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Minireview

IL-1 family in breast cancer: Potential interplay with leptin and other adipocytokines

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ABSTRACT

Obesity is associated with an increased risk of breast cancer. interleukin-1 (IL-1), a pro-inflammatory cytokine secreted by adipose tissue, is involved in breast cancer development. There is also convincing evidence that other adipocytokines including leptin not only have a role in haematopoiesis, reproduction and immunity but are also growth factors in cancer. Therefore, IL-1 family and leptin family are adipocytokines which could represent a major link between obesity and breast cancer progression. This minireview provides insight into recent findings on the prognostic significance of IL-1 and leptin in mammary tumours, and discusses the potential interplay between IL-1 family members and adipocyte-derived hormones in breast cancer.

1. Introduction

Recent epidemiological and molecular evidences have established obesity as a risk factor for breast cancer incidence (post-menopausal) and morbidity [1]. One of the mechanisms that might explain the relationship between obesity and hormone-dependent breast cancer development is estrogen overproduction by adipose tissue derived from elevated androgen aromatization. However, the mammary adipose tissue is also an important source of angiogenic factors, paracrine mitogens and anti-mitogens, including growth factors and "adipocytokines". This last term comprises adipokines (leptin, adiponectin, visfatin, and resistin) and numerous pro-inflammatory cytokines secreted by adipocytes and involved in the mediation or coordination of inflammatory diseases and obesity [2].

Many reviews have addressed the role of IL-6, TNF-α and MCP-1 as adipocytokines in the pathophysiology of inflammatory processes with respect to breast cancer [3,4], but little attention has been paid to IL-1 family members.

Interleukin-1 (IL-1), one of the major pro-inflammatory cytokines, is increased in patients with cancers [5]. IL-1 is known to be upregulated in many tumour types and has been implicated as a factor in tumour progression *via* the expression of metastatic and angiogenic genes, and growth factors. A number of studies have reported that high IL-1 concentrations within the tumour microenvironment are associated with a more virulent tumour phenotype. For example, solid tumours in which IL-1 has been shown to be upregulated include melanomas, colon, lung, head and neck cancers, and patients with high IL-1 producing tumours have generally bad prognoses [6–9].

Members of IL-1 family are adipocytokines since they have been well documented not only in breast cancer cells in vitro [10] as well as in vivo [11] but also in human adipose tissue which produces 5- to 10-fold more IL-1 family cytokines than TNF and IL-6 [12].

In breast biopsies, IL-1 is one of the 5 cytokines (along with IL-2, IL-4, IL-10 and G-CSF, most of them mediating IL-1 biological activities) not detected in normal breast and overexpressed in breast carcinoma [13].

IL-1 may not be the only adipocytokine associated with breast cancer but it is considered as an upstream "alarm" adipocytokine since its production (even in small amounts) induces potent secondary responses, in part through its ability to elicit secretion of other cytokines, chemokines, adhesion molecules and receptors for cytokines from diverse cells [5]. Indeed, according to Lewis et al. [14], IL-1 plays an early role in tumour growth and metastasis since in the tumour microenvironment, secreted IL-1 has local effects on other cells (endothelial cells, stromal cells, and

Abbreviations: IL-1, interleukin-1; IL-1ra, interleukin-1 receptor antagonist; HMEC, human mammary epithelial cells; ObR, leptin receptor; BMI, body mass index

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infiltrating cells) that result in increased production of transcription factors (NF-kappaB, AP-1), adhesion molecules, proangiogenic and prometastatic mediators such as VEGF, IL-6, IL-8, matrix metalloproteinases (MMPs), macrophage-inflammatory protein-1 (MIP-1) and bFGF. Therefore, IL-1 is an upstream signal that initiates the production of other mediators in cancer and recent studies have determined the necessity of IL-1 in tumour growth and invasiveness, and angiogenesis [15].

