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Review Article

A LITERATURE REVIEW ON THE ROLE OF ADIPOCYTOKINES IN BREAST CANCER AND METABOLIC SYNDROME

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ABSTRACT

Adipocytokines, bioactive molecules secreted by adipose tissue, have emerged as critical regulators of physiological processes and key contributors to the pathogenesis of various diseases. The relationship between adipocytokines, breast cancer (BC), and metabolic syndrome (MetS) represents a complex network involving intricate signaling pathways, such as those governing inflammation, insulin resistance, and angiogenesis. Understanding the dual role of specific adipocytokines in both promoting and inhibiting BC progression, while also influencing MetS development, provides valuable insights. This review synthesizes current literature, illuminating the molecular mechanisms underlying these associations, highlighting their potential as biomarkers and therapeutic targets, and emphasizing the need for integrated strategies to manage the interconnected risks of BC and MetS. Further research focusing on specific BC subtypes and longitudinal studies is crucial for translating these findings into clinical practice.

Keywords: Adipocytokines, Breast cancer, Metabolic syndrome, Obesity, Inflammation, Insulin resistance.

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INTRODUCTION

Introduction to adipocytokines

Adipocytokines, also known as adipokines, constitute a diverse group of signaling molecules secreted primarily by adipose tissue, playing a pivotal role in regulating metabolic functions within the body. These bioactive substances act as messengers, orchestrating a complex interplay between adipose tissue, metabolic pathways, and various physiological processes, including the regulation of energy balance, glucose and lipid metabolism, appetite control, obesity-related low-grade inflammation, cardiovascular function, and the development of metabolic diseases and cancer progression [1]. The clinical significance of understanding this network is underscored by the increasing prevalence of obesity and metabolic syndrome (MetS) worldwide, which are established risk factors for several cancers, including breast cancer (BC). As our understanding deepens, the involvement of adipocytokines in the intricate relationship between BC and MetS has emerged as a compelling area of research, bridging the gap between obesity, metabolic dysregulation, and breast cancer (BC) development. Adipocytokines can be broadly categorized based on their inflammatory potential, including pro-inflammatory mediators such as leptin, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1 beta, IL-6, and IL-8, and anti-inflammatory ones such as adiponectin and IL-10. These molecules represent potential predictive clinical parameters in both BC and MetS [2].

KEY ADIPOCYTOKINES IN BC AND MetS

Several key adipocytokines mediate the complex interactions between metabolic health and BC. Leptin, functioning both as a hormone and cytokine, is an obesity related molecule predominantly produced by adipocytes, is well-recognized for regulating appetite and energy balance, and its involvement in lipid metabolism and insulin sensitivity links it directly to MetS [3]. Furthermore, leptin exhibits pro-oncogenic actions in BC cells by binding to its receptor (LEPR), activating Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways, inducing proliferation, inhibiting apoptosis, and promoting angiogenesis via vascular endothelial growth factor (VEGF) production [3,4]. Studies by Koprivčić *et al.* [5] and Obi *et al.* [6] underscore leptin's influence, establishing its dual role in obesity-related metabolic disturbances and BC.

In contrast, adiponectin, produced exclusively by adipocytes, exhibits potent anti-inflammatory and insulin-sensitizing properties. Research has unveiled mechanisms through which adiponectin modulates insulin signaling and glucose metabolism [7,8]. Crucially, an inverse correlation exists between adiponectin levels and BC risk, particularly in postmenopausal women, reinforcing the link between metabolic health and cancer susceptibility [4,9]. Resistin, initially identified for its role in insulin resistance, is increasingly implicated in cancer pathogenesis. It contributes to pro-inflammatory processes [10,11] and may induce protein kinase C alpha (PKCα) phosphorylation, a pathway associated with increased cancer cell invasiveness and potentially contributing to the epithelial-to-mesenchymal transition (EMT) [2,12].

Visfatin, also known as nicotinamide phosphoribosyltransferase, possesses insulin-mimetic properties. Findings suggest a potential dual role in regulating insulin sensitivity while possibly promoting cancer cell proliferation, adding complexity to the adipocytokine network [12,13]. TNF-α, a major pro-inflammatory cytokine produced by immune cells and adipocytes, is strongly associated with insulin resistance and other components of MetS. In BC, TNF-α promotes angiogenesis, infiltration, and tumor progression, often via nuclear factor kappa-light-chain-

enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase signaling [2,14]. Similarly, IL-6, produced by various cells including adipocytes, contributes to tumor progression through JAK/STAT and extracellular signal-regulated kinase activation [2,15] and is implicated in MetS through effects such as stimulating hepatic glucose production. The exploration of these adipocytokines reveals a multifaceted interplay where metabolic health and BC risk are deeply intertwined, providing a foundation for developing targeted interventions.

