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The Adipose-Tumor Signaling Network in Colorectal Cancer: Metabolic Reprogramming, Immune Escape, and Therapeutic Vulnerabilities

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Abstract

Background: Obesity is increasingly recognized as a biologically active modifier of colorectal cancer (CRC), yet body mass alone does not explain how adipose tissue influences tumor behavior. Dysfunctional visceral fat releases adipokines, cytokines, lipids, and stromal signals that may reshape malignant-cell metabolism, angiogenesis, immune surveillance, and treatment response. Aim: To integrate current evidence on the adipose-tumor interface in CRC, with particular attention to leptin-centered signaling, inflammatory and metabolic reprogramming, stromal remodeling, molecular subtypes, and therapeutically actionable vulnerabilities. Methods: Mechanistic studies, translational investigations, clinical cohorts, systematic reviews, and major conceptual frameworks published through 2024 were synthesized. Results: Obesity-associated adipose dysfunction creates a signaling environment enriched in leptin, inflammatory cytokines, free fatty acids, and altered immune-cell activity. These signals converge on JAK/STAT3, PI3K/AKT/mTOR, MAPK/ERK, NF-kappaB, HIF-1 alpha, and Wnt/beta-catenin networks, promoting proliferation, survival, angiogenesis, epithelial-mesenchymal plasticity, and immune escape. Cancer-associated adipocytes may also supply lipid substrates and facilitate extracellular-matrix remodeling. The balance between leptin and adiponectin, rather than either adipokine alone, may better represent the metabolic state of the tumor host. Interactions with consensus molecular subtypes, especially metabolically enriched CMS3 and mesenchymal CMS4 disease, support a precision-oncology framework. Conclusion: Adipose tissue should be viewed as an active component of CRC biology. Integrating metabolic phenotype, adipokine signaling, and tumor molecular features may uncover clinically useful biomarkers and therapeutic strategies beyond conventional anthropometry.

Keywords: Colorectal cancer, Adipose tissue, Leptin, Tumor microenvironment, Metabolic reprogramming

Introduction

Colorectal cancer (CRC) is biologically heterogeneous and develops within a host whose metabolic state can influence carcinogenesis, treatment tolerance, and tumor evolution. The worldwide rise in overweight and obesity has therefore become relevant to oncology rather than only to prevention. Excess adiposity is associated with higher CRC risk, with stronger associations in men and for central adiposity, and the relationship is supported by large epidemiologic analyses. The central mechanistic question is no longer whether obesity and CRC coexist, but how the endocrine, inflammatory, vascular, and metabolic functions of adipose tissue alter the behavior of an established tumor. [1]

Adipose tissue is a dynamic organ composed of mature adipocytes, preadipocytes, endothelial cells, fibroblasts, macrophages, lymphocytes, and adipose-derived stromal cells. In obesity, adipocyte hypertrophy, tissue hypoxia, altered extracellular matrix, macrophage recruitment, insulin resistance, and abnormal adipokine secretion convert this compartment into a state of chronic low-grade inflammation. CRC cells arising near mesenteric and visceral fat are therefore exposed to a metabolically active microenvironment capable of providing growth signals, inflammatory mediators, and energy substrates. [2]

The biological bridge between obesity and CRC includes hyperinsulinemia, insulin-like growth factor signaling, altered sex hormones, oxidative stress, chronic inflammation, adipokine imbalance, and changes in the gut microbiome. Among adipokines, leptin has attracted particular interest because its receptor is expressed by colorectal epithelial and cancer cells and because leptin can activate pathways already central to colorectal tumorigenesis. Yet human studies have not produced a simple linear relationship between circulating leptin and clinical outcome, suggesting

that context, receptor biology, tumor genotype, sex, fat distribution, and coexisting metabolic abnormalities matter. [3]

Research Gap

Most clinical studies reduce obesity to body mass index, while most mechanistic studies examine one mediator at a time. This separation obscures the integrated adipose-tumor ecosystem in which adipocytes, immune cells, cytokines, lipids, extracellular matrix, and tumor-intrinsic pathways interact. A clinically useful framework requires connection of these levels and careful distinction between circulating biomarkers, local adipose biology, and tumor-cell receptor signaling.

