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Cross-Talk Between Adipose Tissue Dysfunction and Tumor Microenvironment: Therapeutic Insights from Nano-Nutraceuticals

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ABSTRACT

Adipose tissue is not merely a fat storage site but an active endocrine organ involved in energy homeostasis, immune modulation, and systemic inflammation. Dysfunctional adipose tissue, particularly in obesity, is characterized by chronic low-grade inflammation, altered adipokine secretion, and immune cell infiltration—all of which contribute to the development and progression of various cancers. The tumor microenvironment (TME), comprising cancer cells, stromal cells, immune cells, and extracellular matrix components, is similarly influenced by these aberrant signals from adipose tissue. This review explores the intricate bidirectional communication between adipose tissue dysfunction and the TME, focusing on shared inflammatory, metabolic, and immunological pathways. Furthermore, we highlight the emerging potential of nano-nutraceuticals nutrient-based compounds delivered through nanotechnology for modulating this cross-talk. Nano-nutraceuticals offer targeted delivery, improved bioavailability, and reduced systemic toxicity, making them promising candidates for cancer prevention and therapy in the context of obesity-associated malignancies. This review underscores the need for integrated therapeutic strategies targeting both adipose tissue dysfunction and the TME to enhance cancer treatment outcomes.

Keywords: Adipose tissue dysfunction, Tumor microenvironment, Obesity, Nano-nutraceuticals, Cancer therapy

INTRODUCTION

Adipose tissue, traditionally recognized as a passive energy reservoir, has emerged as a dynamic endocrine organ intricately involved in metabolic regulation, immune modulation, and intercellular communication[1, 2]. In pathological states such as obesity, adipose tissue undergoes significant structural and functional remodeling, characterized by chronic low-grade inflammation, hypoxia, oxidative stress, and dysregulated secretion of adipokines and cytokines[3–5]. This dysfunctional state creates a systemic pro-inflammatory milieu that not only promotes metabolic disorders but also significantly contributes to tumor initiation, progression, and metastasis. Increasing evidence underscores the bidirectional cross-talk between dysfunctional adipose tissue and the tumor microenvironment (TME), a complex and heterogeneous ecosystem comprising cancer cells, immune cells, fibroblasts, extracellular matrix components, and various soluble mediators[6–8]. The interaction between dysfunctional adipocytes and the TME plays a pivotal role in modulating cancer cell proliferation, invasion, angiogenesis, immune evasion, and therapy resistance[9]. Key molecular mediators such as leptin, adiponectin, interleukins, and tumor necrosis factor-alpha (TNF-α) are central to this cross-communication, influencing oncogenic signaling pathways including PI3K/Akt, JAK/STAT, and NF-κB. Additionally, metabolic reprogramming within the TME, partly driven by adipocyte-derived lipids and metabolites, supports the energetic and biosynthetic demands of rapidly proliferating tumor cells[9]. Understanding the intricate interplay between adipose tissue dysfunction and the TME is crucial for developing novel therapeutic strategies aimed at disrupting this pathological liaison. In recent years, nano-nutraceuticals such as bioactive compounds derived from natural sources and delivered via nanotechnology-based carriers have garnered significant attention for their potential to modulate both metabolic dysfunction and tumorigenesis[10, 11]. These nano-formulations enhance the solubility, stability, bioavailability, and targeted delivery of nutraceuticals, thereby amplifying their therapeutic efficacy while minimizing systemic toxicity. Notably, nano-

nutraceuticals such as curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) have demonstrated promising anti-inflammatory, antioxidant, anti-adipogenic, and anti-cancer properties. Their dual action on adipose tissue homeostasis and tumor cell signaling pathways positions them as attractive candidates for integrative cancer therapy[12]. This review explores the molecular mechanisms underlying the cross-talk between adipose tissue dysfunction and the TME, with a focus on how this interaction fuels tumor progression. It further highlights the emerging role of nano-nutraceuticals in mitigating this pathological synergy by targeting key regulatory pathways. By bridging the gap between metabolic dysfunction and oncology, this integrative approach offers novel insights into preventive and therapeutic strategies that harness the potential of nutrition-based nanomedicine in cancer management.

