant for metabolically dysregulated patients, because oxidative stress, folate-cycle variation, and immune-metabolic imbalance may interact with adipokine signaling when tumors develop in inflammatory host environments.[56,57]

CONCLUSION

Adipokines form a mechanistic bridge between metabolic disorders and tumor progression. Their actions extend across angiogenesis, proliferation, apoptosis resistance, extracellular matrix remodeling, immune modulation, and therapeutic response. The central message is that adipokines are actionable components of host-tumor communication and should be incorporated into translational models of cancer biology. Tumor genomics remains indispensable, but metabolic phenotype, adipose tissue quality, and adipokine signaling add a second layer of clinically relevant information.

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