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Signal Transduction Pathways Mediated by Unsaturated Free Fatty Acids in Breast Cancer Cells

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1. Introduction

Breast cancer is the most common cancer of women, and its incidence is especially rising in developing countries and representing 23% of all female cancers around the world. The geographical variation at incidence is highest in the developed world and lowest in the developing countries. However, the breast cancer incidence has shown an alarming increasing trend in recent years. It is estimated that more than one million women are diagnosed with mammary cancer every year, and more than 400,000 will die worldwide from this disease and 55% related deaths, occur in low and middle income countries. Therefore, it is estimated that 1.7 million women will be diagnosed with this malignant disease in 2020 (Curado et al., 2009; El Saghir et al., 2007; Porter, 2008).

The normal mammary contains lobules and ducts that consist of a bi-layered luminal epithelium associated with myoepithelial cells and surrounded by the basement membrane (BM) that separates the epithelium from the stroma. Breast cancer is a genetically and genomically heterogeneous disease that initiates in a premalignant lesion, denominated atypical ductal hyperplasia (ADH), characterized by abnormal growth of cell layers within the duct or lobule. ADH is thought to be precursor of ductal carcinoma in situ (DCIS), which is a non-invasive lesion that contains abnormal cells (Hansen and Bissell, 2000). The transformation of mammary epithelial cells is an accumulation of epigenetic and genetic alterations with changes in the interactions within the microenvironment to give rise to metastatic breast cancer. During these multisteps, the control of different cellular process become deregulated, such as proliferation, survival, differentiation and migration and aberrant tumour-stromal cell interactions facilitate this process by initiating a desmoplastic response with significant matrix remodeling and progressive stiffening of the stroma (Paszek and Weaver, 2004; Van't Veer and Weigelt, 2003; Weigelt et al., 2005; Nguyen and Massague, 2007). In the metastasis, cells detach from the primary tumour and must invade through BM, enter the vasculature (intravasate), survive in lymphatic o circulatory system, exit into vasculature (extravasate) and establish a new tumor in a foreign microenvironment. Some of the components that are required for the malignant process are well established, as well as the breast cancer higher risk-markers in the women. However, there are differences in the risk to acquire breast cancer, between premenopausal and postmenopausal women. Early age at the onset of menarche, late age at first childbirth, the nulliparity and shorter duration of lactation

are markers of increased risk in the etiology of premenopausal breast cancer. These factors are not associated with breast cancer in postmenopausal women (McPherson et al., 2000; Chambers et al., 2002; McGee et al., 2006; Gout and Huot, 2008). Nevertheless, the dietary factors associated with higher intake of fat and abdominal fat accumulation increase the risk of breast cancer in postmenopausal women and leads to increased synthesis of estrogen, higher levels of estrogens and free fatty acids (FFAs) in blood (Boyd et al., 2003: Hankinson et al., 1998). The aim of the chapter is describe the signal transduction pathways mediated by three unsaturated free fatty acids (oleic, arachidonic and linoleic acid) and their role in cellular processes that participate in proliferation and invasion.

2. Free fatty acids and breast cancer

Breast cancer is the most frequently diagnosed malignant neoplasia worldwide and is a health problem in women of developed and emergent countries, where lately has been observed an increase in frequency and mortality. Particularly, breast cancer incidence in western women is approximately five times greater than that in Asian women, however when low-risk ethnic groups migrate to the west, their incidence of postmenopausal breast cancer rises progressively in successive generations, suggesting that environmental or lifestyle factors rather than genetic factors are important (Sakamoto and Sugano, 1991; Ferlay et al., 2007).

Diet has been prominent among the potential environmental factors, because numerous studies in women using different study designs and different geographical areas have been carried out to establish the relationship between diet and breast cancer. The results have shown that obesity and certain dietary factor such as a higher intake of fatty acids (FAs) and meats seem to increase the risk of breast cancer (Boyd et al., 2003; Lahmann et al., 2004; Carmichael, 2006). Actually, it is clear that a combination of high total energy intake and inadequate physical exercise allows genetically susceptible individuals to become obese, while the increased metabolic activity in their enlarged adipose deposits releases an excess of compounds, including FFAs (Proietto et al., 1999).

The unsatured FAs are divided in monounsatured (MUFA) and polyunsatured (PUFA). The principal sources of MUFAs are vegetable oils and meat, while PUFAs are mostly found in eggs, fish and seafoods. PUFAs are classified into two families -n-3 and n-6 PUFAs, the n-3 include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), α-linoleic acid (ALA) and steridonic acid (SA), while n-6 including linoleic acid (LA), arachidonic acid (AA), docosapentaenoic acid (DPA) and γ-linoleic acid (GLA). It has been suggested that these exogenous FAs may participate in the etiology, evolution and/or progression of breast cancer, whereas epidemiological studies demonstrated that both the amount of fat and the type of FA present in the diet affect the tumorigenesis, cancer growth and metastasis process (Goodstine et al., 2003; Bartsch et al., 1999; Welsch, 1992).

Oleic acid (OA) is the most abundant dietary MUFA, and it has an inverse relationship with breast cancer (Franceschi et al., 1996; London et al., 1993; Voorrips et al., 2002; Wirfalt et al., 2002; Gaard et al., 1995). In addition, epidemiological studies show that olive oil, with high content of OA, presents preventive properties to the acquisition of breast cancer (Trichopoulou et al., 1995; Owen et al., 2000; Wahrburg and Assmann, 2001). In contrast, some studies show a positive correlation between MUFA and breast cancer (London et al., 1993; Wirfalt et al., 2002; Gaard et al., 1995).