Leptin is secreted mainly by adipocytes. However, leptin expression has been observed in non-adipocytes cells like breast cancer cell lines, and this expression can be modulated by IL-1 [16–18]. The primary role of IL-1 in the induction of leptin during inflammation [16] suggests that some of the biological activities of IL-1 may be specifically mediated by leptin. Moreover, recent data demonstrate a genuine interplay (ie a mutual regulation) between leptin and IL-1 family members in different models including breast cancer [19–21]. We have recently reported such an interplay in metabolic diseases and obesity [22] and it may also occur in breast cancer.

Therefore, it was important to review for the first time the recent advances regarding the action of IL-1 members as adipocytokines in breast cancer, with a special focus on their interactions with other adipocytokines, in particular leptin.

2. IL-1 family: generalities

IL-1 family is mainly represented by pro-inflammatory cytokines IL-1α and IL-1β, interleukin-1 receptor antagonist (IL-1ra) and their receptors.

There are mainly two cell-surface IL-1 receptors: IL-1RI (type I receptor) and IL-1RII (type II receptor) but the type I receptor, an 80-kDa protein with a cytoplasmic domain of approximately 215 amino acids, is the only receptor responsible for IL-1 signaling. The type II receptor, a 60-kDa protein with a truncated cytoplasmic domain of 29 amino acids, binds IL-1 and thereby prevents it from binding to the type I receptor but does not deliver a biological signal. The type II receptor is then considered as a "decoy" receptor. IL-1α and IL-1β bind to the type I receptor with the same affinity. IL-1ra also binds to type I receptor and type II receptor with nearly the same affinity as IL-1α and IL-1β and yet does not trigger a response, antagonizing competitively the inflammatory effects of IL-1 [for a review, see [5]]. Thus IL-1ra is a naturally occurring inhibitor, which is unique in the cytokine world. An excess of IL-1ra is necessary to counteract the effects of IL-1 in vitro. This excess reaches 1000 in breast cancer tissue homogenates [11].

Since IL-1ra does not induce signal transduction, the "activity" of IL-1ra is regulated only by its levels of production which are controlled by regulatory molecules (inhibitors and enhancers). A deregulation in the balance between IL-1 and IL-1ra is one of the factors influencing the course, the susceptibility to and the severity of many diseases [23]. In the past few years, IL-1ra has attracted considerable clinical attention because its serum levels are elevated in pathologies as diverse as sepsis, cancer, metabolic diseases and auto-immune diseases [24] whereas the plasma IL-1ra/IL-1 ratio in a healthy population is close to 1 and exhibits minimal variation [25]. A significant increase of plasma IL-1ra is associated with post-treatment fatigue in breast cancer survivors [26].

The increase in circulating IL-1ra levels corresponds to a delayed event in response to IL-1 production and may represent a preventive mechanism in long-acting and/or excessive inflammatory response. In contrast, the inflammatory site is more likely unbalanced in favor of IL-1, especially in severe lesions [27] and insufficient production of endogenous IL-1ra may contribute to the pathogeny of these conditions [see [22] for more details].

Recombinant IL-1 receptor antagonist (recIL-1ra or anakinra) is an anti-inflammatory protein routinely used as a therapeutic molecule in rheumatoid arthritis [28] in subcutaneous daily injections (20–200 mg) with relatively few side effects, mainly local inflammatory reactions at the injection site. As documented by Arend [23], recIL-1ra clinical trials have been also conducted in different diseases like sepsis and graft versus host disease. Anakinra is well absorbed in humans and its safety is well documented with few adverse reactions, making it an ideal candidate in the adjuvant therapy in cancers. More recently, Larsen et al. [29] discussed the possibility of using anakinra for treatment of type 2 diabetes while Ricci et al. reported that local delivery of IL-1ra in colon mucosa through genetically engineered sporulating bacteria successfully reduced disease progression in a murine model of ulcerative colitis [30].