ADIPOCYTOKINES AND BC RISK

The link between adipocytokines and BC risk is intricate and context-dependent, significantly influenced by the metabolic environment shaped by adipose tissue, particularly visceral fat associated with MetS. Elevated leptin levels, commonly observed in obesity, are associated with increased BC risk. Mechanistically, leptin promotes BC cell proliferation and survival, potentially through activating JAK/STAT and Akt (protein kinase B) pathways, and stimulates angiogenesis [3,4,16]. However, the significance of this association may vary depending on menopausal status and specific BC subtypes. Conversely, higher levels of adiponectin are generally correlated with a reduced risk of BC, especially in postmenopausal women [4,17]. Adiponectin exerts anti-proliferative effects, induces apoptosis, and possesses anti-inflammatory properties, potentially mediated via AMP-activated protein kinase (AMPK) activation and inhibition of the mammalian target of rapamycin pathway. This inverse relationship highlights the protective potential of maintaining metabolic health [9,18].

Evidence also suggests that increased levels of resistance may correlate with a heightened risk of BC, particularly postmenopausal [19]. Resistin fosters inflammation and potentially insulin resistance, creating a microenvironment conducive to tumor growth, possibly through NF-κB activation [10,11], higher resistin levels were linked to increase the risk of heart failure and myocardial infarction and while decreased resistin expression in obesity and insulin resistance, hence the prognostic role of resistin differ by different patient population [20]. Furthermore, adipocytokines such as TNF-α and IL-6 are major contributors to the chronic low-grade inflammation characteristic of obesity and MetS. This inflammatory milieu is increasingly recognized as a key driver of tumorigenesis, promoting cell proliferation, angiogenesis, and metastasis [2,21], although adiponectin can counteract some of these effects through its anti-inflammatory actions [9].

Epidemiological studies provide crucial evidence linking adiposity and specific adipokine levels to BC risk, often revealing differences based on menopausal status [17,19]. Synthesizing this evidence underscores the complexity; the net effect on BC risk likely depends on the balance between pro-tumorigenic signals (from leptin, resistin, TNF-α, and IL-6) and anti-tumorigenic signals (from adiponectin), modulated by factors such as hormonal status, BC subtype, and genetic background. Therapeutic interventions targeting these pathways, such as modulating leptin signaling [22], are under investigation but necessitate careful consideration of the systemic roles of these molecules.

EFFECTS OF ADIPOCYTOKINES ON MOLECULAR SUBTYPES OF BC

BC is a heterogeneous disease with multiple subtypes; the main molecular subtypes of BC include hormone receptor positive (estrogen receptor [ER+] and progesterone receptor [PR+]), human epidermal growth factor receptor (EGFR) 2, and triple negative BC (TNBC) [23].

Adipocytokines exert diverse effects on different molecular subtypes of BC, with evidence from the literature it was found that leptin stimulates aromatase expression by increasing estrogen levels through androgen aromatization in ER-positive BC, whereas in TNBC, leptin interacts with insulin-like growth factor 1 (IGF-1) to trans activate the EGFR, enhancing the invasion [24].

In ER-positive BC, adiponectin may promote proliferation through E-Cadherin expression, which enhances tumor growth and metastasis, and in ER-negative BC, adiponectin provides anti-proliferative and pro-apoptotic roles as reported by Naimo *et al*. [25].

Resistin is involved in cancer progression by promoting angiogenesis. Studies found that resistin expression varies across different molecular subtypes of BC significantly, with higher levels observed in receptor negative (ER-/PR-) and TNBC Vallega *et al*. 2016 [20].

High Visfatin levels were found in hormone receptor ER/PR molecular subtypes of BC, as evidenced from the literature [23].

In the TNBC subtype, TNF-α contributes to the aggressive properties of TNBC cells by upregulating TNFA1P3, whereas inducing cytotoxic cell death in the ER-positive BC subtype [26].

MetS AND BC CONNECTION

MetS, a constellation of conditions including central obesity, insulin resistance, dyslipidemia, and hypertension, significantly elevates the risk of developing BC and may negatively impact prognosis [27,28]. This connection is multifactorial, involving shared risk factors and interconnected biological pathways mediated substantially by adipocytokines. Lifestyle factors such as physical inactivity, poor diet, and resulting obesity are primary drivers for both MetS and increased BC risk [29].

