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Linking adiponectin and autophagy in the regulation of breast cancer metastasis

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Abstract

Adipokines within the tumor microenvironment may play important roles in regulating the early steps of breast cancer metastasis. Adiponectin (AdipoQ) is the most abundant adipokine and exists in multiple forms: full-length multimers (fAd) and a cleaved, globular isoform (gAd). While these isoforms are observed as having distinct biological properties, nearly all investigation into AdipoQ in breast cancer has focused on the anti-tumor roles of fAd, while mostly ignoring gAd. However, evidence from other disease settings suggests that gAd is linked to processes known to promote metastasis. Here we discuss key areas in which knowledge about AdipoQ in breast cancer is lacking, expressly focusing on data suggesting that gAd is elevated in the microenvironment and may act directly on invasive breast cancer cells to support their initial metastatic progression. We discuss autophagy as a potential mechanism of action for this effect. Overall, given that AdipoQ and AdipoQ receptor agonists have been proposed as therapeutic strategies, it is necessary to better understand the various functions of these regulatory molecules in metastatic breast cancer. Doing so will help ensure the most effective approaches to treating this disease, for which there remain no curative options.

Keywords

Adiponectin; autophagy; breast cancer; metastasis

Introduction

Exceptionally poor survival rates in patients with metastatic breast cancer make clear the inadequacy of current therapeutic options for this disease. New insights are imperative. Primary breast tumor cells are surrounded by a complex and largely undefined microenvironment consisting of stromal cells such as fibroblasts, macrophages, neutrophils, endothelial cells, immune cells, as well as the extracellular matrix (ECM). The

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests. This manuscript does not contain clinical studies or patient data.

Authorship statement

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microenvironment influences tumor cells at all stages of cancer development and progression, including metastasis [1,2].

Adipocytes are integral members of the mammary stroma and can exist in high ratio at the invasive front of human breast carcinomas [3]. Adipocytes were long considered mere lipid storage units and, until recently, were disregarded as members of the microenvironment that could influence the behavior of tumor cells. Mounting evidence now underscores that adipocytes are indeed active players in breast cancer progression [3–6]. For example, co-culturing human breast cancer cells with mature adipocytes increases cancer cell invasion *in vitro* and the number and size of lung metastases *in vivo* [4]. Multiple genes including matrix metalloproteinase 9 (MMP-9) and vascular endothelial growth factor A (VEGFA) are upregulated in a three-dimensional model of breast cancer growth in an adipose microenvironment, suggesting adipose-induced increases in invasive potential [6].

One way in which adipocytes directly influence breast cancer cells is through their recently characterized function as endocrine cells that secrete adipokines--autocrine, endocrine, and paracrine-acting bioactive molecules [7,8]. The adipokine secreted in greatest abundance is adiponectin (AdipoQ) [9]. Identified nearly concurrently by four distinct investigative teams in the mid-1990s, AdipoQ is also designated Acrp30 (adipocyte complement-related protein of 30 kDa) [10], apM1 (gene product of the adipose most abundant gene transcript-1) [11], and GBP28 (gelatin-binding protein-28) [12]. AdipoQ is widely known to promote glucose homeostasis and insulin sensitivity, and is thus well studied for its role in type 2 diabetes, metabolic syndrome, cardiovascular disease, and other obesity-related diseases [13].

There already exist a number of excellent, comprehensive reviews on AdipoQ and its role in cancer [14–21]. Overall, the prevailing evidence indicates that low levels of AdipoQ in the circulation portend poorer breast cancer risk and prognosis, and that AdipoQ in breast tissue at the site of tumor growth has a direct anti-carcinogenic effect. The intent of this review is to explore areas in which there are key gaps in the literature. Specifically, we consider evidence suggesting that a largely ignored cleaved, globular isoform of AdipoQ is elevated in breast cancer tissue and may promote metastatic disease. We propose autophagy as among the possible mechanisms through which this effect is mediated.

Adiponectin Biology

The structure of AdipoQ facilitates its oligomerization into full length (fAd) isoforms. Yet, AdipoQ also undergoes cleavage into a globular fragment (gAd) by leukocyte elastase, a serine protease associated with poor breast cancer prognosis. gAd has highest affinity to adiponectin receptor, AdipoR1, which is elevated in breast cancer cells and is a key mediator of AdipoQ-induced AMP-activated protein kinase (AMPK) activation.