Aim

To critically review the adipose-tumor signaling network in colorectal cancer and define how adipokines, inflammatory mediators, lipid transfer, immune remodeling, and tumor molecular programs may contribute to progression, treatment resistance, and therapeutic vulnerability.

Adipose Tissue Remodeling in the Cancer Host

Visceral adipose tissue differs biologically from subcutaneous fat. It has greater lipolytic activity, drains through the portal circulation, and is closely linked to insulin resistance, hepatic metabolic dysfunction, and systemic inflammation. In obesity, enlarged adipocytes may outgrow their oxygen supply, develop cellular stress, and release danger signals that attract monocytes and promote macrophage accumulation. These changes shift the adipose secretome toward interleukin-6, tumor necrosis factor- α , chemokines, and leptin while adiponectin commonly falls. This remodeling creates conditions that can support neoplastic growth and reduce metabolic homeostasis. [4]

Macrophage phenotype is especially important because adipose inflammation and tumor inflammation can reinforce each other. Obese adipose tissue contains increased numbers of macrophages arranged around damaged adipocytes, while CRC-associated macrophages can acquire programs that support angiogenesis, matrix remodeling, invasion, and immune suppression. The simplistic division into M1 and M2 states does not capture the full spectrum observed in tumors, but it remains clear that obesity can alter myeloid-cell recruitment and function in ways that favor a permissive tumor microenvironment. [5]

Adipose-derived stromal cells provide another route of communication. These cells can migrate toward tumor-derived chemokines, contribute to fibroblast-like populations, release growth factors, and influence extracellular-matrix organization. Obesity changes the abundance and behavior of stromal progenitors and may therefore affect the architecture surrounding primary and metastatic CRC. The peritumoral adipose compartment should consequently be viewed as a source of both soluble mediators and cellular participants in tumor progression. [6]

Leptin and Leptin-Receptor Signaling

Leptin is a 16-kDa adipokine encoded by LEP and produced predominantly by adipocytes. Its circulating concentration generally reflects fat mass, although sex, insulin, glucocorticoids, inflammation, and renal function also modify levels. Leptin acts through the leptin receptor, with the long isoform Ob-Rb possessing the intracellular motifs required for full signaling. Beyond hypothalamic energy regulation, leptin influences immunity, angiogenesis, hematopoiesis, and cellular proliferation, creating a biologically credible connection between obesity and tumor biology. [7]

In CRC models, leptin can activate Janus kinase 2 and STAT3, resulting in transcriptional programs that promote survival, proliferation, inflammatory signaling, and stem-like behavior. Persistent STAT3 activation is already recognized as a major oncogenic node linking malignant cells to cytokines in the tumor microenvironment. Leptin therefore does not introduce an isolated pathway; it can amplify a signaling circuit that CRC cells may already exploit through interleukin-6-family cytokines and other receptor systems. [8]

Leptin also engages PI3K/AKT/mTOR signaling. Experimental work in colorectal carcinoma has linked leptin and leptin-receptor expression with phosphorylated AKT, mTOR activity, proliferation, and reduced apoptosis. The PI3K/AKT/mTOR network integrates growth-factor

signaling with nutrient availability and protein synthesis, so chronic adipokine exposure may connect host energy status directly to tumor-cell anabolic programs. This pathway also interacts with feedback loops and genomic alterations in PIK3CA, PTEN, and upstream receptor systems, which may explain variable responses among tumors. [9]

The MAPK/ERK cascade provides a further route by which leptin can enhance proliferation and migration. RAS-RAF-MEK-ERK activity is central to CRC biology, particularly in tumors harboring RAS or BRAF alterations, and cross-talk between Ob-R signaling and this network may be highly context dependent. In cells with constitutive oncogenic activation, additional leptin signaling may change pathway intensity or parallel survival signaling rather than acting as the initiating event. This distinction is important when translating in-vitro observations into biomarker or therapeutic hypotheses. [10]