RecIL-1ra drug development has been also reported at a preclinical stage in murine models of melanoma [31] and fibrosarcoma [32] where sustained IL-1ra was delivered in vivo from biodegradable microspheres. Additionally, IL-1ra blocked IL-1 induced production of colony-stimulating growth factors (CSF) by fibroblasts, lymphocytes and monocytes in acute and chronic myelogenous leukemias [33,34]. All these data confirm that recombinant IL-1 receptor antagonist is a potential drug in cancer treatment [14]. Current clinical trials in breast cancer include other cytokines alone or in combination with other drugs [35].

3. IL-1 family and breast cancer

Normal human mammary epithelial cells (HMEC) express the receptors for IL-1 family members since IL-1β inhibits significantly the proliferation of HMECs and IL-1ra blocks this growth inhibition [36]. Both expression and distribution of IL-1 family members have been well studied in human mammary cancer tissue where they regulate tumour activity within the microenvironment surrounding breast tumour [37–39]. IL-1 levels are significantly increased in ductal invasive tissues as compared in benign tissues [11] and elevated levels of IL-1β are correlated with invasiveness and aggressiveness of breast cancer [37] and with a high tumour grade [13]. In addition to proliferation, IL-1 has been linked to invasion, angiogenesis and inhibition of apoptosis in cancer cells [14,15].

IL-1 family members also modulate the hormone activity of estrogens and their receptors. Indeed, IL-1 expression is observed mostly in estrogen receptor negative breast cancers, which are usually more invasive and metastatic and associated with poor prognosis [39]. It has been shown that breast cancer cell proliferation induced by IL-1 is mediated by P450 aromatase and steroid sulfatase (STS), two estrogen-producing enzymes [40]. Aromatase activity that converts androgens to estrogens has been identified in 50-60% of breast cancers whereas STS converts conjugate estrogens to free potent estrogens and is found in almost all types of breast cancer [41]. Honma et al. [40] have reported that when IL-1β (10 ng/ml) is added to the medium of SK-BR3 breast cancer cell line, the amount of aromatase activity is significantly enhanced to 120% of the control. In MCF-7 cells, the level of STS activity was also significantly enhanced to 130% of the control by IL-1β and this enhanced activity was completely reversed by the addition of IL-1ra (100 ng/ml) in the medium. In these cells, IL-1β also significantly increased cell proliferation in the presence of E1-S (STS-inhibitor). All together, these data suggest that increased IL-1 levels in breast cancer tissue enhance the proliferation of cancer cells through stimulating the activity of steroid catalyzing enzymes such as STS and aromatase that produce bioactive estrogens.

Moreover, IL-1 down-regulates expression of estrogen receptors in mammary cancer cell lines [42,43], leading to estrogen bioavailability whereas IL-1ra levels are directly correlated with those of estrogen receptors [39]. High IL-1ra levels and low IL-1 levels at the tumour site are associated with a good prognosis of breast can-

cer and correlate with increased expression of estrogen receptors [11]. In a more recent work, high circulating IL-1ra concentrations represent a prognostic factor in breast cancer patients over 50 years old, especially when tumour cells lack of estrogen receptors [44]. IL-1 receptors are expressed in estrogen-dependent (MCF-7, ZR75-1) as well as in estrogen-independent cell lines (MDA-MB 231) [11]. In contrast, genes of IL-1$_\alpha$, IL-1β, and IL-1ra are preferentially expressed in highly malignant and invasive mammary cell lines (BT 20, BT 549, HS 578T, and MDA-MB 231) and are not detected in other cell lines tested (MCF-7, T47-D, ZR75-1, and SKBR-3) [10]. In one study, however, the authors found no IL-1β expression in the three breast cancer cell lines MCF-7, MDA-MB231 and MDA-MB468 [36]. Collectively, this body of work suggests an autocrine/paracrine functional IL-1 system in the model of breast cancer.