The PUFAs ALA, EPA and DHA function as inhibitors of the progression of human breast cancer, whereas n-6 PUFA, LA is a stimulator of this disease (Rose et al., 1994; Rose et al.,

1995; Rose et al., 1997; Menendez et al., 2006). The n-3 PUFAs mechanism by which may low the breast cancer risk is through an inhibition on biosynthesis of AA-derived eicosanoids, which are linked to inflammation and carcinogesis processes. The PUFAs n-3 are incorporated into membrane phospholipids, where they partially replace the AA, and it suppresses the biosynthesis of AA-derived eicosanoids, and stimulates the EPA-derived 3-series prostanoids and 5-series leukotrienes synthesis (Crawford et al., 2000).

Her-2/*neu* overexpression induces aggressive breast carcinoma and low sensibility to chemotherapy and anti-estrogens therapy (Crawford et al., 2000 Hudelist et al., 2003;). ALA, EPA, DHA, GLA and OA are dietary fatty acids with a protector effect to the breast cancer adquisition, the mechanism involved is the downregulation of Her-2/*neu* in SK-Br3 and BT-474 human breast cancer cell lines. In contrast, LA induces tumorigenesis by an increase on Her-2/*neu* (Menendez et al., 2006). In addition, stearic acid a satured FA in the western diet has been found to have "anti-cancer properties" both *in vivo* and *in vivo* (Wickramasinghe et al., 1996; Hardy et al., 2003; Singh et al., 1995; Tinsley et al., 1981).

3. Peroxisome proliferator-activated receptors (PPARs)

3.1 Definition

Peroxisome proliferator-activated receptors (PPARs) are regulators of lipid metabolism and their main function is to allow the release of fatty acids from plasmatic transport proteins, and promote the cellular uptake. These receptors are transcription factors that belong to the nuclear hormone receptor superfamily, and are activated by lipids from the diet or from intracellular signaling pathways, which include saturated and unsaturated fatty acids, and fatty acids derivates. PPARs are classified in three groups namely, PPARα (NR1C1); PPARβ/δ (NR1C2) and PPARγ (NR1C3). PPARα is expressed in tissues with high fatty acid metabolism, including liver, kidney, small intestine, heart, brown adipose tissue and muscle. It regulates the expression of enzymes that participate in the mitochondrial and peroxisomal fatty acid oxidation. PPARβ/δ is expressed ubiquitously, regulates the β-oxidation and plays an important role in energy consumption in peripheral tissues. PPARγ presents two isoforms that differ at their N terminus, δ1 and δ2, and is expressed in white and brown adipose tissue, intestine, brain, vascular cells, skeletal muscle and some immune cells. It promotes lipid storage, because it regulates the differentiation of adipocytes. In addition, PPARα and PPARβ regulate the expression of lipoprotein lipase (LPL) and fatty acid translocase, which induce fatty acid release from lipoproteins, and the uptake of cholesterol and fatty acids respectively (Feige et al., 2006; Michalik et al., 2006).

3.2 Structure

PPARs isotypes have a protein domain organization common to nuclear receptor superfamily (Figure 1). N-terminal A/B domain contains the ligand-independent activation function 1 (AF1). The C-terminal domain presents the DNA-binding domain, consisting of two zinc-finger motifs that is a hallmark of nuclear receptors, and targets the receptor to specific DNA sequences. D domain is the hinge region, and confers structure flexibility to the receptor dimmers, allowing them to bind with several specific DNA sequences. The C-terminal E/F domain contains the ligand binding domain (LBD), and a ligand-dependent activation function 2 (AF2). This domain also exposes the main surfaces for dimerization and for the cofactors interaction (co-activators or co-repressors). The LBD consists of 12 α helices and 4 β sheets that delineate a Y-shape hydrophobic pocket, representing the ligand-binding cavity.