Adipose Tissue Dysfunction: Characteristics and Mechanisms

Inflammation and Immune Dysregulation

In obesity, adipose tissue undergoes significant structural and functional remodeling, beginning with its expansion due to excessive caloric intake[13, 14]. This expansion is often accompanied by adipocyte hypertrophy, which outpaces angiogenesis, leading to localized tissue hypoxia. Hypoxic conditions, in turn, result in increased adipocyte apoptosis or necrosis. The dying adipocytes release danger-associated molecular patterns (DAMPs) and other signals that recruit immune cells, particularly macrophages, into the adipose tissue[15]. These infiltrating macrophages surround necrotic adipocytes in crown-like structures, a hallmark of inflamed adipose tissue, and secrete pro-inflammatory cytokines that perpetuate tissue inflammation[16, 17].
A major immune shift also occurs in the cellular landscape of obese adipose tissue. Under normal physiological conditions, adipose tissue is enriched with anti-inflammatory M2 macrophages and regulatory T cells that promote tissue homeostasis[18]. However, in obesity, the immune cell profile transitions toward a pro-inflammatory phenotype dominated by M1 macrophages, neutrophils, and Th1-type CD4+ T cells. This shift contributes to the chronic low-grade inflammation characteristic of metabolic syndrome and alters systemic immune responses[18]. The elevated production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) not only disrupts insulin signaling but also primes the body for systemic inflammation, thereby affecting distant organs and tissues, including tumor sites[18].
This chronic inflammatory state can significantly modulate cancer progression. The increased cytokine load from dysfunctional adipose tissue can influence the tumor microenvironment (TME) by promoting the recruitment of immune cells that favor tumor progression, such as tumor-associated macrophages and myeloid-derived suppressor cells[19, 20]. These immune alterations lead to a microenvironment that supports angiogenesis, suppresses anti-tumor immune responses, and fosters tumor cell proliferation and metastasis. Thus, adipose tissue inflammation acts as a bridge linking metabolic dysfunction to oncogenesis, especially in cancers associated with obesity.

Altered Adipokine Secretion

Beyond inflammation, adipose tissue also functions as an endocrine organ by secreting various adipokines—bioactive peptides that play critical roles in metabolic homeostasis and immune regulation. In obesity, the adipokine secretion profile is dramatically altered, disrupting systemic and local signaling pathways[21, 22]. One of the most prominent adipokines, leptin, is upregulated in obese individuals and exerts multiple oncogenic effects. It promotes cell proliferation, angiogenesis, and migration in cancer cells via activation of signaling pathways such as JAK/STAT3, PI3K/AKT, and MAPK[23, 24]. Elevated leptin levels also enhance the expression of vascular endothelial growth factor (VEGF), further promoting neovascularization in tumors.
In contrast, adiponectin, another key adipokine, is typically downregulated in obese states. Adiponectin is known for its anti-inflammatory, anti-proliferative, and insulin-sensitizing properties[25]. Its decreased levels are associated with an increased risk of several obesity-related cancers, including breast and colorectal cancers. Adiponectin exerts tumor-suppressive effects by inhibiting NF-κB signaling, reducing oxidative stress, and promoting apoptosis in cancer cells. The imbalance between leptin and adiponectin creates a tumor-promoting environment by favoring survival signals over apoptotic cues in neoplastic cells[26].
Other adipokines such as resistin and visfatin are also implicated in tumor biology. Resistin has been associated with inflammation-induced tumorigenesis, while visfatin mimics insulin and can activate similar pathways to support cellular metabolism in tumors[27]. Collectively, these changes in adipokine secretion due to adipose tissue dysfunction not only contribute to systemic metabolic dysregulation but also foster a biochemical milieu conducive to cancer initiation and progression[27]. Understanding these adipokine-mediated mechanisms provides a potential avenue for therapeutic interventions that could restore a healthier adipokine balance to impede tumor development.