A Korean study showed that a rare polymorphism of IL-1ra gene (IL-1RN*2) reduces the risk of breast cancer, especially when associated with a low body mass index (BMI) [45], suggesting that a genetic aspect of IL-1 may influence the susceptibility to tumour development. Further studies will be necessary to clarify the role of this polymorphism in breast cancer, especially its influence on systemic and local production of IL-1ra since we have previously found that IL-1RN*2 allele accentuates the differential IL-1ra expression in blood and at the inflammatory site [46].

4. Leptin and breast cancer

Another mechanism explaining the association between obesity and breast cancer implicates leptin, which is now considered as a pro-inflammatory adipocytokine [47].

Numerous studies have demonstrated that leptin stimulates the proliferation of breast cancer cell lines [48–51]. The presence of leptin and its receptor (ObR) has been described in vitro in the normal human breast epithelial cell line MCF10A [17] and HBL100 [49] respectively, as well as in breast cancer cell lines [17,49,52]. We have recently investigated leptin and ObR expression in vivo in epithelial or ductal tissues of breast tumours [53–55]. We have identified leptin as a proliferative factor in human breast carcinoma since immunohistochemical expression of leptin on biopsies correlates with the different stages of tumour invasion in ductal tissues [54,55]. In addition, leptin is not expressed in healthy breast tissue [54] but is detected in normal tissue adjacent to ductal carcinoma, suggesting leptin may be a prognostic marker of early tumourigenicity in human ductal breast carcinoma.

We have also detected the presence of leptin receptor (ObR) in human breast carcinoma but not in normal breast tissue [53]. These data are consistent with another study in which an immunohistochemical staining failed to reveal the presence of ObR in normal mammary epithelium [56]. ObR expression was investigated by immunohistochemical staining from tissue sections of invasive breast carcinomas and varied from 75–83% [55,56] to 41% [57] depending on the study.

Enhanced expression of ObR in tumours simultaneously with high levels of circulating leptin in serum is a risk factor and may explain the association between obesity and breast cancer [58]. Both leptin and ObR expressions are more abundant in tumours with a high grade [57]. Interestingly, leptin and ObR are co-expressed in primary breast carcinoma, suggesting that leptin acts on mammary tumour cells via an autocrine pathway [55].

Finally, leptin is able to induce the aromatase gene expression in MCF-7 cells through an enhanced binding of AP-1 to specific DNA sites in the promoter region [59]. AP-1 transcription factors are known to regulate the expression of many cytokines. AP-1 are more abundant in estrogen receptor negative breast tumour samples than in estrogen receptor positive ones [60]. Interestingly, Chavey et al. [13] showed that in breast cancer, high AP-1 levels correlated with high levels of expression of several cytokines, including IL-1β. Moreover, leptin derived from breast and abdominal adipose tissue of obese women increases aromatase activity and is a potential stimulator of estrogen synthesis that favored growth of breast glandular epithelium [61]. The fact that ObR expression positively correlates with estrogen receptor and tumour size [55] points to a possible interaction between leptin and estrogen systems to promote breast carcinogenesis and confirms the potential role of leptin as a growth factor.

5. Interaction between IL-1 family and leptin

Since the discovery of leptin as an adipocytokine, many other metabolic activities have been demonstrated, leptin interfering with fetal development, haematopoiesis, reproduction and immunity [see [62] for a review]. Although leptin is not a classical cytokine, several immune cells (such as polymorphonuclear leukocytes, monocytes, macrophages and lymphocytes) bear ObRs and their activity can be modulated by leptin [63–67]. For example, leptin increases macrophage activation and cytokine release [62].