The transcription activity of PPARs is mediated by the formation of heterodimmers with the retinoic X receptors (RXR, NR2B). RXRs present three isoforms, resulting in different combinations of heterodimers, which influence the recognition of target gene promoters. Heterodimmers bind to specific response elements namely PPARs response elements (PPREs), which consist on one direct repeat of AGGTCA consensus sequence spaced by a nucleotide. However, PPAR-RXR complex formation does not require ligand and DNA binding activity (Feige et al., 2006).
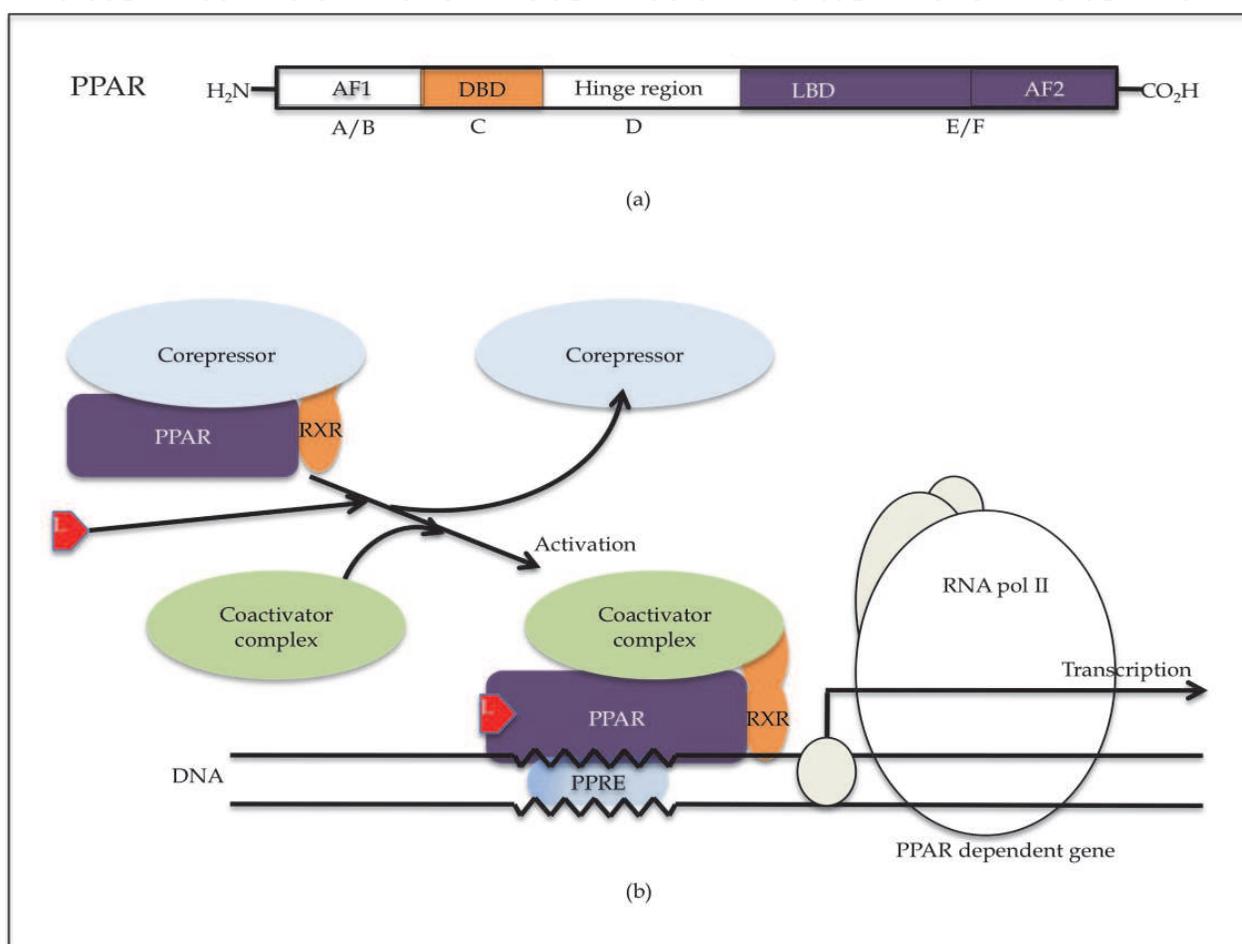

Fig. 1. General features and architecture domains in human PPARs. (a) Schematic representation of PPAR domains: A/B domain, contains a ligand-independent activation function 1 (AF1), C domain, contains the DNA-binding domain (DBD), D domain contains the hinge region and the C-terminal includes the E/F domain with the ligand-binding domain and the ligand-dependent activation domain (AF2). (b) General mechanism of genomic expression by PPAR/RXR heterodimers. Upon ligand (L) binding to PPAR through the LBD domain, the PPAR associates with coactivator to turn on target genes via the PPAR response element (PPRE) located in the promoter of target genes.

3.3 PPARs and breast cancer

Peroxisome proliferators are a variety of compounds that bind to PPARs and induce DNA replication and proliferation in rodent hepatocytes, while PPARα long-term activation promotes the development of hepatocarcinomas in rodent liver (Michalik et al., 2004, Peters

et al., 2005). However the participation of PPARs in the promotion and development of human cancers is unclear. PPRAα expression in humans is less than rats and its activation induces a reduced transcription response, and it has not involved in hepatocytes proliferation. In humans, PPARβ/δ is highly expressed in colorectal cancer and is implicated at its carcinogenesis and metastasis. However, PPARα and PPARβ/δ have not been implicated in breast cancer. PPARγ is expressed in a variety of tumor including breast cancer. PPARγ activation by using troglitazone and GW7845 ligands prevents preneoplastic mammary lesion in rats (Mehta et al., 2000; Suh et al., 1999). In human breast cancer cells, PPARγ activation by exogenous ligands prevents growth, induces apoptosis, and promotes changes in epithelial gene expression accompanied with a less malignant state. In addition, overexpression of PPARγ decreases proliferation and induces apoptosis in the absence of exogenous ligands (Meng et al., Yin et al., 2001; Elstner et al., 1998; Mueller et al., 1998).

4. GPR40 and GPR120

G-protein coupled receptors (GPCRs) are the largest membrane receptor family in the human genome. These receptors mediate a great variety of cell functions including proliferation, survival, immune response, blood pressure regulation, cardiac and smooth muscle contraction and have been implicated in cancer progression and metastasis. GPCRs present a common structure constituted for a single peptide chain that traverse the membrane seven times, exposing three loops on either side of the membrane, with the N-terminus toward outside and the C-terminal on the cytosolic face of the plasma membrane. GPCR activation is mediated by ligands binding to its extracellular domain that induces conformational changes, allowing the cytosolic domain bind to G protein associated with the inner face of plasma membrane. G proteins are heterotrimers which contain three subunits namely α, β and γ. The ligand binding to GPCR promotes G protein activation, which is mediated for the dissociation of GDP bound to the Gα subunit and its replacement with GTP, and then leads to dissociation of Gα from G$\beta\gamma$ subunits. However, this activation is short because GTP bound to Gα is hydrolyzed to GDP in seconds. Gα-GTP and G$\beta\gamma$ subunits complexes induce several signal transduction pathways that is determined for the ligands. G-protein α-subunits present a great variety of effectors (Table 1), and they have been classified in four main families (G$_s$, G$_{i/0}$, G$_{q/11}$, G$_{12/13}$). The $\beta\gamma$ subunits transmit signals independently of α-subunits and second messengers, some of the functions mediated by these subunits including regulation of ligand receptor affinity and receptor phosphorylation (Hardy et al., 2005; Yonezawa et al., 2004; Ichimura et al., 2009).

