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Role of leptin in the pathogenesis of breast cancer

Papel da leptina na patogênese do câncer de mama

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Abstract

Leptin is a small polypeptide codified by the Obese Gene (OB), deeply related with the body fat mass and energetic balance. Due to its diverse biological effects and downstream signal transducers, multiple classifications have been attributed to leptin, as hormone, cytokine, adypokine, growth factor, and developmental factor, among others. This scenario gives us an idea of the size of the potential biological effects generated by this molecule. The concentration of leptin in the body is determined by the amount of adipose tissue; therefore, hyperleptinemia is a common finding in obese individuals. In addition, high levels of circulating leptin may confer a poor prognosis for any pathological condition. Although leptin history has been reported for more than 20 years, its relationship with cancer has gained notoriety in the past ten years, where studies focused on discussing the issue of obesity as a strong risk factor for cancer developing. Further, growing evidences have pointed leptin as a pivotal mediator of immune response, which aggravates the scenario of cancer occurrence in the presence of obesity. Therefore, leptin can present at least two faces in the pathogenesis of breast cancer, acting by immune and non-immune mechanisms. In this paper we review the dynamic of the leptin axis in breast cancer and further discuss its role in disease, immunopathogenesis and prognosis.

Key words: Leptin. Breast cancer. Obesity. Immune response.

Resumo

A leptina é um pequeno polipeptídeo codificado pelo gene OB, profundamente relacionado com a massa de gordura corporal e o balanço energético. Devido aos seus diversos efeitos biológicos e transdutores de sinal regulados, múltiplas classificações biológicas tem sido atribuídas à leptina, incluindo hormônio, citocina, adipocina, fator de crescimento, e fator de desenvolvimento, dentre outros. Este cenário nos dá uma idéia do tamanho do potencial de efeitos biológicos gerados por esta molécula. A concentração

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de leptina no corpo é determinada pela quantidade de tecido adiposo; portanto, hiperleptinemia é um achado comum em indivíduos obesos. Além disso, níveis elevados de leptina circulante pode conferir um pior prognóstico para qualquer condição patológica. Apesar da história da leptina ter sido reportada por mais de 20 anos, sua relação com o câncer ganhou notoriedade nos últimos 10 anos, quando estudos focaram e discutiram o papel da obesidade com um forte fator de risco para o desenvolvimento de câncer. Adicionalmente, evidências crescentes apontam a leptina como mediador primordial da resposta imune, o que agrava o cenário da ocorrência de câncer na presença de obesidade. Assim, a leptina pode apresentar pelo menos duas faces na patogênese do câncer, agindo através de mecanismos imunológicos e não-imunológicos. Neste trabalho, revisamos a dinâmica do eixo leptina no câncer de mama e discutimos seu papel na doença, imunopatogênese e prognóstico.

Palavras-Chaves: Leptina. Câncer de mama. Obesidade. Resposta imune.

How do Cancer Cells Respond to Leptin Stimuli?

Leptin is an adipokyne produced by adipocytes that controls the energetic metabolism. Obesity is a known risk factor for cancer development (MATHÉ, 2000). The proinflammatory signaling sustained by augmented metabolic hormones, as leptin, suggests a role for these molecules in cancer pathogenesis. Abnormalities in leptin levels have been associated with severe metabolic modifications (LAUGHLIN; MORALES; YEN, 1997) which are also a common finding in cancer (KULKARNI et al., 1997).

For its biological function, it is necessary that leptin binds to its receptor, which is an IL-6 type class I cytokine receptor. Leptin receptors have an extracellular leptin - binding domain - and a full intracellular domain that is required to the activation of second messenger pathways and for the normal leptin action (ALLISON; MYERS, 2014).

Pioneer studies in this area have highlighted the importance of leptin receptors in the pathological metabolic responses. Due its wide distribution in cells, such receptors have been implicated in a wide of abnormal events in cancer. *In vitro* studies have demonstrated that leptin is a major player that regulates a wide range of proteins responsible for signal transduction and gene transcription in cancer (TAKAHASHI et al., 1996).