Adiponectin structure and isoform formation

Located on chromosome 3q27, the AdipoQ gene is comprised of two introns and three exons [22] and encodes for a 244-amino acid protein expressed principally in adipose tissue [10,11,23]. AdipoQ is synthesized as a monomer containing four domains: 1) an amino-terminal signal peptide; 2) a species-specific variable domain; 3) a collagen domain with 22

characteristic Gly-X-Y repeats (X and Y represent any amino acid); and 4) a carboxyl-terminal globular domain. This globular domain is structurally akin to tumor necrosis factor alpha (TNF- α) [24], a pro-inflammatory cytokine with well established links to cancer [25]. AdipoQ is homologous to members of the complement 1q proteins, which have a propensity to multimerize [10,26,27]. Indeed, the full length 30 kDa monomer (fAd) oligomerizes into trimers of low molecular weight through generation of a collagen triple helix [24]. These trimers further multimerize into hexamers and multimers of middle and high molecular weight, respectively, through reversible disulfide bonding at the collagen domain [28–30]. These fAd isoforms comprise the majority of circulating plasma AdipoQ, which range in levels of 2–30 $\mu\text{g/ml}$.

AdipoQ has well-characterized metabolic roles in skeletal muscle and liver, but is known to function in other target tissues and cell types including adipose tissue, macrophages, endothelial cells, and cancer cells to affect other biological processes (e.g., angiogenesis, oxidative stress, inflammation) [31]. However, whole-body tissue distribution of AdipoQ is not well characterized, nor are mechanisms explaining the movement of AdipoQ from circulation to tissue and vice versa.

Freubis and colleagues established that a fragmented form of AdipoQ containing the carboxyl-terminal globular domain (gAd) also is present in human plasma [27]. They hypothesized that, like other complement system proteins, plasma AdipoQ normally circulates as an inactive precursor that undergoes an activating event, such as proteolytic cleavage. This was later confirmed through the seminal work by Waki and colleagues, who determined that leukocyte elastase cleaves full length murine adiponectin at the amino-terminal collagenous domain into 25-kDa, 20-kDa, and 18-kDa fragments comprised of the globular domain [32]. Leukocyte elastase is a serine protease normally secreted by activated monocytes and neutrophils and is the most active of the three mammalian elastases. Compellingly, breast cancer cells, but not normal breast epithelial cells, also secrete leukocyte elastase [33] and thus may contribute to the role of monocytes and neutrophils as an additional important source of this protease. High leukocyte elastase expression in human breast tissue is associated with metastasis [34] and lower breast cancer survival [33–35]. Low levels of elafin, a natural elastase inhibitor, also correlate with poor breast cancer prognosis in breast cancer patients [36]. In mouse xenografts, elastase inhibition through both shRNA-induced silencing of elastase and use of exogenous elafin decreased tumor burden and prolonged survival [36]. These findings are consistent with the proteolytic function of leukocyte elastase, which is capable of remodeling the ECM to promote tumor cell invasion through the surrounding stroma.

Adiponectin receptors

AdipoR1 and AdipoR2 function as the two main AdipoQ receptors [37]. Structurally conserved from yeast and 67% identical in sequence, both are type II integral membrane proteins (intracellular amino terminus and extracellular carboxyl terminus) [38]. AdipoR1 is the primary target for gAd, while fAd has an intermediate affinity for both AdipoR1 and AdipoR2. AdipoR1 expression is widespread, albeit particularly pronounced in skeletal muscle, and AdipoR2 is chiefly expressed in the liver [21,39]. Importantly, both receptors

have been detected in normal breast epithelial cells [40] and breast cancer cells [40–42], the latter of which appear to express AdipoR1 at higher levels than AdipoR2 [41,43,44]. AdipoR1 is the main signal transmitter for AMPK, a primary AdipoQ signaling molecule [37,39,45], while AdipoR2 primarily acts through peroxisome proliferator-activated receptor- α (PPAR α) signaling [37]. A third AdipoQ receptor is T-cadherin [46–49], a cell surface protein that binds AdipoQ isoforms of hexameric and high molecular weight [47]. T-cadherin is observed to mediate pro-angiogenic effects of AdipoQ [48], although its function as an AdipoQ interactor is not as well understood as that of AdipoR1 and AdipoR2. Overall, the relationship between AdipoQ and its receptors in breast cancer remains an area that requires further study.