FFAs stimulate PPARs and mediate the transcription of genes involved in glucose and lipid metabolism. However, several biological effects such as proliferation are independent of PPARs and are mediated by GPCRs. The non-esterified (free) fatty acid receptor 1 (FFAR1) or GPR40 (G-protein-coupled receptor 40) is a GPCR located on chromosome 19q13.1 that is activated by medium and long chain saturated and unsaturated FFAs. FFAR1 is expressed in the pancreas (α cells in islets and insulin-secreting β cells), K and L cells of small and large intestine and mononuclear peripheral blood cells. FFAR1 is coupled with both G$\alpha_{i/0}$ and G$\alpha_{q/11}$. GPR120 is a GPCR located on chromosome 10q23.33 that is activated by saturated FFAs with a carbon chain length of 14 – 18, and with saturated FFAs with a chain length of 16-22. In addition, GPR120 is expressed in the intestine, adypocites, taste buds, monocytes and lung, and is coupled with G$\alpha_{q/11}$ (Ichimura et al., 2009)

G protein family	Members	Effects	Associated effector protein	2nd messenger or downstream effectors
G_s	G_s and G_{olf}	Up	Adenylyl cyclase Ca²⁺ channel	cAMP Ca²⁺
		Down	Na+ channel	Change in membrane potential
$G_{i/o}$	G_{i1}, G_{i2}, G_{o1}, G_{o2}, G_z, G_t and G_{gus}	Up	K⁺ channel Phospholipase C	Change in membrane potential IP₃ and DAG
		Down	Adenylyl cyclase Ca²⁺ channel	cAMP Ca²⁺
$G_{q/11}$	G_q, G_{11}, G_{14} and $G_{15/16}$	Up	Phospholipase C	IP₃ and DAG
$G_{12/13}$	G_{12} and G_{13}	Up	Small GTPases RhoA	MAPK (Mitogen-activated protein kinase) cascades and monomeric G-proteins (Ras, Rac and Rho)

Table 1. Properties and effectors of G protein family. Keys: Up= Stimulation; Down= Inhibition; IP₃: Inositol 1,4,5-triphosphate; DAG= 1,2-diacylglycerol; cAMP= cyclic AMP.

In breast cancer cells, have been reported the expression of FFAR1 and GPR120 as well as their expression in human mammary non-tumorigenic epithelial cells MCF10A. Furthermore, oleic acid induces an increase in cellular Ca²⁺ concentrations and proliferation through a FFAR1-dependent pathway in breast cancer cells (Hardy et al., 2005, Yonezawa et al., 2004).

5. Signal transduction pathways mediated by oleic and arachidonic acids in breast cancer cells

5.1 Signal transduction pathways mediated by oleic acid in breast cancer cells

OA is an essential FFA monounsaturated and one of the most abundant fatty acids in plasma. However, little is known about the signal transduction pathways mediated by OA in breast cancer cells. The Src family has an important role in a great variety of cell functions, including cell cycle progression, growth, survival and migration. Src kinases are involved in breast cancer, because in breast tumors and human mammary carcinoma cell lines, Src kinase activity is enhanced relative to that in normal breast tissue, while in breast cancer cells the activated Src increases the adhesion, survival and integrin expression (Park et al., 2004; Parsons and Parsons, 1997; Rosen et al., 1986). In breast cancer cells MDA-MB-231, OA induces Src activation, given by its phosphorylation at tyrosine (Tyr)-418, as well as ERK1/2 activation, given by its phosphorylation at threonine (Thr)-202 and Tyr-204, and ERK1/2 activation is dependent on Src kinase activity. In contrast, OA induces only ERK 1 activation in mammary non-tumorigenic epithelial cells MCF10A (Soto-Guzman et al., 2008).

Transactivation of epidermal growth factor receptor (EGFR) induced by GPCRS occurs via activation of metalloproteinases (MMPs) and subsequent release of EGF-like ligands, such as HB-EGF, from growth factors precursors in the plasma membrane. Furthermore, it has been proposal that Src family kinases also are mediators of GPCR-induced EGFR transactivation, because Src induces EGFR tyrosine phosphorylation after stimulation of LPA and α2A-adregernic receptors coupled with Gi, whereas angiotensin II promotes the association of Src with Shc, Grb2 and EGFR, and then Src activated phosphorylates EGFR at

Tyr-845 and Tyr-1101. In addition, it has been reported that the mechanism of MMPs activation requires Src kinase activation (Prenzel et al., 1999; Fischer et al., 2003). In MDA-MB-231 cells, ERK1/2 activation induced by OA requires EGFR and MMPs activations. These findings show that ERK1/2 activation induced by OA requires EGFR transactivation and they suggest that Src and/or MMPs activities mediate EGFR transactivation.

The AP-1 transcription factor consists of homo- or hetero-dimers of proteins encoded by the *fos* and *jun* gene families, and their combination determine the genes that are regulated. AP-1 participates in fundamental cellular processes and control cellular responses including proliferation, differentiation, oncogenic transformation, apoptosis and metastasis (Eferl and Wagner, 2003; Tulchinsky, 2000; Shaulian and Karin, 2001). In MCF7 cells, an overexpression of c-Jun enhances motility and invasion, whereas Fra-2, a member of Fos family, plays a pivotal role in cell invasion and motility in MCF7 and MDA-MB-231 breast cancer cells (Smith et al., 1999; Rinehart-Kim et al., 2000; Milde-Langosch et al., 2008; Milde-Langosch et al., 2004). In addition, OA induces AP-1-DNA complex formation through an ERK1/2, Src and MMPs-dependent pathway, as well as, it requires EGFR transactivation in MCF7 breast cancer cells. Mammary non-tumorigenic epithelial cells MCF10A present a constitutive AP-1-DNA binding activity and OA stimulation does not induce an increase on AP-1-DNA complex formation (Soto-Guzman et al., 2008). These findings strongly suggest that AP-1 activation induced by OA promotes the invasion process by the expression of genes regulated for AP-1, including MMP-1, MMP-3, MMP-9, ARP2/3 and p41Bm CapG. Furthermore, AP-1-DNA binding activity induced by OA is restricted to breast cancer cells (Bahassi el et al., 2004; Benbow and Brinckerhoff, 1997; Lee et al., 1987).