The expression of both leptin and IL-1 families has been shown to be associated in several pathological situations [19–21,68], suggesting an interplay between them. We have recently reported an interplay between IL-1 family and leptin in metabolic diseases and obesity [22] but the simultaneous production of both these adipocytokines has never been described in human breast cancer. In a murine model of breast cancer, MCF-7 cells produce a high amount of IL-1α, which in turn induces leptin expression in stromal cells or in infiltrating immune cells recruited in tumour microenvironnement [19]. In rats, elevated concentrations of IL-1β in peripheral blood increase leptin levels concomitantly with the total body fat mass, and stimulate growth of mammary epithelium [69].

Recent work has demonstrated that leptin regulates IL-1 family members in a diabetic context [70]. Leptin decreases β-cell production of IL-1ra and induces IL-1β release. IL-1ra modulation by leptin is cell-specific since leptin induces IL-1ra expression in monocytes [71] and in macrophages [72], suggesting an anti-inflammatory role of leptin in these cells. Lower IL-1ra levels are also detected in serum of leptin-deficient mice deficient ob/ob after stimulation with LPS [72]. In HepG2 and THP-1 cells, the activation of the IL-1ra promoter by leptin involves the activation of MAP kinase and the binding of a yet uncharacterized factor to the nuclear factor kappa B binding site of the IL-1ra promoter [73]. Other works have shown leptin synthesis by human preadipocytes is stimulated in a paracrine manner by IL-1β and TNFα (which are secreted by macrophages infiltrating adipose tissue) [74]. IL-1β is a mediator of inflammatory effects of leptin since leptin production induced during local and systemic inflammation is observed in IL-1β+/+ mice but not in IL-1β−/− mice [16].

As it is recognized that leptin acts both at the central nervous system and at the peripheral level, it may also exert its effects in morbid obesity through the IL-1 pathway and IL-1ra may contribute to central leptin resistance by inhibiting the leptin-induced reduction in food intake [75].

6. Interaction between IL-1 family and other adipocytokines

The interplay between the different adipocytokines plays a key role in the development of obesity-related cancers like breast cancers [3,76].

We have recently explored simultaneously the expression of leptin and adiponectin both in breast cancer cell lines and in mammary tissue of ductal carcinoma [77,78] and suggested antagonistic properties of these two adipocytokines in breast cancer

development. Other studies have shown antiproliferative effects of adiponectin in human breast cancer cell growth *via* activation of cell apoptosis and inhibition of cell cycle [79,80], suggesting that adiponectin could act in vivo as a paracrine/endocrine growth inhibitor towards mammary epithelial cells.

To date, only one study has explored the simultaneous levels of leptin, adiponectin and resistin in serum of breast cancer patients [81] and few studies have addressed the interplay between IL-1 members and other adipocytokines. IL-1 has been described to abolish completely adiponectin secretion in adipocytes [74] while IL-1ra induction by adiponectin has been reported in human leukocytes [82]. A low serum level of adiponectin is generally considered as a risk factor in the breast cancer development among post-menopausal, but not pre-menopausal women [81,83]. Similarly, low circulating levels of IL-1ra may be indicator of a good prognosis since in healthy population, individuals with low serum IL-1ra concentrations have higher levels of adiponectin [84]. However, a dichotomy may exist between circulating and tissue levels of adiponectin since high tissue adiponectin levels are more likely associated with increased risk for breast cancer [85]. We have previously found such a dichotomy between the systemic production of IL-1ra and its local production at the inflammatory site, and suggested separate regulatory mechanisms in different compartments [46].

7. Conclusion

Leptin and IL-1 family members are «adipocytokines» secreted by adipose tissue and also by epithelial tissue of breast tumour. The interplay between IL-1 family cytokines and leptin has been well documented in metabolic diseases and obesity and not in human breast cancer.

In this minireview, we clearly demonstrate an important role for the IL-1 family members and other adipocytokines in breast cancer

Table 1
Summary of the association of IL-1 family members (a), leptin and adiponectin family (b) with the risk (susceptibility) and prognosis of breast cancer. BC: breast cancer; CL: breast cancer cell lines; ER: estrogen receptor; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; DCIS: ductal carcinoma in situ.