In general, all types of cancer are able to respond to leptin stimuli. Pituitary adenomas express a pattern of leptin receptors similar to that found in the normal pituitary gland during fetal stages (SHIMON et al., 1998), suggesting a role for leptin in cell proliferation (JIN et al., 1999). Furthermore, such cancerous cells expressing such receptors are capable to store the leptin within the pituitary, affecting the secretion of other hormones in a paracrine manner (KORBONITS et al., 2001). Similarly, blasts from patients with acute myeloid leukemia often rescue the high expression of these receptors, which has been associated with disease recurrence due to anti-apoptotic properties of leptin (KONOPLEVA et al., 1999). Normal bone marrow cells are stimulated for leptin, which acts controlling its expansion and differentiation (HINO et al., 2000). Leptin receptors are also overexpressed in primary and metastatic breast cancer, with significant enrichment in undifferentiated tumors (GAROFALO; SURMACZ, 2006). High soluble leptin receptor (Sob-r) is found in healthy volunteers when compared to breast cancer women exhibiting hyperleptinaemia (MOHAMMADZADEH et al., 2014a).

After the linkage between leptin and its receptors in cancer cells, a broad cascade of signaling events is activated enrolling multiple components. Although virtually all cancer cells may react to leptin stimuli, it seems that each type of cancer presents a differential capacity to respond, depending upon the specific organ of origin. An *in vitro* study demonstrated the existence of dose and time-related responses of cancer lineages to leptin exposure. In addition, growth stimulation was found in breast, esophagus

and prostate cancers, while inhibition was observed in the pancreatic lineage (SOMASUNDAR et al., 2003a).

Leptin acts by modulating a wide of pivotal pathways (JAK/STAT, PI3K/AKT, ERK1/2), expression of antiapoptotic proteins, inflammatory factors (TNF-α, IL-6), and angiogenic factors (vascular endothelial growth factor, VEGF and hypoxia-inducible factor 1a, HIF-1a) (DUTTA et al., 2012). Some studies have elucidated specific pathways triggered by leptin, and its biological effects in cancer cells. Despite the differences among cancer topography, most of these signaling cascades are shared by tumors (ATTOUB et al., 2000; HARVEY et al., 2000; OGUNWOBI; MUTUNGI; BEALES, 2006; SOMASUNDAR et al., 2003b).

In breast cancer lineages, leptin triggers cell proliferation by activating the STAT3 and p42/p44 MAPK pathways (DIEUDONNE et al., 2002). Further, it was reported that leptin activates NFkB in mammary cancer cells and promote the development of aggressive phenotypes (ROSE; GILHOOLY; NIXON, 2002). Mitogenic signals are provided after leptin exposure for breast cancer cells through MAPK and PI3K cascades (FRANKENBERRY et al., 2006), as well as by downregulation of the tumor suppressor p53 (CHEN et al., 2006).

In a retrospective analysis, it was observed that a significant number of studies on leptin have approached to female breast cancer. Leptin mediates the normal development of breast tissue in humans (NEVILLE; MCFADDEN; FORSYTH, 2002) and is clearly enrolled in mammary carcinogenesis (HU et al., 2002). Women naturally present higher leptinaemia than men, due to its upregulation by estrogen (HAVEL et al., 1996). Moreover, the breast is a lipid-rich tissue, and adipocytes are an important source of leptin (NALABOLU; PALASAMUDRAM; JAMIL, 2014). Thus, mammary cells are immersed in a leptin-enriched environment, and it may be aggravated by overweight and obesity. In fact, breast cancer is strongly associated with obesity and overweight (BRAY, 2002).

In the breast, leptin exerts the proliferative control of both normal as malignant cells (HU et al., 2002) and is overexpressed in the neoplastic mammary tissue (ISHIKAWA; KITAYAMA; NAGAWA, 2004). Leptin can promote the development of aggressive cancer phenotypes (ROSE; GILHOOLY; NIXON, 2002), an event regulated by sex hormones (MORAD; ABRAHAMSSON; DABROSIN, 2014). Positive correlation of leptin with hormonal receptors is reported, suggesting that breast cancer cells respond to this hormone via an autocrine pathway (RÉVILLION et al., 2006). Leptin-induced second messengers are described as enrolled in generating estrogens and activating estrogen receptor signaling, which may affect the chemoresistance against estrogen inhibitors, as tamoxifen (SULKOWSKA et al., 2006).

High leptin in breast cancer may be a product resulting from the pro-inflammatory environment, and it is also responsible for potentiating this situation. Patients with breast cancer are under high systemic TNF-α (tumor necrosis factor alpha) (PANIS et al., 2012), one of the inducers of leptin synthesis (ZHANG et al., 2000). An additional mechanism of leptin is the local angiogenesis promotion (CALDEFIE-CHÉZET et al., 2013).