In breast cancer cells MCF7 and MDA-MB-231, OA induces cell proliferation and it is mediated at least in part through FFAR1, epidermal growth factor receptor (EGFR), PI3K, phospholipase C (PLC), Src, MMPs, MEK1/2 and ERK1/2. However, OA does not induce cell proliferation in mammary non-tumorigenic epithelial cells MCF10A. These findings suggest that cell proliferation induced by OA is a restricted process in breast cancer cells. OA signaling is coupled with GPCR activation via Gi/Go proteins, because inhibition of Gi/Go proteins prevents cell proliferation, an increase in cellular Ca^{2+} concentration and ERK1/2 activation. However, the participation of GPR120 remains to be investigated, because it is able to bind medium chain FFA, such as OA (Soto-Guzman et al., 2008; Hardy et al., 2005; Yonezawa et al., 2004).

Cancer metastasis involves several steps including cell detachment, migration, invasion, intravasation, extravasation and proliferation in distal sites. Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that localizes to focal adhesions and is activated by diverse signaling molecules that mediate cell growth and differentiation including growth factors, Src family kinases members, bioactive lipids and extracellular matrix (ECM) components. FAK is a critical signaling molecule involved in the various stages of tumorigenesis and metastasis processes through regulation of migration, cell survival, proliferation, spreading, invasion and metastasis. In breast cancer tumors, FAK gene is amplified, its protein is overexpressed and FAK expression correlates with increased invasion and metastasis tumors. In addition, tumor cells overexpressing FAK have a tendency to invade surrounding tissues and metastasize *in vivo*, where FAK induces the formation of podosomes and invadopodia that promote an invasive cell phenotype (Hsia et al., 2003; Parsons et al., 2000; Parsons, 2003; Zhao and Guan, 2009; Cance et al., 2000). In MDA-MB-231 breast cancer cell cultures, OA induces FAK activation, given by its phosphorylation at Tyr-397, migration and invasion (Navarro-Tito et al., 2010; Soto-Guzman et al., 2010).
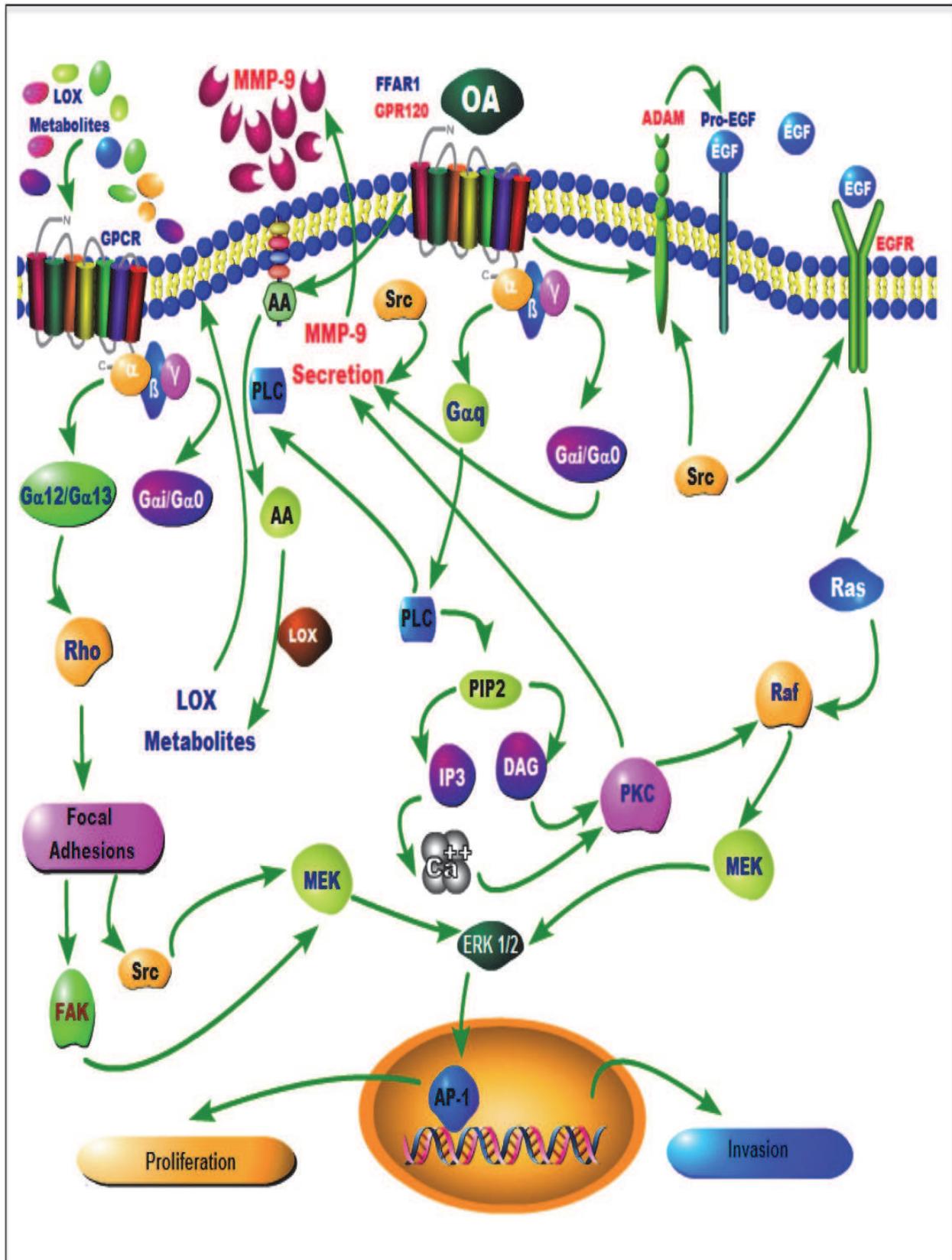
Fig. 2. Overview of the signal transduction pathways mediated by OA in breast cancer cells.