Metabolic Reprogramming

One of the hallmark features of cancer cells is their ability to undergo metabolic reprogramming to meet the demands of rapid growth and proliferation[28]. Dysfunctional adipose tissue in obesity plays a key role in

fueling this metabolic shift. Adipocyte dysfunction leads to increased lipolysis and the release of free fatty acids (FFAs) into circulation. These FFAs are taken up by tumor cells and used as a source of energy and as precursors for membrane biosynthesis[28]. Tumors with high lipid uptake exhibit enhanced survival and aggressiveness, particularly under nutrient-deprived or hypoxic conditions commonly found within the TME.

Furthermore, obesity-induced insulin resistance exacerbates hyperinsulinemia, which stimulates the insulin/IGF-1 signaling pathway—a key driver of cancer cell metabolism and proliferation. Insulin resistance also promotes glucose uptake in peripheral tissues, leading to elevated blood glucose levels[1, 29, 30]. Tumor cells exploit this glucose surplus through aerobic glycolysis, known as the Warburg effect, to produce ATP and metabolic intermediates for rapid growth. The simultaneous availability of both glucose and lipids in the obese host creates a metabolic landscape that greatly benefits neoplastic transformation and progression.

In addition, adipose tissue-derived exosomes have been identified as carriers of metabolic enzymes and regulatory microRNAs that influence cancer cell metabolism[31, 32]. These extracellular vesicles can deliver components that enhance glycolysis, lipid metabolism, and mitochondrial function in cancer cells. This intercellular transfer of metabolic cargo further exemplifies the active role of dysfunctional adipose tissue in orchestrating tumor-supportive metabolic reprogramming[32]. Consequently, targeting adipose-tumor metabolic crosstalk offers a promising strategy to interrupt the metabolic symbiosis that underpins obesity-driven tumorigenesis.

Tumor Microenvironment (TME): Composition and Dynamics

Cellular Components

The tumor microenvironment (TME) is a complex and dynamic network of various cellular components that collectively contribute to tumor initiation, progression, and metastasis[8]. Among the most prominent are cancer-associated fibroblasts (CAFs), which secrete extracellular matrix (ECM) components and growth factors that support tumor cell survival and invasiveness. Immune cells such as T cells, macrophages, and neutrophils are often recruited to the TME, where their phenotypes are skewed toward tumor-promoting roles. Tumor-associated macrophages (TAMs), for example, frequently adopt an M2-like phenotype, facilitating immune suppression, angiogenesis, and matrix remodeling[33]. Similarly, regulatory T cells (Tregs) suppress cytotoxic immune responses, enabling immune evasion by tumor cells. Endothelial cells within the TME promote the formation of aberrant vasculature, crucial for sustaining tumor growth[33]. Mesenchymal stem cells (MSCs), recruited from adipose tissue and other sources, also differentiate into CAFs and secrete immunomodulatory cytokines. Notably, in the context of obesity, dysfunctional adipose tissue releases an abundance of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and adipokines (e.g., leptin), which modulate the behavior of these cellular components[33]. The convergence of these cell types and inflammatory cues creates a pro-tumorigenic environment, characterized by chronic inflammation, immune suppression, and enhanced tumor cell plasticity and survival.