Adiponectin-Leptin Disequilibrium

Adiponectin generally moves in the opposite direction to leptin during obesity. It promotes insulin sensitivity and can activate AMP-activated protein kinase while restraining inflammatory and anabolic signaling in several experimental systems. In CRC, lower adiponectin has been associated with metabolic risk and may remove a counter-regulatory influence on mTOR, inflammation, and cellular proliferation. The resulting high-leptin/low-adiponectin state may therefore be more informative than either hormone considered independently. [11]

Clinical studies measuring circulating leptin, adiponectin, or resistin in patients with adenomas and CRC have produced heterogeneous findings. Differences in disease stage, sex distribution, fasting status, assay methodology, renal function, weight loss, and prediagnostic obesity can substantially influence circulating concentrations. Local tissue expression may also diverge from serum levels. These limitations help explain why an adipokine can appear biologically pro-tumorigenic yet show inconsistent associations with prognosis in observational cohorts. [12]

Inflammation and Immune Remodeling

Cancer-related inflammation is a recognized enabling feature of malignancy. In obesity, adipose-derived interleukin-6, tumor necrosis factor-alpha, interleukin-1beta, and chemokines can provide a chronic inflammatory background that converges with tumor-derived signals. NF-kappaB and STAT3 form an important transcriptional bridge between inflammation and oncogenesis by regulating survival genes, cytokines, angiogenic mediators, and immune-evasion programs. Their reciprocal activation can produce a self-sustaining circuit in which malignant and stromal cells continually reinforce one another. [13]

Obesity can also reshape adaptive immunity. Excess nutrients and adipokines influence T-cell differentiation, exhaustion, and trafficking, while myeloid-derived suppressor cells and tumor-associated macrophages can limit effective cytotoxic responses. Leptin itself is immunologically active and may enhance some T-cell functions in nonmalignant settings, yet chronic obesity is characterized by immune dysregulation rather than uniformly heightened immunity. For CRC, the clinical effect is likely to depend on microsatellite instability, tumor mutational burden, local microbiota, and the balance of effector and suppressive populations. [14]

The immune implications are especially relevant to deficient mismatch repair and microsatellite instability-high CRC, where abundant neoantigens and immune-cell infiltration create sensitivity to checkpoint blockade. Obesity-related inflammation could theoretically alter checkpoint expression, T-cell metabolism, and myeloid composition, but current evidence does not justify using obesity or leptin as an immunotherapy-selection biomarker. The key research need is to determine whether host metabolic phenotype modifies antitumor immunity differently across molecularly defined CRC subsets. [15]

Lipid Transfer and Metabolic Reprogramming

Cancer cells require carbon, reducing power, membrane lipids, and ATP to sustain proliferation. Adipocytes can contribute to this demand by releasing free fatty acids, glycerol, and adipokines, particularly in inflamed or lipolytic adipose tissue. Tumor cells may increase expression of fatty-

acid transporters and lipid-handling proteins, allowing exogenous fatty acids to support beta-oxidation, phospholipid synthesis, and signaling-lipid production. This creates a form of metabolic cooperation between tumor and host tissue rather than a purely cell-autonomous metabolic program. [16]

Metabolic reprogramming in cancer is not synonymous with glycolysis. CRC cells can switch among glucose, glutamine, fatty acids, and other substrates according to genotype, oxygen availability, treatment pressure, and stromal supply. The concept of metabolic flexibility is particularly relevant to obesity because abundant lipids and insulin-related signals may change the relative value of oxidative and anabolic pathways. Such plasticity may also help tumor cells survive hypoxia and chemotherapy, creating a rationale for combining metabolic interventions with standard oncologic treatment. [17]

AMPK and mTOR operate as opposing energy-sensing systems that can integrate nutrient availability with proliferation. AMPK restrains anabolic activity during energy stress, while mTOR complex 1 promotes protein and lipid synthesis when growth factors and nutrients are sufficient. Obesity-associated hyperinsulinemia, leptin signaling, and amino-acid availability may favor mTOR activity, whereas metabolic stress can reactivate AMPK and autophagy. The therapeutic challenge is that these pathways are essential to normal tissues and are embedded in redundant signaling networks. [18]

