ANTICANCER RESEARCH *34*: 1127-1140 (2014)

Review

Mapping Oxidative Changes in Breast Cancer: Understanding the Basic to Reach the Clinics

ANDRE MENCALHA[1], VANESSA JACOB VICTORINO[2], RUBENS CECCHINI[3] and CAROLINA PANIS[3]

[1]*Biophysics and Biometry Department, Roberto Alcantara Gomez Biology Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil;*
[2]*Laboratory of Medical Investigation (LIM51), Department of Emergency Medicine, University of São Paulo, São Paulo, Brazil;*
[3]*Laboratory of Physiopathology and Free Radicals, Department of Pathology, Universidade Estadual de Londrina, Londrina, Brazil*

Abstract. *Since long, oxidative stress-driven modifications in breast cancer were faced as detrimental cellular events that cause obligatory cell damage. Recent studies show that the products generated during redox reactions are able to modulate pivotal processes regarding breast cancer survival, proposing a new way of looking at the events linked to oxidative stress. Therefore, it is necessary to understand the basis of oxidative stress generation in breast cancer by reviewing the two most important events that perpetuate the malignant transformation: mitochondrial dysfunction and DNA damage/misguided repair. In this context, the present review addresses the main events related with redox events reported in breast cancer studies, highlighting the impact of the oxidative environment on DNA damage and the role of the mitochondria as a determinant of oxidative modifications. In addition, we further discuss the main stand-out findings concerning the modulatory role of the metabolites derived from redox stresses, with a special focus on the oxidative changes detected in the breast cancer microenvironment and its systemic impact.*

Oxidative stress is implicated in the basis of most known chronic pathologies (1). The frequent occurrence of oxidative changes in biological environments is mainly due to the constant metabolic activity of mitochondria, which during the respiratory chain process gives rise to significant amounts of reactive species (RS). To compensate for this production of pro-oxidative species, cells are equipped with a wide range of redox sensors, which rapidly trigger the antioxidant defenses. When this process is operative, the redox status of the cell is held. However, if either the production of RS is excessive or the antioxidant defenses are not sufficient, it is established the pro-oxidative condition called oxidative stress. The excessive RS can promptly react with the surrounding cellular structures, resulting in DNA, lipid and protein oxidative-driven modifications (1-3).

Oxidative changes have been described in cancer cells when compared to normal non-cancerous cells, suggesting a role for the lasting occurrence of a pro-oxidant status in malignant conditions (4, 5). Therefore, a growing number of studies have focused on investigating the redox changes that take place in solid tumors, especially in breast cancer.

Most of the risk factors for breast cancer development and progression are to some extent implicated with RS generation (1, 2). Breast tumors are naturally embedded into an incredibly pro-oxidative environment, as the mammary gland is plenty in surrounding adipose tissue. Therefore, the exceeding RS quickly acts on the lipidic neighborhood yielding several active metabolites that can regulate a wide range of cellular processes. Malondialdehyde, 8-F2-isoprostanes and 4-hydroxinonenal are well known examples of low-molecular weight aldehydes derive from lipid peroxidation processes that have been reported as new putative markers of the oxidative status in patients with breast cancer (6-10).

This pro-oxidant environment seems to be decisive during the initial stages of disease to ensure cancer spreading to advanced stages, as well as it may affect adaptation of tumor cells against the RS derived from anti-neoplasic drugs (11, 12). This uninterrupted generation of RS also impacts on

Correspondence to: Carolina Panis, Laboratório de Patologia e Radicais Livres, Departamento de Patologia Geral - Centro de Ciências Biológicas Universidade Estadual de Londrina, 86051-990 Londrina, Brazil. Tel: +55 4333714521, Fax: +55 4333714267, e-mail: carolpanis@sercomtel.com.br; carolpanis@hotmail.com

Key Words: Oxidative stress, breast cancer, DNA damage, redox homeostasis, review.

other cell components, such as the DNA and the nuclear system of oxidative damage repair. Chemical processes induced by RS on DNA provoke significant DNA damage by oxidation, methylation, de-amination and de-purination. RS can also affect the DNA repair enzymes by oxidizing its catalytic moieties, which impedes the correct excision of the affected DNA sequences (1).