A model of reciprocal catalytic activation between FAK and Src kinases has been proposal, where phosphorylation of FAK at Tyr-397 creates a high affinity-binding site recognized by the SH2 domain of Src family kinases, and it leads to the recruitment and activation of Src through FAK, accompanied with formation of FAK–Src complex. Src family kinases associated with FAK, phosphorylate FAK at additional tyrosine residues, such as Tyr-576 and Tyr-577, inducing a maximal FAK kinase activity. Then, maximal activity of FAK stimulates an intermolecular phosphorylation between FAK molecules at Tyr-397, leading to signal amplification (Owen et al., 1999; Salazar and Rozengurt, 2001). In line with this model, OA mediates FAK activation in a fashion dependent of Src kinase activity in MDA-MB-231 breast cancer cells (Navarro-Tito et al., 2010).

AA is one of the major polyunsaturated fatty acids present in mammalian cell membrane phospholipids. AA is mainly produced from membrane glycerophospholipids in the nuclear envelope and from plasma membrane via the activity of cytosolic phospholypase A2 (cPLA2). Alternatively, phospholipase C (PLC) produces AA, by metabolize phosphatidylinositol and phosphatidylinositol phosphate to inositol phosphates (IP3) and diacylglycerol (DAG). DAG is metabolized by DAG lipase to 2-arachidonyl-glycerol (2-AG) and then AA is released from 2-AG by monoacylglycerol lipase or fatty acid amidohydrolase. Free AA is enzymatically metabolized by three major pathways: lipoxygenases (LOXs), cyclooxygenases (COXs) and cytochrome P450 epoxygenases (CYP). LOXs pathway produces several hydroperoxyeicosatetraenoic acids (HPETEs) and hydroxyeicosatetraenoics acids (HETEs), while COXs pathway is mediated by two enzymes, namely COX-1 and COX-2, these enzymes produce PGG2 and PGH2, which are subsequently converted into prostaglandins (PGs) and thromboxanes (TXs). CYP pathway produces HETEs and epoxides. AA and its metabolites are involved in biological processes, including chemotaxis, inflammation, angiogenesis, cell survival, mitogenesis and apoptosis (Brash, 2001; Piomelli, 1993; Harizi et al., 2008). In line with this notion, OA mediates the AA production via PLC/DAG lipase/monoacylglycerol lipase or fatty acidamidohydrolase and then AA is metabolized through LOXs and their metabolites mediate FAK activation and cell migration in MDA-MB-231 breast cancer cells. In addition, a positive feedback between ERK1/2 activation and COXs/LOXs metabolites maintains proliferation and migration in high metastatic potential breast cancer cells (You et al., 2009; Navarro-Tito et al., 2010).

LOXs are a family of nonheme iron dioxygenases including 5-, 8- 12- and 15-LOX, whose main products are 5(S)-, 8(S), 12(S)- and 15(S)-HETE, respectively. Among them, 12(S)-HETE promotes the formation of focal adhesion plaques via a *Pertussis toxin* (PTX) sensitive pathway, leading to enhance adhesion to fibronectin in murine B16 amelanotic melanoma cells, whereas it stimulates ERK1/2 phosphorylation through a PTX sensitive pathway in prostate cancer cells. 12(S)-HETE acts on target cells through a GPCR coupled with Gi/Go proteins (Harizi et al., 2008, McCabe et al., 2006, Liu et al., 1995). In breast cancer cells MDA-MB-231, OA promotes FAK activation and migration in a fashion dependent on LOX metabolites and a GPCR coupled with Gi/Go (Navarro-Tito et al., 2010). These findings strongly suggest that OA induces FAK phosphorylation and cell migration via the production of 12(S)-HETE, which is secreted into the extracellular space and activates a GPCR coupled with Gi/Go and/or G12/G13.

MMPs are a family of zinc-dependent endopeptidases that collectively are capable of degrading all ECM components. However, MMPs substrates also include other proteins such as MMPs, proteinase inhibitors, growth factors, growth factors binding proteins,

chemokines, cytokines, cell surface receptors and cell adhesion molecules. MMPs have been implicated in several aspects of tumor progression, including cell migration, angiogenesis, tumor cell growth and invasion through BM, and interstitial matrices. MMPs gene family is composed of at least 20 members and is subgrouped into different types based on sequence characteristic and substrate specificity. Particularly, MMP-2 (gelatinase A) and MMP-9 (gelatinase B) are associated with tumor progression and metastasis due to their ability to degrade type IV collagen, the main component of BM, and their elevated expression in malignant tumors. In breast cancer, these gelatinases are highly expressed and is suggested that play an important role in breast cancer invasion, metastasis and angiogenesis (Pellikainen et al., 2004; Duffy et al., 2000; Egeblad and Werb, 2002; Curran and Murray, 1999).

Increased levels of PKC are associated with malignant transformation in breast cancer cells lines and a positive correlation between elevated PKC levels and invasive potential of breast cancer cell lines is suggested. In line with these notions, OA promotes MMP-9 secretion an invasion through a PKC-dependent pathway in MDA-MB-231 breast cancer cells. However, OA is not able to produce invasion in the non-invasive MCF7 breast cancer cells. Human mammary non-tumorigenic epithelial cells MCF10A present a constitutive secretion of MMP-9 and OA does not induce an increase on its secretion, and does not promote MMP-9 secretion in non-tumorigenic epithelial cells MCF12A (Soto-Guzman et al., 2010). These findings strongly suggest that MMP-9 secretion induced by OA is restricted to breast cancer cells and therefore OA may contribute to invasiveness and metastasis process in breast cancer cells (Soto-Guzman et al., 2010).