Leptin and Immune System Control

The concept that adipocytes could be considered as immune cells has been largely discussed. During the past few years, researches have been demonstrating several functions for adipocytes. Now it is recognized, for example, that adipose cells are able to secrete a variety of hormones and proteins that regulates several cellular responses (ALEXAKI et al., 2009; SCHÄFFLER; SCHÖLMERICH; SALZBERGER, 2007; VIELMA et al., 2013) called as adipokynes.

During the past 20 years, the leptin signaling has been investigated and its role in immunological responses has gained increased impact (COJOCARU et al., 2013; FRENCH; DEARING; DEMAS, 2011). Leptin is a modulator of several innate and acquired immunological responses and it targets several immune cells (Table 1). In innate immunity, it has been reported that leptin stimulates dendritic cells, monocytes, macrophages, neutrophils, basophils, eosinophils, mast and natural killer cells.

Table 1 - Influence of leptina signaling in imune cells

	Cell type	Observation on leptina action	References
Innate imune responses	Macrophages	Increase responsiveness differentiation and activation.	Acedo et al., 2013; Kim, Kim and Do, 2013; Maya-Monteiro et al., 2007; Vaughan and Li, 2010
	Dentric cells	Generation, maturation, survival and fuction.	Mattioli et al., 2009; Moraes-Vieira et al., 2014; Al-Hassi et al., 2013; Lam et al., 2007
	Natural killers	Development, survival, and function.	Haas et al., 2008; Huebner et al., 2013; Lamas et al., 2013; Lo et al., 2009.
	Polymorphonuclear cells	Function, survival, migration, degranulation.	Suzukawa et al., 2011; Wong, Cheung and Lam, 2007; Taildeman et al., 2009.
	Phagocytes	Survival and function	Jitprasertwong et al., 2014; Sun et al., 2013.
Adaptative imune responses	T – cells	Differentiation, Proliferation	Batra et al., 2010; Kim et al., 2010.
	B – cells	Survival and activation	Agrawal et al., 2011; Lam et al., 2010.

The mechanisms by which leptin controls the response of immunological system vary according to the kind of target cell and levels of its production. Leptin can potentiate innate immune response by up-regulating toll- like receptor 2 (TLR-2), where its action seems to be more likely to enhance the differentiating inducing capacity of other signaling molecules (JAEDICKE et al., 2013). The expression and responsiveness of TLR are regulated by leptin, contributing to its regulatory function in immune system (BATRA et al., 2007).

Leptin has a notable role in macrophages responses as well, where it primers macrophages to be more responsive to a stimulus, as lipopolysaccharide (LPS) (VAUGHAN; LI, 2010). In macrophages, leptin induces its activation and increases the formation of cytoplasmic lipid bodies and inflammatory mediators within macrophages (MAYA-MONTEIRO et al., 2008). Also, leptin up-regulates chemokines expression (KIGUCHI et al., 2009). It seems that leptin exerts an important function in macrophage differentiation phenotype in adipose tissue as well. Leptin exposure induces macrophages to express a M2 phenotype characterized by a high MR (CD206), CD209 and low CD40, CD80 and CD86 markers. However, at the same time, macrophages produce cytokines as TNF-α, IL-1 (interleukin-1), IL-10 (interleukin-10), MCP-1 (monocyte chemotactic protein-1) and MIP-1α (macrophage inflammatory protein-1 alpha) which are observed in M1 phenotype (ACEDO et al., 2013). Furthermore, leptin and adiponectin mediate

a crosstalk between macrophages and adipocytes by a B-cell- activating factor (BAFF) (KIM; KIM; DO, 2013).

Dendritic cells are antigen-presenting cells (APCs) and first line of immune defense that have a critical role in the regulation of adaptive immune response. The importance of leptin signaling over dendritic cells regulation has already been stated. Altered leptin levels can modulate the capacity of dendritic cells to induce differentiated Th17 cells (MORAES-VIEIRA et al., 2014) and may impact their ability to activate T cells (RAMIREZ; GARZA, 2014). In addition, leptin enhances the dendritic cells functions (LAM et al., 2007) and its ability to stimulate the activation of CD8+ T cells by increasing dendritic cells migratory capacity, up-regulating the expression of CCR7, increasing actin polymerization and increasing cytokines production (MATTIOLI et al., 2008).

Recently it has been demonstrated that leptin is required for the generation, complete maturation and survival of dendritic cells (MATTIOLI et al., 2009; MORAES-VIEIRA et al., 2014). Leptin may be involved in several functions of dendritic cells. For example, leptin induces dendritic cells migration in homeostatic and inflammatory conditions by increasing the expression of CCR7 (AL-HASSI et al., 2013). Induction of CD40 expression in dendritic cells and its maturation are also controlled by leptin signaling through activation of Akt pathway.