Globular adiponectin and breast cancer metastasis

There is a considerable body of literature supporting the premise that AdipoQ is protective against breast cancer progression. However, key distinctions must be drawn between clinical epidemiologic measurement of circulating versus tissue AdipoQ levels. Furthermore, although it has been well noted that AdipoQ isoforms have distinct biological properties [27,50–52], all clinical and nearly all experimental investigation of AdipoQ in breast cancer has focused exclusively on fAd to the exclusion of gAd. In disease settings outside of breast cancer, gAd is linked to biological pathways and functions known to promote the metastatic potential of tumor cells.

Clinical evidence

Multiple widely cited epidemiologic investigations have found inverse associations between serum AdipoQ levels and breast cancer risk [20,43,53–56] and prognosis [57–59]. However, the verdict is not unanimous, with some studies reporting no association [20,58,60] and others even noting that high AdipoQ levels are associated with increased breast cancer risk [20].

Yet, AdipoQ not only exists in circulation, but also has been detected in breast cancer and adjacent normal breast epithelial tissue [61]. Thus, AdipoQ has the opportunity to act both directly on breast tumor cells as well as in the tumor microenvironment and thereby directly alter breast cancer progression. Currently, it is unknown whether data on circulating AdipoQ levels are generalizable to a study of tissue AdipoQ. Indeed, correlations between circulating and tissue concentrations are variable and thus circulating measurements may not accurately depict actual tissue levels [62,63]. In fact, investigations into the relationship between breast cancer outcomes and AdipoQ expression in tissue report that elevated tissue concentrations are associated with malignancy. Using enzyme-linked immunosorbent assay (ELISA) analysis of frozen breast biopsy specimens, Karaduman and colleagues found elevated total AdipoQ levels in malignant breast tumor tissue versus benign breast fibroadenomas [64]. In immunohistochemical analysis of formalin-fixed and paraffin-embedded surgical specimens, Jeong and colleagues similarly found elevated AdipoQ and AdipoR1 in invasive breast cancer tissue versus ductal carcinoma *in situ* [65].

All of these serum/plasma and tissue-based clinical studies are based on measurement of fAd or total AdipoQ [20,53–55,57,58]. Considering the dearth of data on the relationship

between gAd and breast cancer outcomes, it is instructive that recent study of gAd in rheumatoid arthritis reported considerably elevated gAd levels in patient synovial fluid versus circulating blood [51]. This suggests that gAd may be localized in areas of inflammation and repair, typical of tumor microenvironments. Indeed, inflammation and cancer have long been linked, and immune inflammatory cells such as monocytes and neutrophils are among the numerous cell types found in tumors and their surrounding milieu [66,67].

Experimental evidence

The theme emerging from experimental studies of the biological activity and function of AdipoQ is that it plays an anti-tumoral role in breast cancer [41–43,53–55,57,58,68–76] as well as hinders its progression [58,70] (Table 1). However, these data are limited primarily to fAd. For instance, *in vitro* data suggest that fAd at varying concentrations is pro-apoptotic [42,72]; inhibits proliferation [42,68,71,72,77] and cyclin D1 expression [42,72]; decreases adhesion [70], migration, and invasion [70,77]; and attenuates the oncogenic effects of leptin [69]. In mouse models of spontaneous mammary tumor development, AdipoQ haploinsufficiency has been found to promote tumor development [78]; complete loss (knockout) was observed to inhibit tumor development, but result in more aggressive late-stage tumors by blocking AdipoQ-mediated tumor vascularization [79,80].