Hypoxia and Angiogenesis

Hypoxia, or low oxygen availability, is a hallmark of both obese adipose tissue and solid tumors, serving as a major driver of angiogenesis and tumor aggressiveness[34]. In obesity, hypertrophic adipocytes expand beyond their vascular supply, resulting in localized hypoxic regions. Similarly, rapidly proliferating tumor cells outpace their blood supply, creating intratumoral hypoxia. This condition triggers the stabilization and activation of hypoxia-inducible factors (HIFs), particularly HIF-1α, which in turn upregulates genes involved in angiogenesis, metabolism, and survival. One of the most critical downstream targets of HIF-1α is vascular endothelial growth factor (VEGF), a potent stimulator of new blood vessel formation[35]. However, the vasculature induced by VEGF in tumors is often abnormal—leaky, disorganized, and inefficient—failing to restore oxygen balance but facilitating tumor cell dissemination. Additionally, obesity-related metabolic stress enhances HIF signaling and synergizes with VEGF pathways, exacerbating abnormal angiogenesis[35]. This hypoxic and angiogenic environment fosters tumor invasiveness, immune escape, and resistance to therapies, including chemotherapy and radiation. Moreover, hypoxia modulates immune cell infiltration and polarization, further reinforcing the immunosuppressive nature of the TME. Therefore, hypoxia and the resulting pathological angiogenesis represent pivotal links between obesity and enhanced tumor progression.

Immune Suppression

The tumor microenvironment (TME) is adept at circumventing immune surveillance by creating an immunosuppressive milieu that impairs anti-tumor immunity[7, 27]. One of the primary mechanisms involves the expansion of regulatory T cells (Tregs), which inhibit the function of cytotoxic T lymphocytes and natural killer (NK) cells through cytokine release and cell-contact mechanisms. Another critical contributor is the accumulation of myeloid-derived suppressor cells (MDSCs), which inhibit T cell activation and promote tumor-supportive inflammation[36]. These cells secrete immunosuppressive mediators such as arginase-1, nitric oxide, and reactive oxygen species, all of which dampen immune responses. Checkpoint molecules like PD-1, CTLA-

4, and their ligands (PD-L1, B7) are upregulated within the TME, facilitating T cell exhaustion and tumor immune escape.[36] Obesity compounds this immunosuppressive environment through adipose-derived exosomes and inflammatory cytokines like IL-6 and leptin, which modulate immune cell function. Leptin, in particular, promotes Treg proliferation and MDSC recruitment[37]. Furthermore, obesity-induced chronic low-grade inflammation alters the differentiation and polarization of immune cells, promoting a phenotype that supports tumor progression rather than elimination[37]. Together, these factors create a hostile environment for anti-tumor immunity, enabling tumors to grow unchecked despite the presence of immune effector cells.

Cytokine and Adipokine Signaling

Cytokines and adipokines derived from adipose tissue play crucial roles in shaping the tumor microenvironment (TME) through sustained inflammatory signaling. In obesity, hypertrophic adipocytes and infiltrating immune cells secrete elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and MCP-1[4, 38]. These mediators not only contribute to systemic inflammation but also influence the local TME by promoting the recruitment, activation, and polarization of immune cells, particularly macrophages and neutrophils, toward tumor-supportive phenotypes[39]. Leptin, an adipokine whose levels are elevated in obesity, promotes angiogenesis, cellular proliferation, and immune suppression[40]. Conversely, adiponectin, generally reduced in obesity, has anti-inflammatory and anti-tumorigenic effects. The imbalance between pro- and anti-inflammatory adipokines drives a feed-forward loop of chronic inflammation, stimulating tumor growth and resistance to therapy. Moreover, these signals can directly activate oncogenic pathways such as JAK/STAT, NF-κB, and PI3K/AKT in tumor cells, enhancing survival, proliferation, and metastatic potential[41]. Stromal cells within the TME, including CAFs and endothelial cells, also respond to these signals, further amplifying the pro-tumorigenic environment[41]. This dynamic cross-talk underscores the central role of adipose-derived factors in reprogramming the TME toward malignancy.