A central feature of MetS is insulin resistance, leading to compensatory hyperinsulinemia. Insulin, beyond its metabolic functions, acts as a growth factor, potentially promoting BC cell proliferation and survival via the insulin/IGF-1 signaling pathway [29,30]. Adipocytokines such as TNF-α, IL-6, and resistin contribute to insulin resistance, whereas adiponectin enhances insulin sensitivity. Chronic inflammation is another critical link. Visceral adipose tissue in MetS is a major source of pro-inflammatory adipocytokines (TNF-α, IL-6), fostering a systemic inflammatory state conducive to tumorigenesis by influencing cell proliferation, angiogenesis, invasion, and metastasis [21,27,31]. Adiponectin counteracts this through its anti-inflammatory effects [9,32,33].

Furthermore, MetS involves altered sex hormone metabolism. Adipose tissue, especially postmenopausal, is a significant site of estrogen synthesis via aromatase. Obesity and MetS lead to increased adipose mass and potentially elevated aromatase activity, resulting in higher circulating estrogen levels, which are particularly relevant for hormone receptor-positive BC [34-37]. Leptin may further enhance aromatase expression [16]. Consequently, the overall adipocytokine profile in MetS typically shifts toward a pro-inflammatory and pro-proliferative state (characterized by higher leptin, resistin, TNF-α, IL-6, and lower adiponectin), directly impacting BC initiation and progression [4,12,27,30]. Understanding these intricate connections underscores the importance of managing MetS not only for cardiovascular health but also potentially for BC prevention and management. Fig. 1 illustrates the specific molecular mechanisms linking key adipocytokines to both BC pathways and MetS characteristics.

ADIPOCYTOKINES AS BIOMARKERS

Given their integral role in linking MetS and BC, adipocytokines are under investigation as potential biomarkers for various clinical applications, including risk assessment, diagnosis, prognosis, and monitoring treatment response. Aberrant levels, such as low adiponectin or high leptin/resistin, might identify individuals at elevated risk for developing BC, particularly those with concurrent MetS [38-40]. While unlikely to serve as standalone diagnostic markers, specific adipokine profiles could potentially complement existing diagnostic tools, perhaps aiding in the differentiation of BC subtypes or stages [40]. Furthermore, studies suggest adipokine levels correlate with BC outcomes; high adiponectin is often associated with improved survival, whereas high leptin may indicate a poorer prognosis [6,7,41], potentially assisting

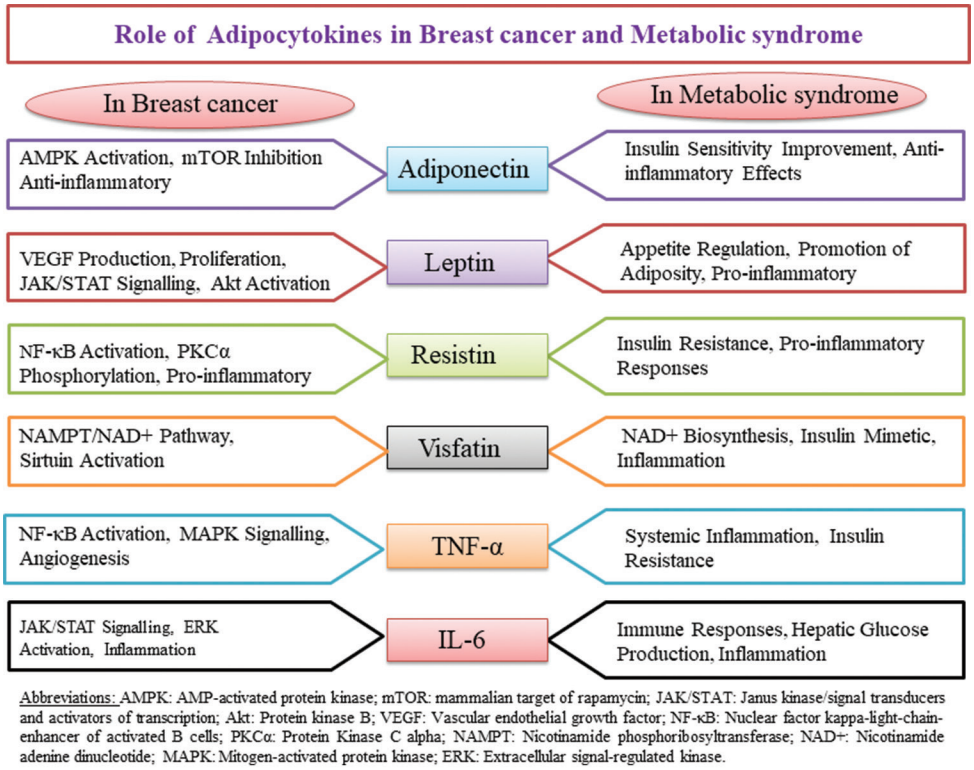

Fig. 1: Molecular mechanisms linking adipocytokines to breast cancer and metabolic syndrome