Angiogenesis, Hypoxia, and Vascular Signaling

Adipose expansion and solid-tumor growth both create hypoxic microenvironments. Hypoxia-inducible factor-1 α promotes glycolysis, angiogenic signaling, invasion, and adaptation to low oxygen. Leptin and inflammatory mediators can enhance vascular endothelial growth factor production, while dysfunctional adipose tissue supplies additional proangiogenic factors. In CRC, this may reinforce the angiogenic switch required for sustained tumor expansion and dissemination. [19]

Tumor angiogenesis produces structurally abnormal vessels with irregular perfusion and regional hypoxia. Anti-VEGF therapy improves outcomes in selected CRC settings, yet resistance commonly develops through pathway redundancy, stromal adaptation, and vascular remodeling. Adipose-derived signals could contribute to this redundancy, although direct evidence that leptin levels predict bevacizumab benefit remains insufficient. Mechanistic studies should therefore distinguish a plausible pathway interaction from a validated predictive biomarker. [20]

Epithelial-Mesenchymal Plasticity and Metastatic Competence

Epithelial-mesenchymal transition is better understood as a spectrum of reversible cell states than as a binary switch. Partial mesenchymal programs can increase motility, invasion, stemness, and treatment resistance while preserving enough epithelial identity for collective migration and metastatic colonization. Inflammatory cytokines, TGF- β , hypoxia, STAT3, and PI3K/AKT signaling can all contribute to these states, providing multiple points at which obesity-related signals may intersect with metastatic biology. [21]

Peritumoral adipocytes may be particularly relevant at invasive fronts, where direct contact with cancer cells, local lipolysis, and matrix remodeling occur together. Adipocyte-derived lipids can support energy-demanding migration, while inflammatory and stromal signals increase matrix metalloproteinases and alter adhesion. Experimental and translational studies increasingly describe cancer-associated adipocytes as active participants in metastasis, although the extent to which this concept applies uniformly across colon, rectal, liver-metastatic, and peritoneal disease remains under investigation. [22]

Interaction With Molecular Subtypes of Colorectal Cancer

The consensus molecular subtype framework divides CRC into four broad biological groups. CMS1 is immune and frequently MSI-high; CMS2 is canonical with strong Wnt and MYC signaling; CMS3 displays prominent metabolic features and frequent KRAS alterations; and CMS4 is mesenchymal with stromal activation, TGF- β signaling, angiogenesis, and the poorest prognosis.

This taxonomy provides a useful scaffold for asking whether host adipose biology has subtype-specific effects rather than assuming a uniform obesity signal across CRC. [23]

CMS3 is especially relevant to metabolic phenotyping because its transcriptional profile reflects altered nutrient handling and metabolic pathways. Obesity-associated hyperinsulinemia, circulating lipids, and adipokines may be more consequential in tumors capable of exploiting these substrates and signals. Direct clinical evidence linking visceral adiposity or leptin to CMS3 remains limited, but the hypothesis is testable using integrated tumor transcriptomics, plasma metabolomics, and CT-derived body-composition data. [24]

CMS4 tumors show stromal infiltration, extracellular-matrix remodeling, TGF-beta activation, angiogenesis, and immune suppression. These features overlap strikingly with biological consequences of dysfunctional adipose tissue. A plausible model is that obesity does not create CMS4 identity but may reinforce an already permissive mesenchymal ecosystem through inflammatory myeloid cells, fibroblast activation, hypoxia, and lipid availability. The poor prognosis associated with CMS4 makes this interaction particularly important for translational studies. [25]

Molecular subtypes are not fixed entities. Intratumoral heterogeneity, metastatic-site selection, and treatment pressure can alter transcriptional states, while bulk-tumor profiling may partly reflect stromal abundance rather than malignant-cell identity. Any attempt to combine metabolic phenotype with CMS therefore requires spatial and single-cell approaches that distinguish tumor, immune, fibroblast, endothelial, and adipocyte contributions. [26]