Extracellular Vesicles and Exosomes

Extracellular vesicles (EVs), particularly exosomes secreted by adipocytes, have emerged as critical mediators of communication between adipose tissue and the tumor microenvironment (TME)[42]. These nano-sized vesicles carry a diverse cargo, including microRNAs (miRNAs), lipids, and proteins that can modulate gene expression and signaling pathways in recipient cells. In obesity, the content and quantity of adipocyte-derived exosomes are altered, often favoring a pro-tumorigenic profile. For instance, specific miRNAs within these exosomes can downregulate tumor suppressor genes or enhance pathways that promote epithelial-to-mesenchymal transition (EMT), a key process in cancer invasion and metastasis[42]. Lipids delivered through exosomes can also alter cellular metabolism in tumor and stromal cells, supporting rapid proliferation and survival. Additionally, exosomal proteins such as MMPs (matrix metalloproteinases) contribute to extracellular matrix remodeling, facilitating cancer cell dissemination[42]. These vesicles also modulate immune responses, either by inhibiting cytotoxic activity or promoting immunosuppressive cell phenotypes, further aiding tumor progression. Importantly, the interaction between adipocyte-derived exosomes and cancer cells has been documented in multiple cancers, including breast, ovarian, and prostate cancers[42]. Their systemic effects and ability to traverse biological barriers make them key players in obesity-associated cancer progression.

Lipid Transfer and Energy Supply

Adipocytes serve as a reservoir of energy-rich lipids that can be mobilized and transferred to nearby tumor cells, creating a direct metabolic support system within the tumor microenvironment (TME). This lipid transfer is particularly relevant in obesity[43], where excessive fat storage and adipocyte dysfunction enhance lipid availability. Tumor cells exploit this nutrient-rich environment by upregulating lipid transport proteins, such as fatty acid-binding proteins (FABP4) and CD36, to uptake free fatty acids and triglycerides from adipocytes[43]. Once internalized, these lipids undergo mitochondrial β-oxidation to generate ATP and metabolic intermediates that fuel tumor growth and survival. This metabolic reprogramming supports not only primary tumor expansion but also metastatic dissemination, particularly in cancers like breast and ovarian, which often metastasize to adipose-rich environments[44]. Furthermore, this lipid-driven energy supply contributes to resistance against chemotherapy and targeted therapies, as tumors become less reliant on glycolysis and more metabolically flexible. Adipocyte-tumor cell interactions also promote the expression of survival pathways such as PPARs and mTOR, further enhancing treatment resistance. This energy symbiosis highlights the importance of targeting metabolic cross-talk between adipose tissue and tumors in cancer therapy[44].

Concept and Advantages

Nano-nutraceuticals represent a cutting-edge fusion of nanotechnology and nutraceutical science, aimed at enhancing the therapeutic potential of natural bioactive compounds[45]. Many plant-derived compounds exhibit promising anti-inflammatory, antioxidant, and anti-cancer properties but suffer from poor water solubility, low bioavailability, and rapid metabolism, which limit their clinical efficacy[12, 45]. Nanoformulation

addresses these limitations by encapsulating bioactive molecules within nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, or solid lipid nanoparticles. These systems improve solubility, protect the active compound from enzymatic degradation, and enable controlled, sustained release[46, 47]. Furthermore, nano-nutraceuticals can be engineered for targeted delivery, enhancing accumulation in tumor tissues or adipose-rich environments while minimizing off-target effects and systemic toxicity. This is particularly advantageous for modulating the complex signaling networks between adipose tissue and the tumor microenvironment (TME), where precise and sustained intervention is crucial. By improving cellular uptake and bio-distribution, nano-nutraceuticals offer a promising approach to counteract inflammation, immune suppression, and metabolic dysregulation inherent in obesity-driven cancers[48]. The integration of bioinformatics and artificial intelligence in nanoparticle design is also accelerating the development of optimized nanoformulations, enabling personalized nutrition-based therapies. Thus, nano-nutraceuticals hold significant potential in both cancer prevention and adjunctive treatment by targeting the adipose–TME axis.