The milieu of electrophilic/nucleophilic substances present in biological fluids and cells can also affect the protein machinery, mainly due to the high reactivity of the RS for the thiol residues, giving rise to an electrophilic stress status (13). Completing this cycle of redox events, nitric oxide (NO) is profusely produced in the breast tumor environment and besides its participation in angiogenesis and vasodilatation phenomena; this species drives nitrosative stress by yielding a wide range of nitrogen-derived RS, mainly peroxynitrite (14, 15).

In the present review we present the set of redox modifications that occur in breast cancer, focusing on mitochondrial metabolic changes and DNA oxidative repair, which constitutes the basis of oxidative modifications in all cancers. Furthermore, we present recent studies that support a role for oxidative stress in patients with breast cancer by discussing findings regarding the redox changes in the breast environment and its systemic impact on the main clinical aspects of breast cancer.

Mitochondria-driven Oxidative Stress: Metabolic and Redox Signaling in Breast Cancer

The re-programming of cellular metabolism in cancer cells is a well-documented effect. Since 1918 modifications of the mitochondria in tumors depending on the type of growth have been presented in the literature (16). Nowadays it is becoming more evident that most cancer cells have to support metabolic transformation in order to promote their survival. One of the alterations of tumor cell metabolism is known as the "Warburg Effect" (17), which postulates that tumor cells prefer deriving energy through glycolysis, opposed to the more efficient process of oxidative phosphorylation (18).

As recently shown by Ramanujan (19), breast cancer cells display alterations in metabolic response, and mutations in mitochondrial DNA (mtDNA) have been reported in a variety of cancers, including breast cancer (20). Cancer cells display mitochondrial dysfunction due to factors such as oncogenic signals and mtDNA mutations, and thus, rely more on the glycolytic pathway in the cytosol to generate metabolic intermediates and ATP (21). Besides, Shaw *et al*. demonstrated that metabolic dysfunction in breast cancer progression is independent on mtDNA copy number and the capacity for oxidative phosphorylation decreases with cancer progression (22).

In another study Sotgia and colleagues (23) examined the bio-energetic state of metastatic breast cancer cells and their surrounding microenvironment using positive lymph node tissue. A glycolytic and oxidative mitochondrial metabolism spatially-segregated and highly-compartmentalized was found. The metastatic breast cancer cells showed increase in mitochondrial mass and activity and, the lymph node-associated stromal cells were glycolytic. Thus, the co-existence of two distinct adjacent metabolic compartments, glycolytic and oxidative, was observed and termed as "reverse Warburg effect". The "reverse Warburg effect" may be determinant of poor overall patient survival and it could be used to identify high-risk breast cancer patients (24). The Warburg effect is also mediated by uncoupling protein-2 (UCP2), as demonstrated by Ayyasamy and collaborators (25). The ectopic expression of UCP2 in breast cancer cells led to a decreased mitochondrial membrane potential and increased tumorigenic properties. UCP2 is over-expressed in breast cancers promoting tumorigenesis *in vitro* and *in vivo*. Despite metabolic phenotypes in triple-negative breast cancer, Kim *et al*. (26) classified 59.8% of breast cancer patients as Warburg-type (tumor: glycolysis, stroma: non-glycolysis), 5.3% as reverse-Warburg-type (tumor: non-glycolysis, stroma: glycolysis), 18.2% as mixed-metabolic-type (tumor: glycolysis, stroma: glycolysis), and 16.7% as metabolic-null-type (tumor: non-glycolysis, stroma: non-glycolysis).