Obesity-Associated Biology and Treatment Response

Obesity can influence cancer therapy through several mechanisms that are not interchangeable: pharmacokinetic variation, altered drug distribution, dose capping, organ dysfunction, inflammation, insulin resistance, and tumor-cell signaling. Early concern that full chemotherapy dosing would cause excessive toxicity in obese patients led to empiric dose reductions in some settings, but professional guidance supports full weight-based cytotoxic dosing when treatment intent is curative. Under-dosing can compromise relative dose intensity and should not be justified by obesity alone. [27]

At the cellular level, PI3K/AKT/mTOR, STAT3, NF-kappaB, and EMT programs can promote resistance to fluoropyrimidines, oxaliplatin, targeted agents, and radiation through enhanced survival, DNA-damage tolerance, stemness, and anti-apoptotic signaling. Because adipokines and inflammatory cytokines feed into several of these networks, the obese host may provide a biological background that facilitates resistance in susceptible tumors. Evidence remains strongest at the mechanistic level; prospective CRC trials incorporating metabolic biomarkers are still needed. [28] Targeted therapy introduces additional complexity. RAS and BRAF mutations dominate selection for anti-EGFR treatment, while VEGF-directed therapy is used independently of body size. Obesity-related growth signaling could theoretically modify pathway dependence, but no adipokine currently overrides validated molecular biomarkers. The appropriate translational strategy is therefore additive: metabolic features may refine risk or resistance models after standard genomic determinants are accounted for, rather than replace them. [29]

Immunotherapy offers another area of interest because obesity has been associated with altered checkpoint biology and outcomes in several cancers. The relationship is inconsistent across tumor types and may reflect sex, treatment class, immune context, and confounding. In CRC, where checkpoint inhibitors are primarily effective in dMMR/MSI-high disease, the priority is to test whether body composition, metabolic inflammation, or adipokines explain residual heterogeneity within an already biomarker-selected population. [30]

Therapeutic Opportunities at the Adipose-Tumor Interface

Direct leptin-receptor blockade remains experimental. Although the pathway is attractive, systemic inhibition risks interfering with neuroendocrine and immune functions, and tumors may bypass a single adipokine through redundant cytokine and growth-factor signaling. More realistic

approaches may target shared downstream nodes or the broader metabolic state of the host. Any such strategy must demonstrate selectivity, pharmacodynamic target engagement, and benefit beyond existing molecularly guided therapy. [31]

STAT3 is an appealing target because it integrates cytokine, growth-factor, and immune signals, yet direct pharmacological inhibition has historically been difficult. Newer degraders, oligonucleotide approaches, and upstream JAK inhibition continue to be explored across malignancies. In CRC, pathway activity may be highest in selected inflammatory or mesenchymal tumors, so biomarker-driven designs are more rational than unselected treatment. [32]

The PI3K/AKT/mTOR axis is similarly attractive but biologically complex. Multiple inhibitors have entered oncology, yet feedback activation and toxicity have limited durable success in many solid tumors. PIK3CA mutations, PTEN status, insulin feedback, and concurrent MAPK activation can all influence response. The metabolic environment of obesity adds another layer because systemic hyperinsulinemia can reactivate signaling even when a tumor pathway is pharmacologically suppressed. [33]

Metabolic interventions may modify several pathways simultaneously. Weight reduction, physical activity, improved insulin sensitivity, and preservation of skeletal muscle can lower inflammatory burden and improve cardiometabolic health, although evidence that these interventions directly reduce CRC recurrence remains incomplete. Exercise is particularly attractive because it affects insulin sensitivity, myokines, inflammation, vascular function, and body composition without requiring a single molecular target. [34]

Metformin has generated interest because of AMPK-related effects, reduced hepatic glucose production, and observational associations with cancer outcomes in diabetes. Randomized evidence has not established metformin as a general anticancer drug in CRC, and its use should follow metabolic indications rather than speculative oncologic benefit. Still, it illustrates how host-directed interventions can be tested alongside tumor-directed treatment. [35]