in patient stratification and guiding treatment intensity. Changes in adipokine levels following lifestyle or pharmacological interventions might also serve as indicators of therapeutic efficacy.

Several candidates are of particular interest. The leptin/adiponectin ratio is often considered more informative than individual levels, reflecting the balance between pro- and anti-cancer signals [35,38]. Elevated levels of resistance and visfatin have also been linked to BC presence and potentially poorer outcomes [13,40]. High levels of inflammatory markers such as TNF-α and IL-6 are associated with both MetS severity and potentially more aggressive BC phenotypes [27,42].

However, the clinical application of adipocytokines as biomarkers faces significant challenges. Levels exhibit considerable inter-individual variability due to genetics, ethnicity, diet, physical activity, and other inflammatory conditions, complicating standardization [43]. Lack of standardized laboratory assays further hinders comparability across studies. Moreover, no single adipokine possesses sufficient specificity or sensitivity for standalone use due to their overlapping roles and reflection of systemic metabolic state rather than solely cancer presence. Distinguishing association from causation and demonstrating direct clinical utility requires further validation in large, prospective trials. Therefore, the most promising future direction likely involves utilizing panels of multiple adipocytokines combined with other metabolic markers, clinical data, imaging, and genomic information to enhance personalized risk assessment and management strategies for individuals at the intersection of MetS and BC risk [37].

INFLUENCE OF ADIPOCYTOKINES ON THE TUMOR MICROENVIRONMENT (TME)

The TME, the complex ecosystem surrounding cancer cells, is profoundly influenced by adipocytokines, particularly in the setting of obesity and MetS. Adipocytes within or adjacent to breast tissue, known as cancer-associated adipocytes, directly secrete adipokines, shaping a local milieu that can either restrain or promote tumor growth [8]. Adipocytokines critically regulate angiogenesis, the formation of new blood vessels essential for tumor growth and metastasis. Leptin and resistin act as pro-angiogenic factors, partly via VEGF production, while IL-6 can also contribute [3,44]. Conversely, adiponectin generally exhibits anti-angiogenic properties, potentially limiting tumor expansion [9,44]. The overall pro-inflammatory, pro-angiogenic adipokine profile characteristic of MetS likely contributes to enhanced tumor vascularization.

Adipocytokines also significantly modulate the immune landscape within the TME. Leptin can impair anti-tumor T-cell function and promote immunosuppressive regulatory T cells [45], whereas resistin may recruit pro-tumor immune cells [43]. Chronic inflammation driven by TNF-α and IL-6 can paradoxically lead to an exhausted or immunosuppressive immune environment [21,46]. In contrast, adiponectin may enhance the activity of cytotoxic cells such as natural killer cells, fostering an anti-tumor immune response [9,45]. The chronic inflammation and altered immune cell function typical of MetS, driven partly by adipokines, likely create a TME less effective at controlling tumor growth and more permissive to metastasis.

Furthermore, adipokines can influence extracellular matrix (ECM) remodeling and invasion by affecting the production and degradation of ECM components. Resistin, via pathways such as PKC-α, might promote processes related to EMT, thereby increasing invasiveness [2,4]. Beyond the TME, adipokines directly signal to cancer cells, influencing proliferation (leptin promotes and adiponectin inhibits), survival (leptin promotes and adiponectin promotes), and metabolism [3,25]. In summary, the dysregulated adipocytokine milieu associated with obesity and MetS actively shapes the BC TME, often creating a pro-tumorigenic niche characterized by increased angiogenesis, inflammation, immunosuppression, and altered ECM dynamics. Understanding these local effects is crucial for developing therapies targeting the TME.