Curcumin Nanoformulations

Curcumin, a polyphenolic compound derived from the rhizome of *Curcuma longa*, possesses potent anti-inflammatory, antioxidant, and anti-cancer properties. However, its clinical utility is significantly limited by poor aqueous solubility, low systemic bioavailability, and rapid metabolic degradation[49, 50]. Nanoformulations of curcumin—such as liposomal curcumin, curcumin-loaded solid lipid nanoparticles (SLNs), and polymeric nanoparticles—have been developed to overcome these challenges[51]. These nano-carriers improve curcumin's pharmacokinetic profile by enhancing solubility, protecting it from metabolic enzymes, and facilitating controlled release. In the context of obesity-associated cancers, nano-curcumin has demonstrated efficacy in modulating key signaling pathways such as NF-κB, PI3K/Akt, and STAT3, which are often activated by chronic inflammation and adipokine dysregulation. Additionally, nano-curcumin can suppress the secretion of pro-inflammatory cytokines from adipose tissue, reduce macrophage infiltration, and promote immune reprogramming within the tumor microenvironment (TME)[52]. Some studies also show that curcumin nanoparticles improve uptake by cancer cells and adipose-resident immune cells, thereby enhancing their anti-tumor effects. Clinical trials are ongoing to evaluate the safety and efficacy of various curcumin nanoformulations. Collectively, these findings suggest that nano-curcumin offers a promising, non-toxic therapeutic strategy to target the adipose–TME axis and mitigate cancer progression in obese individuals.

Resveratrol Nanoformulations

Resveratrol, a natural stilbene found in grapes, berries, and peanuts, is renowned for its anti-inflammatory, antioxidant, and anti-cancer effects[53, 54]. Despite its broad therapeutic potential, resveratrol suffers from poor oral bioavailability due to rapid metabolism and limited water solubility. Nanoformulations of resveratrol—including liposomes, nanospheres, solid lipid nanoparticles, and micelles—have been engineered to overcome these pharmacokinetic hurdles. These nanocarriers enhance the stability, absorption, and sustained release of resveratrol, allowing for improved therapeutic outcomes. In the context of obesity-associated cancer, nano-resveratrol exhibits the ability to modulate adipocyte–cancer cell interactions, suppress adipokine secretion (e.g., leptin), and downregulate inflammatory cytokines like IL-6 and TNF-α. Moreover, nano-resveratrol inhibits angiogenesis and epithelial-to-mesenchymal transition (EMT) by targeting VEGF and matrix metalloproteinases (MMPs), thereby reducing tumor invasiveness and metastatic potential[54, 55]. It also reprograms immune responses within the TME by decreasing the proportion of regulatory T cells and M2 macrophages. Resveratrol nanoparticles have shown enhanced cytotoxicity in vitro and better tumor suppression in vivo compared to free resveratrol. These formulations also show promise in reversing insulin resistance and metabolic dysregulation associated with obesity. Altogether, resveratrol nanoformulations provide a robust platform to address the dual challenge of metabolic inflammation and tumor growth in obesity-driven cancers.

EGCG (Epigallocatechin Gallate) Nanoformulations

Epigallocatechin gallate (EGCG), the major catechin in green tea, is widely recognized for its potent antioxidant, anti-inflammatory, and anti-proliferative effects[56, 57]. However, its therapeutic application is hindered by instability under physiological conditions and poor systemic bioavailability. To enhance its clinical relevance, various nanoformulations such as EGCG-loaded liposomes, PLGA nanoparticles, and chitosan-based nanocarriers have been developed[57, 58]. These nanoformulations not only protect EGCG from degradation but also facilitate targeted delivery and prolonged circulation time. In obesity-associated cancers, EGCG nanoparticles effectively reduce oxidative stress and inhibit chronic inflammation by downregulating pro-inflammatory mediators like IL-1β, IL-6, and NF-κB. They also impair lipid metabolism in tumor cells by suppressing lipogenesis-related genes (e.g., SREBP-1c, FASN), disrupting the metabolic support derived from adipose tissue. Additionally, nano-EGCG promotes apoptosis in cancer cells, inhibits angiogenesis, and modulates immune cell infiltration within the tumor microenvironment (TME)[57]. Notably, it can decrease