It has been reported that the development of natural killer cells is impaired in the absence of leptin. Moreover, the survival and function of natural killer cells is controlled by leptin (HUEBNER et al., 2013; LAMAS et al., 2013; LO et al., 2009). Data regarding the involvement of leptin over natural killer cells are still controversial when considering the weight. It seems that the modulatory effect of leptin signaling over natural killer cells occurs only in lean subjects and not in obese subjects, as natural killer cells from obese animals are leptin resistant (NAVE et al., 2008). However, another study has shown that leptin may stimulate an increase in natural killer cells, granulocyte number and specific monocyte subset independently of overweight (HAAS et al., 2008).

Basophils, eosinophils and mast cells have a distinguish function in innate immunity as also in acquired immunity. Several functions may be applicant to leptin as regarding polymorph nuclear cells activation. Researches have proposed that leptin signaling impacts human basophils activation. Basophils possess a leptin receptor and its activation modulates several functions as it increases survival, induces cellular migration and degranulation. Further, it induces the release of cytokines marker of a Th2 profile (SUZUKAWA et al., 2011). The involvement of leptin in the induction of Th2 profile by regulating eosinophils function was established. Leptin regulate apoptosis, expression of adhesion molecules, chemokines and the release of cytokines such as IL-1β, IL-6, IL-8 and MCP-1 from eosinophils by activating MAPK, JAK and NFκB pathways (WONG; CHEUNG; LAM, 2007). The leptin action over mast cells is not completely described. Despite it is poorly known the effect of leptin signaling on mast cells, it has been demonstrated the presence of a leptin receptor, which suggests a paracrine and/or autocrine immunomodulatory effect of leptin signaling (TAILDEMAN et al., 2009).

Phagocytes play an important role in innate immunity and they may occasionally influence the effector phase of acquired immune response. However, leptin action on phagocytes is not completely understood. Leptin signaling does not seem to have an influence in neutrophil proteome and survival at physiological concentrations. Only higher levels of leptin seem to impact neutrophils proteome (KAMP et al., 2013). Therefore, only after stimulation (e.g. allergic reaction) leptin production is increased and may impact the maintaining of neutrophil survival (SUN et al., 2013) and function (RAFAIL et al., 2008). Data regarding leptin action on monocytes is scarce. For now, it is known that leptin is able to up-regulate IL-18 secretion in monocytes via activation of post-transcriptional pathways (JITPRASERTWONG et al., 2014).

The pro-inflammatory functions of leptin have been stated (IIKUNI et al., 2008). Increase in leptin levels is related to enhancement in inflammatory cytokines production (TSIOTRA et al., 2013). Leptin induces the production of leukotriene B4, IL-6 (interleukin 6), IL-1 and TNF (ANDÒ; CATALANO, 2011; ANDÒ et al., 2014).

Several studies point out the importance of leptin in the control of adaptive immune response (MORAES-VIEIRA et al., 2013; PROCACCINI et al., 2012; VENKEN et al., 2014). Leptin is a recognized modulator of T- lymphocytes function. *In vitro* and *in vivo* studies have demonstrated the crucial role of leptin in the T-cell differentiation, where the deficiency of leptin is associated with reduced polarization of naïve T cells. Therefore, leptin is essential for both Th1 and Th2-dependent immune response (BATRA et al., 2010).

The activity of leptin over differentiation of T-cells is controlled by its receptor. As proposed by Saucillo et al. (2014), leptin is required for activated T cell proliferation, inflammatory cytokine production and for the control of glucose metabolism during T cells activation. Leptin not only induces specifically the differentiation of T-cells, as also increases T- cell proliferation (KIM et al., 2010). *In vivo*, high dose of leptin has a proliferative effect on CD4+ T-cells (UNER; SULU, 2012).

Besides leptin importance on T-cells differentiation, adipocytes by themselves contribute to activation of T-cells. The presence of CD40 on surface of human mature adipocytes may cooperate to response in human T-cells, therefore regulating cytokines production, as IL-6 (POGGI et al., 2009). The survival of T-cells may be controlled by leptin signaling. Leptin stimulation triggers the activation of different signaling pathways to promote the survival., growth, proliferation and to prevent the apoptotic process of T-cells (FERNÁNDEZ-RIEJOS; GOBERNA; SÁNCHEZ-MARGALET, 2008) Also, leptin controls the autophagy process in human T conventional cells by activating the anti-apoptotic gene Bcl-2 (CASSANO et al., 2014). Recent researches propose a new role for leptin produced by T-cells. When derived from T-cells, leptin increase the expression of Th17 cells (WANG et al., 2013; YU et al., 2013).