Altered cancer mitochondrial function may conduct cells to uncontrolled proliferation and protects cells against apoptosis. A mitochondrial transport protein SLC25A43 has been shown to be down-regulated in HER2-overexpressing cells. The knock-down of the gene enconding this protein leads to reduction of chemotherapy treatment efficacy (27). Kaipparettu and co-workers (28) generated hybrids of MCF10-A and MDA-MB468 mitochondria and observed a defect in mitochondrial respiration with increased amounts of reactive oxygen species (ROS) in hybrids with cancerous mitochondria. hybrids with benign mitochondria showed increased ATH synthesis, oxygen consumption and respiratory chain activity. Therefore, the mitochondrion seems to be an interesting target for cancer treatment.

The high metabolic rate of cancer cells drives their intracellular ROS up to an intermediate level, resulting in a shift in redox balance. ROS arise as a by-product of mitochondrial oxidative phosphorylation, oxygen metabolism, and NADPH/NADPH oxidase (NOX) functions (17).

Defective oxidative phosphorylation will lead to production of ROS, which may enhance cell transformation and ultimately lead to tumor initiation, promotion, and progression (29). The mitochondrion is also an important source of ROS. ROS generation may be through mitochondria by respiratory chain, in complex I and complex III. ROS produced by complex I are released in the mitochondrial matrix while those of complex III are generated in both the matrix and the inter-