Adipocytokine	Location	Effect	Reference
(a)			
IL-1α	Tissue	Negative correlation with ER	[10,11,39,43]
	Tissue	Increase in DCIS or IDC vs. benign	[11,38]
	Tissue	Positive correlation with angiogenic factor IL-8	[11,38]
	CL	Genes expressed in malignant and invasive phenotypes	[11]
	CL	Down-regulates expression of ER	[42,43]
	Tissue	Positive correlation with tumour grade and poor differentiation	[10,43]
IL-1β	Tissue	Increase in DCIS or IDC vs. benign	[11,38]
	Tissue	Positive correlation with tumour grade and p53	[37]
	Tissue	Positive correlation with angiogenic factor IL-8	[11,38]
	Tissue	Increase in invasive BC vs. healthy	[13]
	Tissue	Increase in invasive BC vs. benign and DCIS	[37]
	Tissue	Negative correlation with ER and PR	[13]
	Tissue	Negative correlation with ER and bcl-2	[37]
	Tissue	Positive correlation with tumour grade, AP-1	[13]
	CL	Enhances aromatase expression	[40]
	CL	Genes expressed in malignant and invasive phenotypes	[11]
IL-1ra	Tissue	Positive correlation with ER	[11,39]
	Plasma	Increase in BC survivors	[26]
	Tissue	Increase in IDC vs. benign	[11]
	Serum	High levels in patients lacking ER	[44]
	CL	Genes expressed in malignant and invasive phenotypes	[11]
IL-1/IL-1ra	Tissue	Positive association with tumourigenic activity	[39]
IL-1RI and II	Tissue	Increase in DCIS or IDC vs. benign	[11]
(b)			
Leptin	CL	Proliferative effect	[48–51]
	Tissue	Positivity in 80% IDC vs. 0% in healthy	[54]
	Tissue	Positivity in 86% of BC	[55,57]
	CL	Enhances aromatase expression	[59]
	Tissue	Positive correlation with ER-β in primary BC	[57]
	Tissue	Positive correlation with tumour grade	[57]
	Serum	High levels associated with increased risk for BC	[81]
	Serum	Positive correlation with tumour size	[81]
	CL	Regulates epithelial-derived proteins	[90]
ObR	Tissue	Positivity in 75% of invasive BC (IDC + ILC)	[55]
	Tissue	Positivity in 83% of IDC	[56]
	Tissue	Positivity in 41% of IDC	[57]
	Tissue	Increase in BC vs. healthy	[53]
	Tissue	Positive correlation with ER-α in lymph node metastases	[57]
	Tissue	Positive correlation with ER and tumour size	[55]
	Tissue	High levels associated with increased risk for BC	[58]
Adiponectin	Serum	Low levels associated with increased risk for BC	[81,83]
	Tissue	High levels associated with increased risk of BC	[85]
	Tissue	Positivity in 15% IDC vs. 75% in normal adjacent	[78]
	CL	Anti-proliferative effect, apoptotic effect	[79]
Adipo-R	CL	Expressed in BC	[80]
Resistin	Serum	High levels associated with increased risk for BC	[81]