Microbiome-Adipose-Tumor Crosstalk

Diet and obesity also reshape the intestinal microbiome, bile-acid pool, barrier function, and microbial metabolites. CRC-associated dysbiosis can promote genotoxic exposure, inflammation, and altered immune responses, while adiposity and diet influence the same ecosystem. This creates a three-way interaction among microbiota, host metabolism, and tumor biology. Short-chain fatty acids, secondary bile acids, and microbial products may therefore modify both adipose inflammation and epithelial signaling. [36]

A major challenge is directionality. Cancer, chemotherapy, antibiotics, weight loss, and altered diet can all change the microbiome after diagnosis, making cross-sectional associations difficult to interpret. Future studies should use longitudinal sampling and integrate stool metagenomics with metabolomics, inflammatory markers, body composition, and tumor molecular data. Such designs can determine whether microbiome features mediate obesity-related CRC biology or merely track with it. [37]

From Circulating Biomarkers to Integrated Metabolic Phenotyping

Circulating leptin is easy to measure but is not tumor specific. Its concentration is influenced strongly by total and regional adiposity and can change with weight loss, renal dysfunction, and systemic inflammation. Tissue expression of leptin or Ob-R may provide different information because it reflects local receptor availability and paracrine signaling. Several CRC studies have reported associations between tissue leptin expression and clinicopathologic characteristics, but the direction of prognostic effect has not been uniform. [38]

This inconsistency argues against interpreting serum leptin as a stand-alone prognostic marker. A stronger framework would combine adipokines with CT-derived visceral fat, skeletal muscle, insulin resistance, C-reactive protein, diabetes status, and tumor molecular features. Such multimodal phenotyping could distinguish metabolically unhealthy obesity from high BMI with preserved muscle and limited inflammation, which are biologically different states despite similar

body weight. [39]

Spatial technologies offer an additional opportunity. Single-cell RNA sequencing, spatial transcriptomics, multiplex imaging, and metabolomic profiling can identify where adipocyte-derived signals act, which cells express leptin receptors, and how immune or fibroblast states change at tumor-fat interfaces. These approaches are particularly relevant in pericolic fat, mesorectum, liver metastases, and peritoneal disease, where adipose contact differs anatomically. [40]

Clinical and Translational Priorities

Prospective CRC cohorts should measure weight history rather than a single BMI value, because prediagnostic weight loss can obscure prior obesity and create reverse-causation bias. They should also quantify visceral fat, subcutaneous fat, skeletal muscle, and muscle attenuation on routine staging CT. Linking these measurements to serum adipokines and inflammatory markers would allow investigators to test whether leptin adds information beyond direct assessment of body composition. [41]

Clinical trials examining metabolic modifiers should stratify by disease stage, treatment intent, sex, diabetes, and molecular subtype. An intervention that changes insulin or leptin biology may have different consequences in localized versus metastatic disease, in MSI-high versus microsatellite-stable tumors, or in CMS3 versus CMS4 biology. Without this stratification, biologically meaningful effects may be diluted by heterogeneity. [42]

The endpoint must also match the mechanism. Biomarker modulation can establish target engagement, but recurrence and survival require long follow-up in curative settings. Window-of-opportunity studies can examine Ki-67, phospho-STAT3, phospho-AKT, immune-cell composition, and metabolic signatures before and after short interventions, providing mechanistic evidence before committing to large outcome trials. [43]

The strongest precision-oncology model is therefore bidirectional: tumor genomics should inform how a cancer may respond to host metabolic signals, while host phenotype should inform the environment in which that tumor evolves. This model avoids the false choice between tumor-centered and host-centered oncology and recognizes that clinically relevant disease behavior emerges from both. [44]

Future Therapeutic Directions

New therapies could target adipose inflammation, fatty-acid transport, stromal recruitment, or metabolic signaling, but translation will require careful toxicity assessment because these pathways support normal physiology. CD36 and fatty-acid handling are attractive in highly lipid-dependent tumors, while agents affecting fibroblast or macrophage programs may disrupt the supportive microenvironment. Combination strategies are likely to be more effective than single-node inhibition because metabolic networks rapidly adapt. [45]