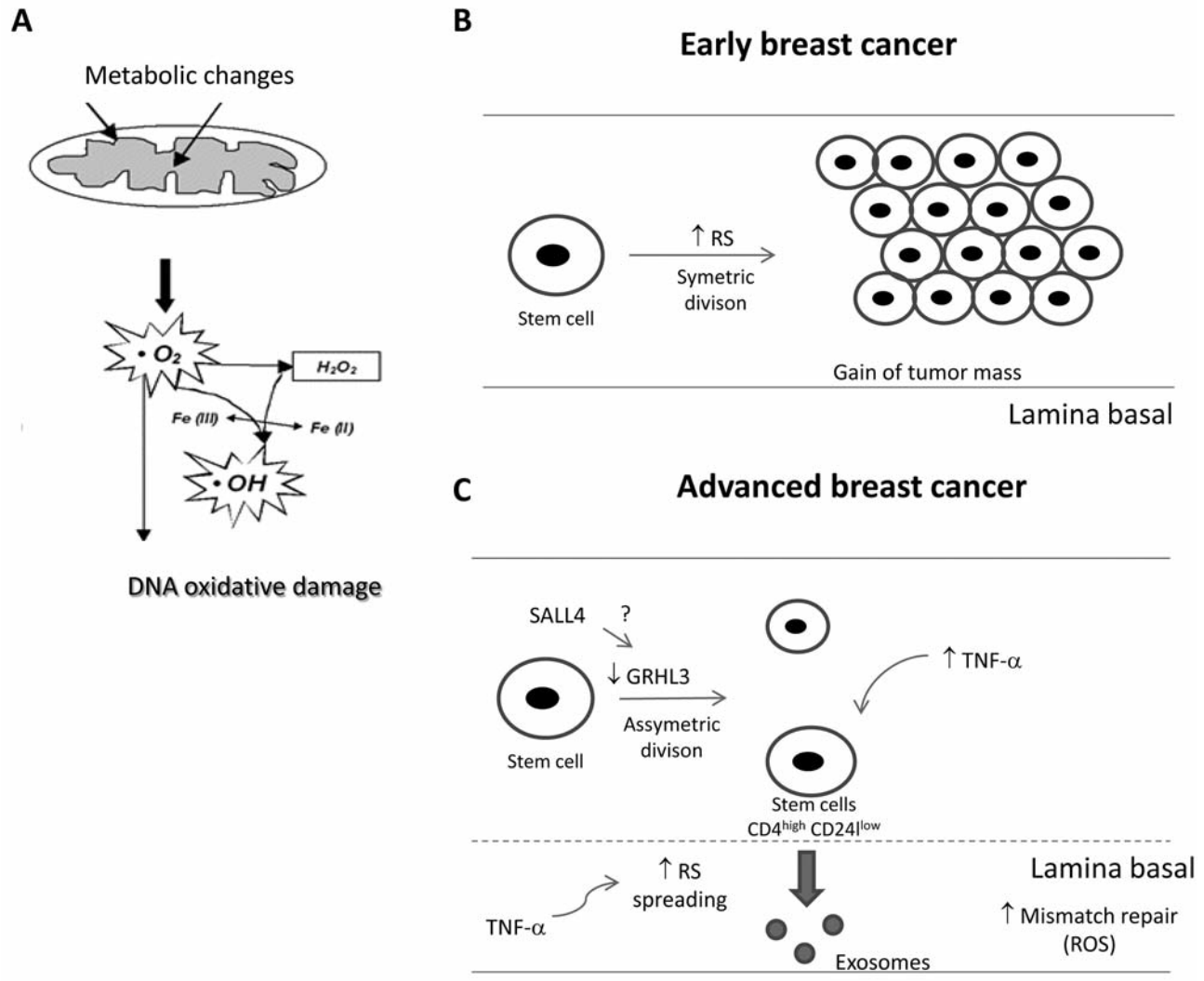

Figure 1. *Overview of oxidative stress status on breast cancer biology. (A) Metabolic changes in mitochondria trigger the imbalance in RS generation, resulting in DNA oxidative damage and misleading repair. (B) Cumulative mutation gives rise to transformed malignant cells in the breast environment, which originate the localized tumor mass characteristic of the early stages of disease. (C) Continuous RS production, in association with other inflammatory-driven modifications propitiates tumor metastasis and mismatch repair of DNA, affecting disease aggressiveness and survival. Some developmental genes are enrolled in this invasion process, as discussed in Reference 128. This Figure was constructed by the authors based on their recent findings in this field.*

membrane space. The mitochondrial inner-membrane enzyme glycerol-3-phosphate dehydrogenase (GPDH) can produce superoxide. During β-oxidation of fatty acids, the electron-transferring flavoprotein ubiquinone oxidoreductase catalyzes the oxidation of electron transferring protein and ROS can be released in the matrix (30). The aggressive phenotype in breast cancer cells, in part, may be due to mitochondrial complex I. Santidrian *et al*. (31) enhanced the function of complex I in breast cancer cells and inhibition of tumor growth and metastasis dependent on autophagy, and a reduced Akt and mTORC1 activity were observed.

The NOX protein family has an important role in producing ROS. NADPH-derived ROS depend of the isoform of the oxidase. NOXs families are represented by seven members: NOX1, NOX2, NOX3, NOX4, NOX5, dual oxidase (DUOX) 1, and DUOX 2. Not all NOX and DUOX release the same ROS and them seems to be involved in cellular signaling and their expression varies according to tissue and cell type. De-regulation of NOXs expression has been linked to tumorigenesis and silencing of DUOXs seems to participate in tumor development and progression (32).

Graham and co-workers (33) analyzed the five members of NOXs in normal breast tissue and non-malignant breast cell lines and indentified the expression of only NOX1, NOX4 and NOX5. They found overexpression of NOX4 localized into the mitochondria of malignant breast cancer cells and in 73% of breast tumors compared to normal breast cells and normal breast tissues, respectively. No correlation of NOX4 and tumor grade was observed. Also, NOX4 increased hydrogen peroxide, but not superoxide. The overexpression of NOX4 was responsible for cellular senescence and resistance to apoptosis induced by anticancer agents. Desouki and coworkers (34) examined breast tumor section and found that 86% of breast cancer cases are highly positive for NOX1. Nevertheless, no correlation of NOX1 expression and tumor grade was observed. Choudhary *et al*. (35) induced carcinogenesis in non-tumorigenic breast cells. Carcinogenesis up-regulated H-Ras gene expression, leading to extracellular signal-regulated kinase (ERK) pathway activation, Nox-1 expression, and increased amounts of ROS. Also, increased TNF-α, matrix metalloproteinase (MMP)-2, MMP-9 and reduced E-cadherin were observed following increase migratory and invasive activity. They revealed that the Ras-ERK-NOX-ROS pathway played an important role in both initiation and maintenance of cellular chronically-induced carcinogenesis and Nox-1 expression was essential for maintaining cell proliferation and ROS elevation.