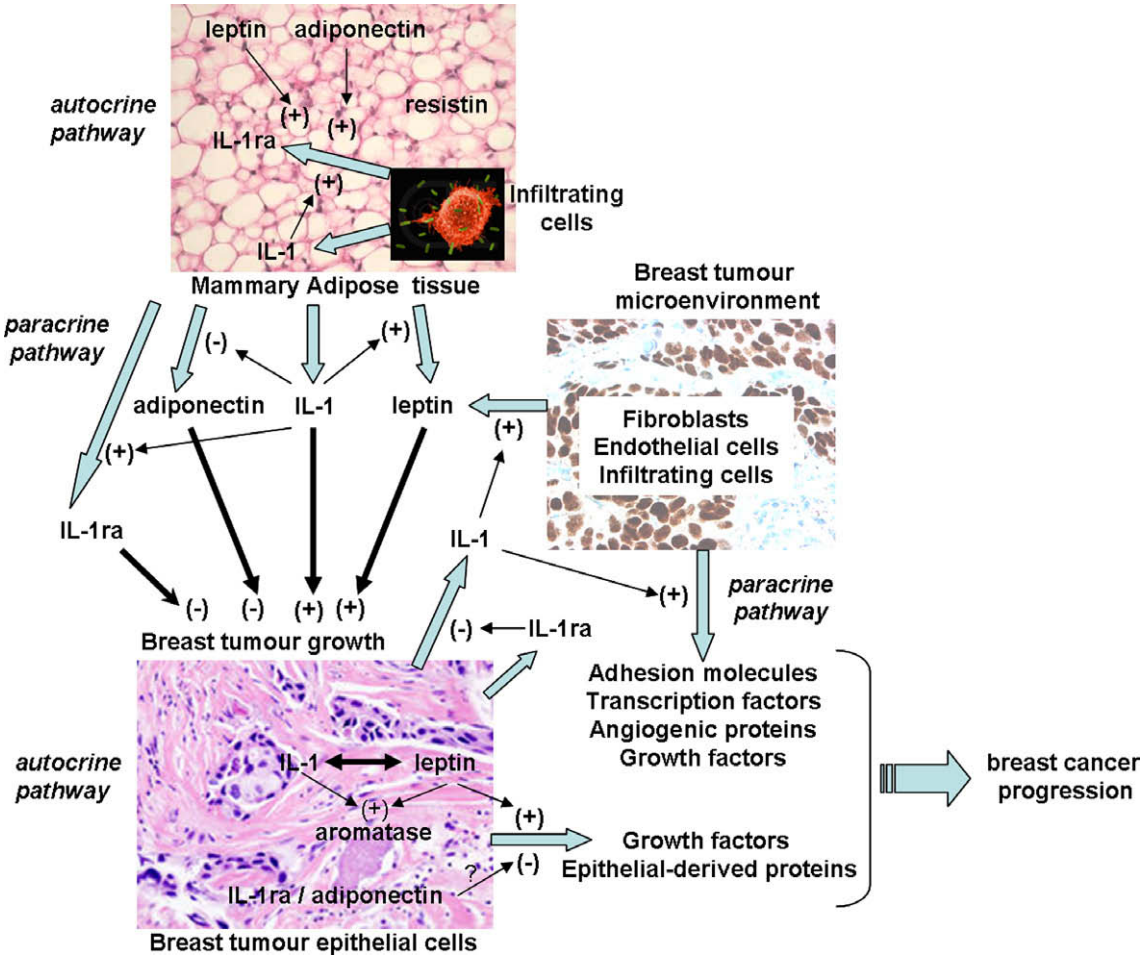

Fig. 1. Proposed model outlining the possible signaling pathways involved between IL-1 family members and other adipocytokines in breast cancer progression. Adipocytokines are produced by mammary adipocytes (leptin, adiponectin, and resistin) or inflammatory cells infiltrating fat (IL-1 family members, resistin) where they cross-regulate [71,82,89]. IL-1 is released from adipose tissue and can regulate in a paracrine manner the other adipocytokines involved in adipocyte-epithelial interactions [74,89]. Leptin and IL-1 act directly on mammary epithelial cells to enhance aromatase production [40,59] and promote tumour growth, migration and invasion in breast cancer [10–11,39–40,48–51]. In contrast, IL-1ra and adiponectin exert a direct growth inhibitory effect on breast cancer cells [11,79,80]. Mammary epithelial tumour cells produce a high amount of adipocytokines [11,13,54,78] and leptin may interplay with IL-1 family members to mediate the secretion of epithelial-derived proteins [90]. In the tumour microenvironment, IL-1 has local effects on stromal or infiltrating cells that result in production of leptin [19] and other tumour growth mediators [14,15] responsible for breast cancer progression.