EGFR and Her-2 overexpression correlates with a reduction on survival and induction of invasion and metastasis in malignante breast cancer. In MDA-MB-231 breast cancer cells, OA promotes MMP-9 secretion and invasion trough an EGFR and Src-dependent pathway (Soto-Guzman et al., 2010). Since, Src family kinases are mediators of GPCR-induced EGFR transactivation, and that OA induces Src activation, it is propose that OA mediates MMP-9 secretion and invasion through and EGFR transactivation-dependent pathway. OA also mediates invasion through a Gi/Go coupled pathway and MMPs activity. It suggests that OA induces invasion via FFAR1 coupled with Gi/Go and/or GPR120 activation and support the proposal that OA mediates invasion via EGFR transactivation. Furthermore, during invasion process, cells induce the formation of invadopodia protrusions, which are actin and proteins associated with MMPs.

5.2 Signal transduction pathways mediated by arachidonic acid in breast cancer cells

AA is a common dietary n-6 cis polyunsaturated fatty acid that is present in an esterified form in cell membrane phospholipids, however AA might be also present in the extracellular microenvironment. AA and its metabolites are implicated in a variety of biological processes including chemotaxis, signal transduction and inflammatory diseases such as artherosclerosis, cancer and rheumatoid arthritis (Brash, 2001).

In MDA-MB-231 breast cancer cells, AA stimulates adhesion to type IV collagen through a 15(S)-lipoxygenase pathway (Palmantier et al., 1996; Nony et al., 2005). AA also induces FAK activation and cell migration via a GPCR couple to Gi/Go and through a LOXs and Src activity-dependent pathway (Navarro-Tito et al., 2008). It suggests that FFAR1 and GPR120 do not participate in the signal transduction pathways and in the cellular processes induced by AA.

The Src family kinases have been implicated in cellular pathways mediated by AA, because AA induces Src activation and cell migration in MDA-MB-231 breast cancer cells. FAK activation is dependent on Src kinase activity; it is agreement with the model of reciprocal catalytic activation of FAK and Src kinases (Navarro-Tito et al., 2008).

Epithelial to mesenchymal transition (EMT) is the process by which epithelial cells are transdifferentiated to a more mesenchymal state. EMT is an essential process during early stages of normal embryonic development, and wound repair. EMT is characterized by the loss of epithelial properties, including cell-cell contacts and baso-apical polarity, accompanied by the acquisition of mesenchymal markers, such as vimentin expression, smooth-muscle actin, N-cadherin, specific myosin isoforms, fibronectin, MMPs, and then cells undergo major changes in their cytoskeleton that enable acquire a mesenchymal appearance with an increase in motility and invasiveness. EMT has been implicated in the progression toward an advanced cancer phenotype, because EMT may endow cancer cells with enhanced motility and invasiveness, and therefore cells acquire the ability to execute the multiple steps of the invasion-metastasis cascade (Hay, 2005; Thiery and Sleeman, 2006; Thiery, 2002; Huber et al., 2005).

Classical cadherins are transmembrane adhesion receptors that mediate cell-cell adhesion through their extracellular domains and connect to the actin microfilaments indirectly via α- and β-catenin in the cytoplasm. They promote the formation of stable cell-cell contacts and the development of adherens junctions. EMT induces disassembled of adherens junctions and the actin cytoskeleton reorganizes from an epithelial cortical alignment associated with cell-cell junctions into actin stress fibers, anchored to focal adhesion complexes. Loss of Ecadherin expression is considered as a hallmark event of EMT, because reduction on E-cadherin levels induces the disruption of epithelial cell-cell contacts that initiates a series of signaling events and a major cytoskeletal reorganization (Halbleib and Nelson, 2006; Gumbiner, 2005; Tepass et al., 2000). E-cadherin expression is negatively regulated by several zinc-finger transcription factors, including Snail1, Snail2, Twist and ZEB1/ZEB2, each of which binds to E-boxes on E-cadherin promoter and represses its transcription (Baranwal and Alahari, 2009; Cano et al., 2000). In mammary epithelial cells MCF10A, AA does not induce a reduction of E-cadherin levels and it does not induce an increase of Snail1, Snail2, Twist and ZEB1 transcription factors. However, AA induces the release of E-cadherin from adherens junctions (Martinez-Orozco et al., 2010).

During EMT, the decrease in epithelial traits is accompanied by acquisition of mesenchymal characteristics including increased expression of smooth-muscle actin, vimentin, fibronectin, MMPs and N-cadherin. Vimentin and N-cadherin are expressed in cells of mesenchymal origin; however they also are expressed in epithelial cells when they become involved in physiological or pathological processes that require epithelial cell migration, such as tumor invasion. Moreover, a reduction on E-cadherin levels and/or release from adherens junctions has been associated with the *novo* vimentin expression and with the metastatic conversion of epithelial cells (Thiery, 2003; Gavert and Ben-Ze'ev, 2008; Gilles et al., 2003; Hazan et al., 2000; Nieman et al., 1999). In line with this notion, AA induces an increase on vimentin and N-cadherin expressions in MCF10A cells (Martinez-Orozco et al., 2010). In addition, vimentin only is expressed in invasive breast cancer cell lines, while its expression in MCF10A and breast cancer cells enhances the migration capacity of these cells (Bindels et al., 2006; Gilles et al., 1999; Hendrix et al., 1996).