Although the preponderance of experimental evidence on the function of AdipoQ in breast cancer is based on fAd, it has been observed in numerous contexts that fAd and gAd have varying biological effects [27,50–52,81,82]. This underscores the importance of understanding the roles of both multimerized and cleaved isoforms of this molecule. To our knowledge, only two investigations to date have shown data regarding a breast cancer-related role of gAd. Grossman and colleagues found that altering the estrogen receptor status of the human breast cancer cell line MDA-MB-231 by transfection of the estrogen-receptor alpha (ER α) gene altered the cellular response to gAd. In estrogen receptor positive MDA-MB-231, but not parental cells, gAd had an anti-proliferative effect [41]. In the same study, fAd did not alter proliferation of either cell line, although this observation is in contrast to several reports that fAd can inhibit breast cancer cell growth [41–43,68,71,72,74,77]. Similarly, Mauro and colleagues observed that gAd inhibited growth in ER α -negative breast cancer cell lines, but increased growth in ER α -positive cells [76]. The role of fAd was not assessed. These findings provide interesting data on the role of estrogen receptors in mediating the response to AdipoQ isoforms, but offer only an early insight into the full range of paracrine or autocrine effects of gAd in breast cancer.

There is evidence in other disease settings that gAd is linked to effects that would assist the progression of metastatic tumor cells. In human microvascular endothelial cells (HMEC-1), gAd, but not fAd, increases migration and angiogenesis (increased capillary tube length and expression of MMP-2, MMP-9, and VEGF) [50]. Partial inhibition of AdipoQ receptors show that AdipoR1 is primarily responsible for mediating these effects. In the human colorectal adenocarcinoma cell line HT-29, both gAd and fAd increase cellular proliferation [52]. However, gAd, but not fAd, has pro-inflammatory effects; gAd increases mRNA expression and secretion of interleukin 8 (IL-8), granulocyte-macrophage colony-stimulating

factor (GM-CSF), and monocyte chemoattractant protein-1 (MCP-1), as well as the nuclear translocation of nuclear factor kappa B (NF- κ B) [52]. gAd has a similar pro-inflammatory effect in human esophageal adenocarcinoma OE19 cells. In these cells, gAd increases mRNA of TNF- α , IL-8, and IL-6 in a dose-dependent manner, while fAd has an opposite effect [83]. Also in esophageal adenocarcinoma cells, gAd increases, but fAd decreases, intracellular reactive oxygen species (ROS) and NF- κ B activation [84]. In monocytes and neutrophils, gAd enhances ROS production resulting from treatment with N-formyl-methionyl-leucylphenyl-alanine [51]. Finally, in H9c2 rat embryonic cardiac myoblasts, gAd decreases apoptosis induced by treatment of hypoxia followed by reoxygenation although, in contrast to the above findings, does so through attenuation of intracellular ROS [85].

Caution should be used when making comparisons across disease settings. In addition, there is inconsistency within the field regarding fAd and gAd source (eg, produced in bacteria or mammalian cells). The absence of glycosylation in bacterially produced protein can affect its functional relevance, posing challenges in drawing overall conclusions based on experimental data on AdipoQ. Still, taken together, these data suggest that gAd may be an important regulatory molecule for the process of breast cancer metastasis, and that it may play a role contradictory to fAd.

Autophagy as a plausible mechanism of action

It is possible that AdipoQ modulates basal levels of autophagy in breast cancer cells, thus altering their behavior and metastatic potential, although this has not been well studied. There are three main types of autophagy: chaperone-mediated autophagy, microautophagy, and macroautophagy. In this review, autophagy connotes macroautophagy. Autophagy is a catabolic process during which a double-membraned vesicle (autophagosome) engulfs cytoplasmic components, subsequently integrating with the lysosomal compartment to form an autophagolysosome for degradation of autophagosomal cargo. The function of autophagy is two-fold: 1) maintenance of a damage-free cellular environment under basal conditions; and 2) provision of substrates that help to preserve intra- and extra-cellular homeostasis under stressful conditions including hypoxia, starvation, and ECM detachment. These functions render autophagy particularly interesting in the context of metastasis. To successfully metastasize, an invasive tumor cell must detach from the primary tumor site; invade the ECM and stroma surrounding the primary mass; intravasate and circulate within the vasculature; and extravasate and flourish within a foreign organ site [67,73,86]. This process is inherently stressful, requiring enhanced survival capabilities of the very select few cells that complete it [2]. Understanding the regulators and functions of autophagy at the numerous junctures of the metastatic cascade is an important topic of ongoing investigation [86].