progression based on their correlation with prognostic indicators (Table 1). In particular, IL-1 and leptin may represent a set of biological predictors for disease course in breast cancer. Based on these observations, we have constructed a hypothetical model describing the role of adipocytokines within the breast cancer microenvironment. In this model (Fig. 1), we hypothesize that mammary adipose cells express both agonists (IL-1, leptin) and antagonists (IL-1ra, adiponectin). These adipocytokines then act in both an autocrine and paracrine manner via their receptors on mammary tumour cells to (a) influence tumour cell proliferation, migration and invasion in breast cancer; (b) regulate the production of epithelial-derived proteins, angiogenic proteins and growth factors; (c) stimulate other cells in the tumour microenvironment to invade and proliferate.

Since mammary glandular epithelium interacts with interstitial cells during the development of breast cancer, further studies will be necessary to clarify the interplay between the different adipocytokines (leptin, adiponectin, resistin, IL-1) in the different compartments involved: epithelium, inflammatory cells, adipose tissue and myoepithelial tissue which has been called "natural tumour suppressor" due partly to its ability to inhibit the proliferation of breast carcinoma cells [86].

Because fat increase is associated with estrogen bioavailability and breast cancer risk, IL-1 family members may be included with other adipocytokines as indicators of breast cancer assessment. In addition, the clinical approach may help to assess the influence of cytokines in the process of breast carcinogenesis in patients according to their diet, nutrition status (lean phenotype, obesity) and to determine the potential diagnosis/prognosis impact of these molecules and their receptors, in order to develop efficient strategies of prevention and molecules with therapeutic benefits. In particular, if it was proven that IL-1ra is able to reduce excessive production of IL-1 and leptin in breast adipose tissue, recombinant IL-1ra currently used as a therapeutic molecule in rheumatoid arthritis [28] could represent an alternative chemotherapy in breast cancer by targeting adipose tumour site with lipidic microencapsulated cells secreting human IL-1ra, as successfully tested in fibrosarcoma [32].

Since adipose tissue from obese patients overexpresses several adipocytokines, some authors have suggested that adipose mass reduction after weight loss may help restore inflammatory levels by decreasing the adipose mRNA expression and secretion of pro-inflammatory adipocytokines. In fact, the loss of body mass is accompanied with a decrease in serum leptin levels [87]. It is also intriguing that in patients with morbid obesity, which is a well-known risk factor of post-menopausal breast cancer, serum levels of IL-1ra are 7-fold higher as compared to non-obese

patients (1750 vs. 250 pg/ml) and decrease after weight loss from bypass surgery [88]. IL-1ra concentrations correlate with lean BMI, the degree of insulin resistance and leptin levels, reflecting IL-1ra production by adipose tissue [12]. In this study, IL-1β and IL-1ra were detected in human adipose tissue at 6–8 and 8–12 pg/mg, respectively, and were mainly localized in visceral adipose tissue unlike leptin which was mainly present in subcutaneous adipose tissue. Modulation of adipocyte IL-1ra by IL-1 suggests an autocrine loop of regulation within adipose tissue [89]. Increased circulating IL-1ra levels in obese patients may have a protective role in response to high leptin levels and pertain to its immunomodulatory and/or metabolic activities as described in sepsis or inflammatory disorders [4]. In rheumatoid arthritis, for example, IL-1ra and leptin are correlated, independently of age and BMI [21].

In conclusion, the fact that adipose leptin and IL-1 members' production is up-regulated while adiponectin production is strongly reduced in obesity may help to explain why obesity is a risk factor of developing breast cancers. The study of simultaneous production of IL-1 family members and other adipocytokines in breast cancer may allow a better understanding to how they are involved in the complex perturbations leading to the dysregulation of tumour cells and their diagnosis/prognosis impact when associated.

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