THERAPEUTIC IMPLICATIONS AND INTERVENTIONS

The established links between adipocytokines, MetS, and BC suggest potential therapeutic avenues, although significant challenges persist. Interventions primarily aim to modulate adipokine levels or block their

signalling pathways. Lifestyle interventions, including diet and exercise, remain cornerstone strategies. Weight loss, particularly reduction of visceral fat, lowers pro-inflammatory adipokines (leptin, TNF-α, and IL-6) and can increase adiponectin. Exercise independently improves insulin sensitivity and raises adiponectin levels. Dietary modifications favoring anti-inflammatory components may also favorably modulate the adipokine profile. These interventions address the root causes of MetS and alter the systemic environment, potentially reducing BC risk and improving outcomes [36,47].

Pharmacological targeting represents another approach. Metformin, a common anti-diabetic drug, improves insulin sensitivity and exhibits anti-cancer effects in various studies, possibly acting partly by modulating AMPK and influencing adipokine levels. Thiazolidinediones increase adiponectin but have limited use due to side effect concerns. Strategies targeting leptin signaling, such as antagonists or inhibitors of its receptor (LEPR) or downstream pathways (e.g., JAK/STAT inhibitors), are being explored preclinically [22,48,49]. Similarly, enhancing adiponectin levels or mimicking its effects (e.g., via adiponectin receptor agonists) is under investigation but faces challenges due to adiponectin's complex structure and regulation [9,49,50]. Anti-inflammatory agents targeting key cytokines like IL-6 or TNF-α are established for autoimmune diseases and are being explored in cancer, particularly in obesity-driven inflammation contexts [44].

Significant challenges impede the translation of these concepts into effective therapies. The complexity and pleiotropy of adipocytokines mean that targeting one may cause unintended systemic effects [43,50]. Most pharmacological strategies targeting adipokines directly for BC remain in pre-clinical or early clinical stages. Patient responses vary, necessitating personalized approaches to identify individuals most likely to benefit. Future directions likely involve combination therapies, integrating lifestyle changes with pharmacological approaches targeting both metabolic dysfunction (e.g., metformin) and specific cancer pathways. Integrating adipokine modulation with standard BC therapies requires further study. In addition, the emerging role of the gut microbiome in influencing adipokine production and inflammation presents a potential future therapeutic target. Continued research is essential to translate our understanding into safe and effective clinical interventions, likely requiring personalized, multi-pronged strategies [47,51].

CONCLUSION

This review synthesizes compelling evidence establishing adipocytokines as critical mediators in the complex interplay between adipose tissue, MetS, and BC. The dysregulated adipokine profile characteristic of MetS – typically involving elevated pro-inflammatory and pro-proliferative factors such as leptin, TNF-α, and IL-6, alongside reduced levels of protective adiponectin – contributes significantly to BC risk, progression, and potentially treatment resistance. These molecules exert influence through diverse mechanisms, including modulation of insulin sensitivity, chronic inflammation, angiogenesis, immune responses within the TME, and direct effects on cancer cell signaling pathways such as JAK/STAT, AMPK, and NF-κB.

While adipocytokines hold promise as biomarkers for risk stratification, prognosis, and monitoring, significant challenges related to variability and standardization must be overcome, likely necessitating the use of multi-marker panels integrated with clinical data. Therapeutically, lifestyle interventions targeting weight management and physical activity remain fundamental for modulating the adipokine milieu. Pharmacological strategies targeting specific adipokines or their pathways are under development but require careful consideration due to the pleiotropic nature of these molecules.

The bidirectional relationship between BC and MetS necessitates a holistic approach to patient care, integrating metabolic management into oncology practice. Key unanswered questions remain regarding the precise roles of specific adipokines in different BC subtypes and the long-term impact of adipokine modulation on BC outcomes. Future research should focus on longitudinal cohort studies, clinical trials evaluating targeted interventions (including combination therapies), and further elucidation of the molecular crosstalk within the TME. Recognizing and addressing the pivotal role of adipocytokines offers a crucial opportunity to develop innovative, personalized strategies to mitigate the dual burden of MetS and BC.

AUTHORS CONTRIBUTION

Deepthi Enumula, Yashaswi Guntupalli, Vanitha Rani N, and Prathap Reddy B contributed toward the manuscript writing. Conceptualization by Deepthi Enumula, Bhawna Dev, Shyam Sunder A, and Shabna Morais, manuscript editing by Deepthi Enumula, Yashaswi Guntupalli, and Vanitha Rani N, final draft preparation by Deepthi Enumula, Vanitha Rani N, and Shabna Morais. All authors have read and agreed to send the manuscript to this journal.

CONFLICTS OF INTERESTS

All the authors declare that they do not have any conflicts of interest.

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