It seems that leptin negatively modulates T-regulatory cells (Treg) function (GOLDSTEIN, MASCITELLI; PEZZETTA, 2008; MATARESE et al., 2010). Therefore, Treg response is increased by defectiveness on leptin/leptin receptor signaling (TALEB et al., 2007). This inverse relationship between leptin production and proliferation of Treg cells is linked to the increased of adaptive immune cells as CD8+ T- cells and CD4+ Th1 cell (ANDÒ; CATALANO, 2011; ANDÒ et al., 2014; WAGNER et al., 2013). Also, leptin impacts Treg proliferation by activating the mTOR pathway (PROCACCINI et al., 2012; PROCACCINI et al., 2014).

The role of leptin has also been discussed for humoral immune system responses. Leptin is able to control immunological responses in B-cells, since they display of functional leptin receptors. The survival and proliferation of B-cells are promoted by leptin signaling. The maintenance of B-cells homeostasis is mediated by leptin signaling through the induction of the expression of the antiapoptotic gene Bcl-2 and cyclin D1, conferring pro-survival responses (LAM et al., 2010). It has been demonstrated that leptin can activate human B cells with expression of CD25 and HLA-DR (human leukocyte antigen DR). B cells activation by leptin signaling increase the production of pro-inflammatory cytokines as IL-6 and TNF-α. As a compensatory mechanism, leptin increases the secretion of IL-10 (interleukin 10) by B cells in a dose- dependent manner (AGRAWAL et al., 2011). Also, leptin has an important role on B-cells during starvation. It seems that leptin treatment prevents B-cell development alteration during starvation (TANAKA et al., 2011).

In spite of leptin role in cancer, it is well known that immunological disturbances in the Th1/Th2/ Th17 balance may affect cancer risk and outcome.

Altogether, these evidences indicate that leptin can exert control on the immunosurveillance, influencing cancer development.

Leptin and the Pathogenesis of Breast Cancer

Non-immunological mechanisms

The mechanisms underlying leptin action and its influence in immune system during breast cancer development need to be clarified and discussed.

Adipocytes are the most abundant cell type that surrounds breast cancer cells. Therefore, it is reasonable that adipocytes may play an important role during breast cancer development and progression. Secreted by adipocytes and also by breast cancer cells and cancer associated fibroblasts, leptin signaling mediates several pathways in order to favor the tumor development. For example, leptin can induce local estrogen production contributing to breast tumorigenesis, promoting angiogenesis, proliferation, migration and invasion. And it also has a proinflammatory effect and interferes in immune system response (ANDÒ; CATALANO, 2011; ANDÒ et al., 2014) independently of breast cancer subtype (ARTAC; ALTUNDAG, 2012). Interestingly, the influence of leptin levels during carcinogenesis seems to be specific for tumor cells, since it promotes breast cancer cells proliferation, but it does not have a recognized impact in normal cells (DUBOIS et al., 2014).

Obesity is a condition that favors the development of several diseases. As leptin impacts tumor angiogenesis, in obese patients, its activation can be considered as a promising target. Considering this, most studies regarding leptin signaling and breast cancer in humans investigate its role in obese patients. In obese breast cancer patients, authors have described a positive correlation of breast cancer cells proliferation and leptin levels (GARCÍA-ROBLES; SEGURA-ORTEGA; FAFUTIS-MORRIS, 2013). Furthermore, in obese, pathways that are induced by leptin and that have an impact in tumor development have been characterized. For example, Notch signaling seems to be induced by leptin in breast cancer cell to promote proliferation and migration (BATTLE et al., 2014).

In postmenopausal women, the adipocytes comprise an increased risk for breast cancer development associated with prognosis (BERSTEIN et al., 2007). Considering this, recent studies have suggested a caloric restriction treatment with low-fat diet and low-carbohydrate diet for overweigh and obese premenopausal women as an effort to prevent the pro-carcinogenic effects of leptin and prevent breast cancer (LLANOS et al., 2014b).

It is known that adipose tissue stimulates breast cancer cell migration in a co-culture assay (SALAMEH et al., 2013). *In vitro* and *in vivo* studies demonstrated that leptin is able to enhance angiogenic properties of circulating angiogenic cells (HEIDA et al., 2010). Understanding the mechanisms by which leptin link to breast cancer is extremely important for the development of preventive and therapeutic strategies.