AdipoQ is positioned through its signaling effectors as a molecule potentially capable of autophagic regulation. One of the major molecules through which AdipoQ exerts its intracellular effects is AMPK [14,87], and AdipoQ-induced activation of AMPK [70,77] indeed has been observed in breast cancer cells. At the same time, AMPK plays a key role upstream of the autophagic regulatory machinery. AMPK directly activates uncoordinated

51-like kinase-1 (Ulk1), an essential member of the multi-channel system in control of autophagic response [88], thus allowing Ulk1 to form a complex that promotes the formation of pre-autophagosomal structures in the initial stages of autophagy [89]. AMPK also indirectly activates Ulk1 by inhibiting the mammalian target of rapamycin complex 1 (mTORC1) through phosphorylation of raptor [88,90]; mTORC1 inhibits Ulk1 complexing and thus autophagy initiation [89,91].

One study has evaluated the relationship between AdipoQ and autophagy in breast cancer. Liu and colleagues observed that fAd upregulated autophagy in MDA-MB-231 cells *in vitro* and *in vivo* [92]. Outside of breast cancer, there is evidence that supports the autophagic stimulatory effects of AdipoQ, although these data are sparse. In colorectal cancer cells, autophagy induction is evident upon treatment with gAd and fAd, as is activation of AMPK and inhibition of mTORC1 [93]. In liver cancer cells, gAd prevents ethanol-induced apoptosis through autophagy induction, and does so in an AMPK-dependent manner [94,95].

Conclusions

There are key gaps in our understanding of AdipoQ in breast cancer progression. This was underscored in a recent review that discussed the contradictory roles of AdipoQ in cancer [96]. Few studies have evaluated AdipoQ levels in breast cancer and surrounding tissues, and none have assessed relative isoform distributions between fAd and gAd. Little is known about how gAd acts on breast cancer cells, although the evidence discussed above suggest that it has metastasis-promoting effects, unlike the documented activities of fAd. In this context, the relative contribution of gAd versus fAd to breast cancer progression also has yet to be explored. Regardless of isoform, the effect of AdipoQ on autophagy and, in turn, on breast cancer development and metastatic potential remains to be fully elucidated.

Based on the literature in total, we propose a model adapted from one recently described in the rheumatoid arthritis field [51] (Figure 1). Briefly, we suggest that gAd, which circulates in plasma at low levels, may be localized in relatively high levels in breast cancer tissue where leukocyte elastase levels are elevated. gAd in turn acts on invasive tumor cells through its high-affinity receptor, AdipoR1, to activate AMPK. AMPK upregulates autophagy through ULK1 activation, enhancing the ability of invasive cells to metastasize.

Overall, existing data provide a range of evidence indicating that multimerized isoforms of AdipoQ are protective against breast cancer and its progression. Yet, upon review, data also provide grounds upon which to speculate that gAd in breast tissue at the site of tumor growth could in fact promote development of metastatic disease in part through acting directly on invasive tumor cells to induce autophagy, which is broadly believed to suppress tumorigenesis but promote the progression of established tumor cells [97]. Indeed, further work is necessary to enhance our understanding of this molecule, particularly given that augmentation of AdipoQ levels has been proposed as a potential therapeutic strategy for breast cancer treatment [98], and that an AdipoQ receptor agonist is in preclinical development [44,98,99]. The ultimate goal is to develop new therapeutic options that help

reduce the great mortality burden of metastasis; metastasis remains the chief cause of death in breast cancer, and breast cancer remains the second deadliest cancer in women [100].

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Figure 1.

Proposed model. (A) Adipocytes and activated inflammatory cells, including activated monocytes and neutrophils, are present in the primary breast tumor microenvironment. (B) Activated inflammatory cells, and breast cancer cells, secrete leukocyte elastase. Adipocytes secrete fAd. Elevated levels of both leukocyte elastase and fAd have been observed in breast cancer tissue. (C) Leukocyte elastase cleaves fAd, resulting in locally elevated gAd levels. (D) gAd has highest affinity to AdipoR1, which is elevated in breast cancer. (E) AMPK is the chief signaling molecule downstream of AdipoR1. gAd acts on invasive tumor cells through AdipoR1 to activate AMPK and upregulate autophagic response, enhancing their potential to metastasize.