Anti-inflammatory strategies require similar caution. Broad suppression may impair host defense and antitumor immunity, whereas pathway-selective approaches could theoretically reduce tumor-promoting inflammation without eliminating immune competence. The success of such strategies will depend on identifying patients in whom inflammatory signaling is truly a driver rather than a correlate of advanced disease. [46]

Angiogenesis, metabolism, and immunity should not be studied in isolation. Hypoxia can alter immune-cell function; lipid metabolism can affect T-cell fitness; and VEGF can promote both vascular remodeling and immune suppression. Multi-omic studies that capture these interactions may identify composite signatures more robust than a single cytokine or adipokine. [47]

Lifestyle interventions remain clinically important regardless of whether they become anticancer therapies. Maintaining healthy body composition, physical activity, and metabolic control can reduce cardiovascular risk, diabetes complications, and treatment morbidity. In survivorship, these benefits matter even when the magnitude of direct recurrence reduction is uncertain. Medical oncology should therefore integrate metabolic health into long-term care without overstating

unproven tumor-specific effects. [48]

For the obese patient with CRC, management should remain anchored in established oncologic principles while recognizing obesity-related surgical, pharmacological, and supportive-care needs. Current reviews call for more explicit guidance on perioperative pathways, surveillance, and multidisciplinary management in this growing population. The next step is to move from generic obesity categories toward biologically informative phenotypes that can be incorporated into trials and clinical decision models. [49,50]

Insulin, IGF Signaling, and the Metabolic Milieu

Hyperinsulinemia is an important companion to adipokine dysregulation in visceral obesity. Insulin can act directly through the insulin receptor and indirectly by reducing hepatic production of insulin-like growth factor-binding proteins, thereby increasing bioavailable IGF-1. Colorectal epithelial cells and tumors frequently express insulin and IGF receptors, allowing systemic metabolic signals to converge with RAS/MAPK and PI3K/AKT pathways. This creates a mechanistic bridge between insulin resistance and tumor growth that is independent of leptin yet highly interactive with it. In clinical research, separating the effects of leptin from insulin and diabetes is therefore essential because these exposures cluster strongly in the same patients. [3]

The relationship is further complicated by treatment and nutrition. Corticosteroids, reduced physical activity, enteral or parenteral nutritional changes, and treatment-related weight gain can alter insulin sensitivity during the cancer journey. Conversely, advanced disease and cachexia can lower insulin and leptin despite highly aggressive tumor biology. Serial metabolic measurements are more informative than a single pre-treatment sample because they can distinguish stable host phenotype from changes induced by cancer or its treatment. [41]

Adipose tissue fibrosis may also influence metabolic signaling. Chronic expansion of visceral fat increases extracellular-matrix deposition, tissue stiffness, hypoxia, and impaired adipocyte plasticity. These changes promote further inflammation and insulin resistance while creating a stromal environment rich in collagen, fibroblast activity, and matrix-remodeling enzymes. The biological overlap with desmoplastic tumor stroma is notable, particularly in CMS4 disease, and deserves direct study at the tumor-adipose interface. [25]

Anatomic Context: Colon, Rectum, Liver, and Peritoneal Fat

The adipose environment surrounding CRC is anatomically heterogeneous. Colon tumors interact with mesocolic fat, rectal tumors with mesorectal fat, liver metastases with hepatic stellate cells and steatotic liver biology, and peritoneal metastases with omental and mesenteric adipose depots. These compartments differ in vascular drainage, immune-cell composition, lipid handling, and stromal architecture. Pooling all CRC locations may therefore obscure site-specific metabolic interactions, especially when obesity changes each tissue differently. [6]