Breast cancers are grouped into distinct molecular subtypes according to presence or absence of estrogen receptors, progesterone receptors and the human epidermal growth factor receptor 2 (HER2)-overexpression. Classifying these subtypes is crucial, since they show different prognoses and should receive distinct therapeutic approaches. Leptin levels may also be associated with the prognosis of specific molecular subtype of breast cancer patients (CHO et al., 2013) and polymorphism on the leptin gene is associated with breast cancer risk (MOHAMMADZADEH et al., 2014b).

The importance of estrogen in the development of breast cancer is well characterized. Leptin signaling in adipose breast tissue increases aromatase expression and has a crucial role in the development and growth of hormone-dependent breast cancer cells (LIU; SAMAD; MUELLER, 2013). In contrast, a dual role of leptin was demonstrated by *in vitro* experiments.

It seems that leptin in combination with estrogen and insulin growth factor I (IGF-1) has a pro-proliferative impact in breast cancer cells while in the absence of estrogen leptin exerts an anti-proliferative effect (LAUTENBACH et al., 2009). Therefore, diseases that enhance leptin and IGF-1 receptor may increase the risk to develop breast cancer (LOPEZ et al., 2013). In addition, in estrogen dependent breast cancer cells, leptin regulate the expression of several genes regarding cell adhesion, cytoskeleton motility, metabolism profile and immune system (BINAI et al., 2013). *In vivo* studies have shown that leptin levels are positively correlated to estrogen levels in a murine model of breast cancer (MORAD; ABRAHAMSSON; DABROSIN, 2014). In estrogen receptor negative breast cancer, leptin signaling has also an important role, where it seems that leptin mediates tumor cell proliferation by interfering in sphingosine kinase 1 (SK1) pathway (Alshaker et al., 2014).

Leptin has an important effect in HER-2 overexpressing breast cancer patients. The leptin receptor and HER-2 protein can interact and co-localize in breast cancer cells. Consequently, leptin impacts HER-2 signaling as it can stimulate the phosphorylation of HER-2 in breast cancer cells, favoring pathways that are related to decreased apoptosis and augmented of tumor cell survival and aggressiveness. In HER-2 overexpressing breast tumors, leptin levels seem to have a negative influence on the sensitivity of lapatinib treatment (GRINER et al., 2013) and it is related to resistance in tamoxifen-treated HER-2 overexpressing cells. The mechanisms by which leptin configures resistance to therapy is through preventing the increase in pro-apoptotic gene expressions (PAPANIKOLAOU et al., 2015). Therefore, inhibition of leptin action on HER-2 overexpressing tumors has been suggested for an adjuvant breast cancer treatment in order to enhance the response to tamoxifen chemotherapy (YOM et al., 2013). Hence, researches have proposed that leptin levels at supra-physiological concentration may inhibit HER-2 breast cancer cells growth and could act by reducing MAPK activity (WEICHHAUS et al., 2014).

Here, it is shown that leptin has a clear impact on the regulation of immunological responses and induces several pathways that are related to aggressiveness phenotype in breast cancer. It is known that leptin plays an important role in the control of immune response in other types of cancer, as stimulating cytokine release for tumor development in colon cancer (ABOLHASSANI et al., 2008) and hematopoietic malignant cells (MOUZAKI et al., 2009). Nevertheless, the relationship of leptin in immunological responses in breast cancer needs to be more explored.

Immune-related mechanisms

The leptin signaling has been discussed over the two past decades and increasing number of data have suggested its role in immunological responses as discussed here. Moreover, studies have suggested an intervention to control leptin levels in order to prevent and treat several diseases and immunological disorders. Taken all data together, it is of extremely importance to investigate and discuss the link among leptin signaling in immunological processes and its impacts on cancer development.

In most studies, leptin levels are increased during breast cancer carcinogenesis. The positive effect of leptin for breast cancer development has been based on results showing that leptin levels are higher in breast cancer tissue than in adjacent non-tumoral tissue (MORAD; ABRAHAMSSON; DABROSIN, 2014). Studies have been performed in breast cancer cells as well as in solid tumors with similar results (OLLBERDING et al., 2013). Leptin seems to favor breast cancer by stimulating cell growth, migration and invasion, as well as regulating inflammation and controlling Th1 and Th2 responses and cytokine production with positive impact on angiogenesis (DALAMAGA, 2013). Such mediators are derived from tumor-associated immune cells, which suggest that the sustained high leptin found in breast cancer

may be the fuel for the immune-driven progress of breast cancer.