Table 1

Experimental studies of adiponectin isoforms in breast cancer cell lines

Isoform	Concentration	Cell line(s)	Summary of selected findings	Ref
Full length	15 µg/ml	MCF7	• Inhibition of proliferation; no effect on apoptosis	[68]
Full length	2.5–250 ng/ml	MCF7	• Inhibition of proliferation and cyclin D1 expression • Upregulation of DNA fragmentation	[73]
Full length	5–500 ng/ml	MDA-MB-231	• Inhibition of proliferation and cyclin D1 mRNA expression • Upregulation and downregulation of mRNA expression of pro- and anti-apoptotic genes, respectively; no effect on DNA fragmentation	[42]
Full length and globular	Full length: 50–5000 ng/ml 2.5–20 µg/ml Globular: 1.25–10 µg/ml (MDA-MB-231)	MDA-MB-231 MDA-MB-361 MCF7 T47D SK-BR-3	• Full length: inhibition of proliferation in MCF7, T47D, SK-BR-3; no effect in MDA-MB-361 and MDA-MB-231 • Globular: no effect on proliferation in MDA-MB-231; inhibition of proliferation upon transfection of ER α gene in MDA-MB-231	[41]
Source and type not specified	20 µg/ml	MDA-MB-231	• Inhibition of proliferation, invasion, and migration	[77]
Full length	15, 20 µg/ml	MCF7 T47D	• Inhibition of proliferation in T47D cells, but no effect on apoptosis • Activation of extracellular signal-regulated kinase (ERK)1/2 in MCF7 and T47D cells	[43]
Globular	1, 5 µg/ml	MDA-MB-231 MCF7 T47D SK-BR-3	• Increase in proliferation (MCF7, T47D) and anchorage-independent growth (MCF7) in estrogen receptor alpha-positive cell lines • Inhibition of proliferation (MDA-MB-231, SK-BR-3) and anchorage-independent growth (MDA-MB-231) in estrogen receptor alpha-negative cell lines • Increase in cell-cell adhesion and cell growth in three-dimensional culture in MCF7 cells	[76]
Recombinant human (isoform not specified)	10 ng/ml–30 µg/ml	MDA-MB-231 MCF7 T47D MCF-10A	• Inhibition of proliferation in MDA-MB-231 and T47D cells, but no effect on apoptosis • Increase in the proportion of cells in the G0/G1 fraction	[74]
Full length	1–15 µg/ml	MDA-MB-231 MCF7 SK-BR-3	• No independent effect on proliferation or apoptosis • Increase in proliferation of MCF7 cells and apoptosis of MDA-MB-231 cells with addition of 17- β estradiol	[75]
Full length	10 µg/ml	MCF7 T47D	• Inhibition of adhesion, migration, invasion, and colony formation in MCF7 and T47D • Upregulation of LKB1 implicated	[70]
Full length	10 µg/ml	MDA-MB-231 MDA-MB-468 MCF7 T47D	• Inhibition of leptin-induced increases in anchorage-independent growth, invasive potential, colony formation (MBA-MB-231, MCF7) and migration (MDA-MB-231 and -468, MCF4, T47D)	[69]

Isoform	Concentration	Cell line(s)	Summary of selected findings	Ref
			<ul style="list-style-type: none"> Upregulation of protein tyrosine phosphatase 1B (PTP1B) implicated 	
Full length	10 µg/ml	MCF7 MCF-10A	<ul style="list-style-type: none"> Inhibition of proliferation of MCF-10A, but not MCF7, cells Upregulation of mRNA expression of genes including estrogen receptor β2 (ERβ2) and caspase 1 (CASP1) in MCF-10 cells 	[71]
Full length	15 µg/ml	MDA-MB-231	<ul style="list-style-type: none"> Inhibition of proliferation and cyclin D1 expression Upregulation of DNA fragmentation 	[72]