The NFkB transcription factor is implicated in cell proliferation, migration, oncogenesis and EMT. NFkB mediates EMT by transcription regulation of Snail1, Snail2, Twist and ZEB1, which are repressor of E-cadherin, claudins and occludins genes. NFkB also promotes the expression of other genes implicated in the EMT process, such as vimentin and MMP-9, whereas it can increase MMP-2 activity by inducing the expression of MT1-MMP (Huber et al., 2004; Karin et al., 2002; Bolos et al., 2003; Cano et al., 2000; Min et al., 2008; Han et al., 2001). In mammary epithelial cells MCF10A, AA induces the NFkB activation and MMP-9 secretion (Martinez-Orozco et al., 2010). These findings suggest that NFkB participates in vimentin expression, secretion and/or expression of MMP-9, and promoting EMT process. In addition, MMPs are implicated in EMT during embryogenesis as well as in early and late stages of cancer progression, angiogenesis and metastasis. Particularly, MMP-9, MMP-13 and MMP-17 have been associated with breast cancer progression, whereas in intestinal epithelial cells, MEK1 and EGF plus TGF-β mediate EMT with an increase on MMP-9 secretion and an increase in the expression of MMP-3, MMP-9, MMP-10 and MMP-14. In line with notion, AA induces MMP-9 secretion in MCF10A cells (Lemieux et al., 2009; Uttamsingh et al., 2008; Duong and Erickson, 2004; Egeblad and Werb, 2002; Nielsen et al., 2001).

EMT is associated with decreased epithelial type cytokeratins (CKs), such as 8 and 18. Breast carcinomas usually retain the expression of epithelial type CKs, but they also express a CKs pattern of myoepithelial cells (Hollier et al., 2009; Wetzels et al., 1991; Malzahn et al., 1998). In mammary epithelial cells MCF10A, AA promotes an increase of CK5 and CK8 expression, strongly suggesting that AA induces an EMT process and therefore an increase in the migratory ability (Martinez-Orozco et al., 2010). It has been reported that the expression pattern of CK5, CK8, CK14 and CK17 are useful in distinguishing benign from invasive breast carcinomas (Otterbach et al., 2000; Takei et al., 1995; Jarasch et al., 1988).

EMT is induced by a variety of cellular growth factors and signaling pathways. These pathways have common targets, such as FAK and Src. FAK and Src represent key players in the regulation of cell matrix interactions and focal contacts formation and mediate a variety of cell functions, such as migration, survival, invasiveness and EMT (Cicchini et al., 2008; Grunert et al., 2003; Mandal et al., 2008; Parsons and Parsons, 1997; Slack et al., 2001; Avizienyte et al., 2002). In murine met hepatocyte (MMH) cells stimulated with TGF-β, FAK activity and its signaling are required for transcriptional up-regulation of mesenchymal and invasiveness markers and delocalization of membrane-bound E-cadherin (Cicchini et al., 2008). In the human embryonic carcinoma cell line NT2/D1 and mouse mammary epithelial cells NmuMG, TGF-β promotes EMT in a fashion dependent on FAK and Src kinase activity and the up-regulatin of caveolin-1 (Bailey and Liu, 2008). In addition, Src family members co-localize with E-cadherin at the sites of cell-cell adhesion in non-migrating epithelial cells, and its activation is required to disrupt cadherin-dependent cell-cell contacts in normal human keratinocytes. In KM12C colon cancer cells, Src induces E-cadherin deregulation through specific integrin signaling and the Src-dependent tyrosine phosphorylation of FAK at peripheral integrin-dependent protrusions (Calautti et al., 1998; Avizienyte et al., 2002; Owens et al., 2000). In line with this notion, AA induces Src and FAK activation and cell migration in MCF10A cells. Cell migration is dependent on Src activity (Martinez-Orozco et al., 2010). Taken together these findings demonstrate that AA induces an epithelial-to-mesenchymal-like transition in MCF10A cells, and they suggest that AA may promote invasion and metastasis in breast cancer.

5.3 Signal transduction pathways mediated by linoleic acid in breast cancer cells

LA is the major PUFA in the most diet and is required for the biosynthesis of eicosanoids. LA is able to induce inappropriate inflammatory responses that contribute to various chronic diseases, including cancer. The signal transduction pathways mediated by LA in breast cancer cells has not been studied in detail and we actually have a little bit of information. In human breast cancer cells, LA induces expression of plasminogen activator protein-1, proliferation migration and invasion, while LA promotes an increase of intracellular Ca^{2+} levels and proliferation in bovine mammary epithelial cells (Yonezawa et al., 2008; Reyes et al., 2004; Byon et al., 2009).

6. Conclusions

The research in the field of signal transduction pathways mediated by FFAs in mammary epithelial cells delineates a new role for FFAs in the invasion and progression of breast cancer. The findings show that FFAs induces activation of protein kinases cascades and transcription factors in cell cultures of mammary epithelial cells, which promote cellular processes including growth, migration, invasion and EMT. Therefore, FFAs may play an important role in the invasion, progression and metastasis processes in breast cancer.

7. References

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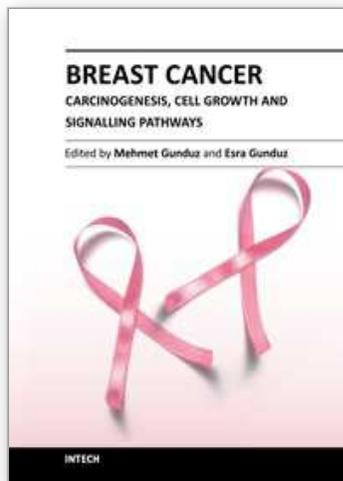
Breast Cancer - Carcinogenesis, Cell Growth and Signalling Pathways

Edited by Prof. Mehmet Gunduz

Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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