The liver is a particularly important metabolic and metastatic organ. Portal venous delivery exposes the liver to insulin, free fatty acids, bile-acid metabolites, and gut-derived products, while obesity can produce steatosis and steatohepatitis. These conditions may alter the hepatic immune microenvironment and the capacity of disseminated CRC cells to establish metastatic niches. Although clinical evidence remains incomplete, integrating liver fat quantification with circulating metabolic markers could clarify whether host hepatic phenotype influences metastatic recurrence after treatment of localized CRC. [16]

Peritoneal disease provides another biologically plausible setting for adipocyte-tumor cooperation because malignant cells can come into direct contact with lipid-rich omental and mesenteric tissue. Evidence from several malignancies shows that adipocytes can donate fatty acids and alter tumor-cell metabolism. Whether a similar process drives CRC peritoneal implantation, chemotherapy resistance, or recurrence is an important question for translational models that reproduce the actual anatomic microenvironment. [22]

Sex, Age, and Host Heterogeneity

Obesity-associated CRC risk and body-fat distribution differ by sex. Men generally accumulate

more visceral adipose tissue, while premenopausal women have a greater proportion of subcutaneous fat; menopause shifts this balance toward visceral deposition. Leptin concentrations also differ by sex even at comparable BMI. These factors can modify the strength of adipokine, insulin, and inflammatory signals and may partly explain sex-specific epidemiologic associations. Future biomarker studies should be powered for sex-stratified analyses rather than treating sex only as a covariate. [1]

Age adds another layer because older adults may gain fat while losing muscle, producing sarcopenic obesity without major change in BMI. Immunosenescence, altered sex hormones, comorbidity, and polypharmacy can further modify inflammatory and metabolic pathways. Integrating age-related body-composition change with tumor biology may be especially useful in CRC, where incidence rises strongly with age and treatment decisions often balance recurrence risk against physiologic reserve. [48]

Interpreting Biomarkers in Clinical Practice

A useful biomarker must add information beyond readily available clinical variables and remain reproducible across laboratories. For leptin, this means demonstrating incremental value over BMI, visceral fat, sex, diabetes, inflammatory markers, and tumor stage. Cutoffs derived from small single-center cohorts are unlikely to generalize because leptin distributions vary markedly across populations. Future studies should therefore prespecify assays, fasting conditions, sampling time, and analytic plans, and should report discrimination, calibration, and clinical utility rather than statistical significance alone. [38]

The distinction between prognostic and predictive value is equally important. A marker can identify patients with worse outcomes without indicating benefit from a particular therapy. Leptin, visceral adiposity, or inflammatory signatures should not be used to select chemotherapy, anti-EGFR therapy, anti-VEGF therapy, or immunotherapy unless an interaction with treatment benefit is demonstrated. This standard protects precision oncology from converting biological plausibility into unsupported treatment decisions. [29]

Biomarkers may prove most useful as components of composite models. Combining a circulating signal such as leptin with CT body composition, C-reactive protein, metabolic comorbidity, and tumor molecular data could capture distinct dimensions of host-tumor interaction. Machine-learning approaches may help model nonlinear relationships, but transparent validation and clinically interpretable outputs are essential if such tools are to influence follow-up intensity or supportive interventions. [39]

The translational value of this field will ultimately depend on intervention. If a metabolic phenotype identifies risk but cannot guide a change in surveillance, supportive care, lifestyle intervention, or therapy, its clinical impact will remain limited. Studies should therefore be designed from the outset with a plausible action linked to the biomarker-defined state, moving the field from association toward decision support. [49]

Conclusion

Adipose tissue is an active participant in colorectal cancer biology rather than a passive energy reservoir. Through leptin and other adipokines, inflammatory cytokines, lipid transfer, immune remodeling, angiogenesis, and stromal interactions, dysfunctional adipose tissue can converge on signaling networks already central to malignant progression. The clinical significance of these mechanisms is likely to depend on fat distribution, muscle mass, metabolic health, and tumor molecular subtype. Future work should replace single-marker and BMI-only models with integrated phenotyping that combines body composition, circulating biology, spatial tumor-microenvironment analysis, and genomics. Such an approach offers the most credible route from obesity epidemiology to actionable precision oncology.

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