The tumor microenvironment releases inflammatory cytokines such as TGF-β. Boudreau and colleagues indicated that TGF-β treatment of both normal and metastatic breast epithelial cells results in NOX-dependent superoxide production in the plasma membrane (36). In this model, increased NOX4 gene and protein expression was observed after TGF-β1 treatment. Knockdown of NOX4 in breast cells significantly reduced superoxide production and it was involved in TGF-β1-mediated cell migration, fibronectin expression, wound healing, but not cell proliferation. Also, *in vivo*, *NOX4* knockdown attenuates metastasis (37). Expression of NOX 5 was evaluated by Antony and collaborators (38). They detected an up-regulation of NOX5 in human breast cancer and found low expression of NOX5 in normal tissues.

It is well-known that ROS-mediated signaling pathways contribute to initiation, promotion and progression of estrogen-dependent breast tumors (39). Estrogens can act by oxidative stress-mediated signaling. In the cells of target tissues, available free catechol estrogen participates in redox reactions. Also, estrogen-induced ROS promote *in vitro* and *in vivo* tumor formation in breast cancer cells (40). Kanchan and collaborators (41) analyzed a panel of human breast cancers and detected increased superoxide anions in ER-positive breast cancer tissues compared to matched normal tissues. As well, correlation between superoxide anion levels and mTORC2 activation was found. ER-dependent superoxide anion generation in breast cancer cells had its origin largely within the mitochondria. Elangovan *et al*. (42) showed that silent information regulator-1 (SIRT1) is critical for estrogen to promote breast cancer and both ERα and ERRα interact with SIRT1 promoter and form a complex. Also, protein disulfide isomerase (PDI) is an ERα-interacting partner. Changes in redox homeostasis induced by nitrosative/oxidative stress cause S glutathionylation of PDI mediating breast cancer cell death through activation of the unfolded protein response (UPR) and abrogation of ERα stability and signaling (43).

The cellular redox environment is influenced by production of ROS (44). p53 is a redox-active transcription factor and ROS are the central molecules in redox signaling. Cellular levels of p53 determine its biological function. At physiological levels, p53 positively regulates the expression of antioxidant genes to protect cells from damaging levels of ROS. At hypo-physiological levels of p53, it decreases basal transcription of antioxidant genes leading to increased ROS. At hyper-physiological levels, oxidative stress can result from the unbalanced induction of antioxidant enzymes by p53 (45). Cytoplasmic p53 rapidly translocates to the mitochondrial outer membrane. While nuclear p53 export is a slow process, stress-induced mitochondrial p53 translocation has been reported to be a faster process (46). Thus, in response to cellular stress, p53 translocates to the mitochondria and directly interacts with Bcl-2 family proteins and the DBD of p53 may be the minimally- necessary domain for achieving apoptosis at the mitochondria in breast cancer cell lines (47).

Mitochondrial ROS may also lead to inflammasome priming through several pathways, as inactivation of MAPK phosphatases, leading to sustained MAPK activity. Increased ROS during hypoxia or stimulation during normoxia can lead to increased stability and accumulation of hypoxia inducible factor-1 (HIF-1) by preventing its degradation. The activation of these proteins, as well as ROS-induced NF-κB activation, leads to transcription of pro-IL-1β and NLRP3 (30). The HIF has its expression up-regulated by the PI3K/Akt1/mTOR pathway and represent secondary mechanisms of adaptation that are driven by external signaling (17). Metastatic breast cancer cells increases HIF1-α and enhance glycolysis in response to low oxygen tension, compared to non-tumorigenic breast cells (48). Either, HIF-1 and the oncoprotein Myc are two prominent transcription factors that drive glycolysis. Cai *et al*. (49) showed that ERRs form a complex with Myc and play an important role by binding to promoter regions of glycolytic genes in cancer cells and as modulators of cancer cell growth. The ERRs may contribute to malignant development in part by conferring metabolic advantages to tumor cells.