Leptin participates in the regulation of IL-1 release. Studies have suggested that leptin and IL-1 production may have a role in angiogenesis and may be associated with an aggressive phenotype in breast cancer(GONZALEZ-PEREZ; LANIER; NEWMAN, 2013). Leptin up-regulates IL-1 production leading to increase in VEGF and VEGFR2 levels which promotes angiogenesis. Moreover, leptin can act as a chemoattractant for monocytes and macrophages. Macrophages have leptin receptors and are able to produce VEGF. Therefore, the crosstalk among breast cancer, leptin and macrophages favors tumor progression as it promotes angiogenesis (ANDÒ; CATALANO, 2011; ANDÒ et al., 2014).

The mammary adipose tissue may constitute an important source of leptin for breast tumor cells, as well as acts as an attractive mechanism for immune cells infiltrating (SANTANDER et al., 2015). Leptin secretion by adipocytes can affect the influx of macrophages into the tumoral microenvironment. Such infiltrated cells secrete pro-angiogenic factors and pro-inflammatory mediators (ANDÒ; CATALANO, 2011).

Experimental data shows that leptin modulates macrophages polarization and functionality. Furthermore breast tumors from obese mice present high content of infiltrating macrophages (SANTANDER et al., 2015). In obese patients, leptin has been associated with the pro-angiogenic signature of breast cancer (GONZALEZ-PEREZ; LANIER; NEWMAN, 2013). The local adipose inflammation is reported in the breast tissue of obese women and is formed by dead adipocytes encircled by macrophages (the crown-like structures). The lipolysis process promotes macrophage activation by NFκB signaling, enhancing the levels of pro-inflammatory mediators as COX-2 (cyclooxygenase 1), IL-1β, IL-6 and TNF-α (HOWE et al., 2013). This scenario have been further associated with local aromatase induction (ROSE; VONA-DAVIS, 2014) which contributes to the pathogenesis of the more aggressive and resistant forms of tumors. Therefore, macrophages seem to be responsible for the paracrine stimulation of breast tumor progress mainly by locally secreting pro-inflammatory cytokines, under leptin stimuli.

Studies concerning other immune cells are necessary to clarify the relationship between leptin and immune responses in breast cancer.

Clinical considerations: Is leptin a predictive or prognostic factor in human cancer?

Increased leptin seems to be a current finding in breast cancer, and some prognostic value has been attributed to this event. The progression of breast cancer is associated with the sustained leptin production, which triggers mitogenesis and metastasis (SURMACZ, 2013).

During the past few years, the role of leptin in the development of several cancers has been discussed (LANG; RATKE, 2009; NALABOLU; PALASAMUDRAM; JAMIL, 2014). Considering breast cancer, leptin has a recognized role in the generation and development of breast cancer as well as in its prognosis (NIU et al., 2013). Therefore, leptin signaling is a promising field to be studied (BASU et al., 2013; GONZALEZ-PEREZ; LANIER; NEWMAN, 2013) since enhanced leptin levels are strongly associated with increased breast cancer risk (GROSS et al., 2013; NACHAT-KAPPES et al., 2012). In addition, several studies suggest that leptin levels could be used as a biomarker of increased risk to develop breast cancer (SANTILLÁN-BENÍTEZ et al., 2013) and the inhibition of leptin receptor seems to be an interesting target for inhibit breast cancer cells proliferation as well (ZHENG et al., 2013).

Augmented levels of leptin are reported in postmenopausal women as compared to premenopausal., with significant higher levels in patients exhibiting lymph node metastasis (NIU et al., 2013). In women after adjuvant chemotherapy, no association of leptin and disease outcome was found

(GOODWIN et al., 2005), as well as no correlation was reported regarding disease-free survival (KIM et al., 2006). Elevated expression of leptin receptor in breast tumors has been associated with poor prognosis in patients exhibiting augmented leptin in plasma (MIYOSHI et al., 2006).

The i*n situ* analysis of breast tumors also reveals that obese women with breast cancer had a significant expression of leptin in the peritumoral stroma when compared with other areas of breast tissue (GNERLICH et al., 2013).