the polarization of M2 macrophages and enhance cytotoxic T lymphocyte (CTL) activity. Preclinical models have demonstrated that EGCG nanoformulations are more effective than free EGCG in inhibiting tumor growth and metastasis, particularly in obesity-related breast and colon cancers. Thus, EGCG-based nanotherapeutics represent a compelling approach for targeting the adipose–TME interaction and suppressing tumor progression.

Quercetin Nanoformulations

Quercetin, a flavonoid present in many fruits and vegetables, exhibits multiple pharmacological activities, including anti-inflammatory, antioxidant, and anti-cancer effects. However, like many natural compounds, its clinical translation is impeded by poor water solubility, limited oral absorption, and rapid clearance[48, 59]. Nanoformulations such as quercetin-loaded nanoparticles, nanoliposomes, and nanoemulsions have been developed to address these issues. These carriers improve quercetin's solubility, enhance cellular uptake, and provide sustained release, significantly boosting its therapeutic efficacy. In the setting of obesity-associated cancer, nano-quercetin exerts pleiotropic effects by modulating both metabolic and inflammatory pathways[60, 61]. It suppresses the expression of key adipokines like leptin and resistin, reduces reactive oxygen species (ROS) production, and inhibits signaling pathways such as PI3K/Akt/mTOR and NF-κB. Nano-quercetin also impedes cancer cell proliferation, induces apoptosis, and inhibits angiogenesis and metastasis by downregulating VEGF and MMPs. Furthermore, it reprograms macrophage polarization and enhances anti-tumor immunity by supporting dendritic cell maturation and increasing T cell infiltration in the tumor microenvironment. Studies have shown that quercetin nanoparticles achieve better tumor suppression and metabolic modulation compared to the free form. These attributes make nano-quercetin a strong candidate for integrative therapy targeting the adipose–TME axis in obesity-linked cancers[62, 63].

Challenges and Future Directions

Despite encouraging advancements in the field, several challenges continue to hinder the clinical translation of nano-nutraceuticals. One major issue is the lack of standardization in nano-nutraceutical formulations, which affects reproducibility and regulatory approval. Additionally, comprehensive data on long-term safety and potential toxicity remain limited, raising concerns about chronic exposure and unintended side effects. Another obstacle lies in scaling up production processes while maintaining consistency and cost-effectiveness, which is essential for clinical and commercial viability. Precision targeting to specific tissues and tumors also presents a significant challenge, as it requires highly selective delivery systems to avoid off-target effects. Moreover, integrative approaches that combine nano-nutraceuticals with conventional therapies, such as chemotherapy or immunotherapy, need further exploration to optimize synergistic effects without increasing toxicity.

Future research should prioritize personalized nano-nutraceutical interventions tailored to individual metabolic profiles. Such precision approaches could enhance efficacy and reduce adverse effects. The integration of artificial intelligence (AI) holds significant promise in this regard, offering tools to analyze complex biological data, predict therapeutic responses, and guide treatment decisions. Overall, addressing these challenges through multidisciplinary collaboration will be vital to unlocking the full potential of nano-nutraceuticals in modern medicine.

CONCLUSION

The pathological interplay between adipose tissue dysfunction and the tumor microenvironment significantly contributes to cancer initiation and progression, particularly in obesity-associated malignancies. Nano-nutraceuticals represent a promising class of therapeutic agents capable of simultaneously targeting inflammatory, metabolic, and immunological pathways. By bridging nutrition, nanotechnology, and oncology, these compounds offer a novel and integrative approach to combat cancer at the interface of metabolism and immune dysfunction. Strategic investment in translational research and clinical validation will be critical for harnessing the full potential of nano-nutraceuticals in cancer therapy.

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