Concerning disease follow-up, Cho et al. (2013) investigated the inflammatory profile of 240 patients newly diagnosed with breast cancer after surgery in a six-year follow-up. The results showed that patients with recurrence displayed higher levels of leptin, when bearing estrogen positive tumors. The high levels of leptin were associated with reduced recurrence-free survival. Polymorphisms in the leptin receptor gene have also been implicated in high risk for breast cancer development (MOHAMMADZADEH et al., 2014b). Single nucleotide polymorphism (SNP) in the genes of adypokine (adiponectin, leptin and its receptors) can influence its concentration in the circulation in breast cancer (LLANOS et al., 2014a).

Therefore, the therapeutic inhibition of leptin pathway could be a manner to benefit the population with breast cancer in the future (GARCÍA-ROBLES; SEGURA-ORTEGA; FAFUTIS-MORRIS, 2013) especially in obese women.

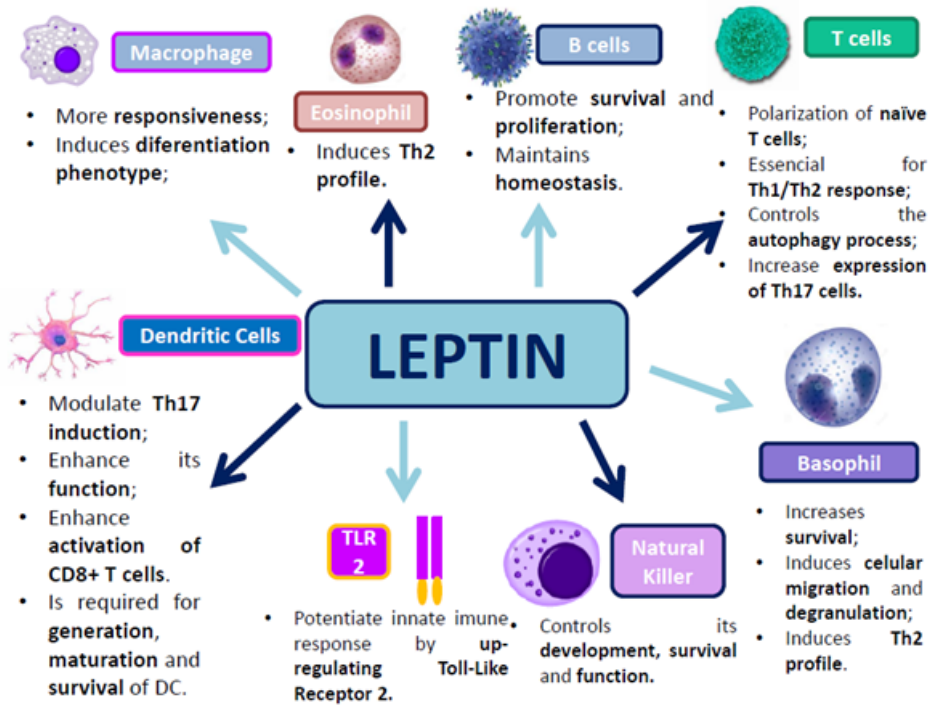
Conclusion

Leptin presents a fundamental physiological role in the immune system function. However, under pathological conditions leptin seems to affect the normal immune functioning, and in the breast microenvironment it is a fuel for cancer. Breast cancer has been strongly associated with obesity and hyperleptinemia, as well as with immunological surveillance disturbances. This complex network suggests a crosstalk among leptin, immune response and breast cancer progression in obese women. An overview of this scenario is presented in Figure 1.

The overexpression of leptin receptors may represent the most detectable alteration in tumors, as well as high leptin in plasma and in tumors is a marker of poor prognosis for breast cancer. Multiple signaling pathways that promote cell proliferation are mediated by leptin, and gradually activated as adipose tissue availability increases. Clinical studies have been a source of controversial findings in this issue for breast cancer. Since each clinical study has been conducted in different populations worldwide, leptin measurement needs to be standardized. Further, genetic factors may affect the results and should explain the wide variability found in clinical studies.

Overweight/obese women present altered metabolic processes including enhanced leptin secretion by adipocytes. Leptin is a poor prognosis factor for cancer development and progression. Breast cancer cells present overexpression of leptin receptors, which in association with hyperleptinemia, is a fuel for pro-tumoral signaling cascades. In addition, high leptin levels also seem to deregulate the normal immune homeostasis. Under physiological conditions, leptin exerts regulatory effects on several immune cells, affecting its development and maturation. Immune cells, especially macrophages and lymphocytes, are commonly infiltrated in breast tumors, and because of the changes driven by leptin, are not able to exert the immunosurveillance. The reduced capacity of immune vigilance strongly affects breast cancer outcome, favoring cancer spreading.

Figure 1- Leptin network in breast cancer environment.



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