Several redox-sensitive signaling pathways seem to be involved in breast cancer development. Cha and colleagues (50) showed that HER2 induces transcriptional activation of lepitin in HER2-overexpressing-MCF10-A cells through

involvement of p38 mitogen-activated protein kinase (MAPK) signaling. Inhibition of mammalian target of rapamycin (mTOR) and serum-glucocorticoid-regulated kinase 1 (SGK1) decreases growth in ERα+ cell MCF7, while its inhibition did not affected metastatic breast cancer cells (51). Park and co-workers (52) found that the antioxidant resveratrol repressed 4-OHE 2 (4-hydroxyestradiol)-induced migration and transformation of MCF-10A cells. Resveratrol suppresses 4-OHE 2 -induced IKKβ activity, IκBα phosphorylation, NFκB DNA binding and COX-2 expression. Also, resveratrol inhibited 4-OHE 2 -induced ROS production and Akt/ERK phosphorylation. Qu *et al*. (53) found an important role for the redox protein thioredoxin-like 2 (TXNL2) in human breast cancer. They found that TXNL2 is overexpressed in human cancers and *in vitro* knock-down of this protein prevented the colony formation, impaired migration and invasion of MDA-MB-231 and BT549 cells through a redox signaling mechanism.

Regarding lipid metabolic genes, Nieva and collaborators analyzed the expression of SREBP-1c, gene target of LXR, and ABCA1, other direct LXR target genes involved in cell cholesterol export and found an up-regulation of SREBP-1c in metastatic breast cancer cells compared to non-metastatic cells, presenting differences in regulation of lipid metabolism pathways in breast cancer cells. Sohn and collaborators (54) showed that the protein levels of Nutrient-deprivation autophagy factor-1 (NAF-1) and mitoNEET (mNT) are elevated in human breast cancer cells, and that suppressing the levels of these proteins results in reduced cell proliferation and tumor growth, decreased mitochondrial performance, uncontrolled accumulation of iron and reactive oxygen in mitochondria, and activation of autophagy.

The peroxisome proliferator-activated receptor- co-activator-1 (PGC-1) family was first described by Puigserver and collaborators (55) as regulators of several mitochondrial genes. PGC-1α e β have been considered as main regulators of energy homeostasis of the cell (56). PGC-1s function is through their ability to interact with transcription factors or nuclear receptors linked to mitochondrial respiration (57). It has been demonstrated that variations of PGC-1s expression occur in tumor cells in order to promote cell survival. Nevertheless, expressions of PGC-1s in cancer have been analyzed by several authors in distinct cancer models and results are still controversial.

High levels of PPARα were associated with poorer overall survival and intermediate/high levels of PPARβ/γ were associated with poorer overall survival in breast cancer patients (58). Jiang *et al*. (59) conducted *in vitro* and *in vivo* analyses of PPAR-γ and PGC-1α expression in breast cancer. The expression of PPAR-γ was higher in MCF-7 cells compared to MDA-MB-231 cells and human breast cancer tissues expressed lower levels of PPAR-γ. Regarding PGC-1α, its expression did not differ between normal and breast cancer tissues. Nevertheless, a reduction in both PPAR-γ and PGC-1α was observed during tumor development (TNM3 and TNM4). Klimcakova *et al*. (60) analyzed the role of PGC-1α in a HER2-induced breast cancer model to examine whether ameliorating mitochondrial functions in cancer could limit tumor growth. In a HER2-positive cell line, they characterized the Warburg effect through increased lactate production, increased glycolytic genes and decreased expression of mitochondrial metabolism genes (as PGC-1α). By ectopically expressing PGC-1α, they found reduced proliferation and enhanced mitochondrial functions *in vitro*. Nevertheless, *in vivo* data demonstrated that, in mice, HER2-initiated mammary tumors expressing PGC-1α grew faster and were larger in size than controls.

Aerobic glycolysis can be directly induced by an inflammatory microenvironment independently of genetic mutations and signals from adjacent cells. Vaughan *et al*. (61) treated MCF-10A and MCF-7 cells with TNF-α and showed a decrease in PGC-1α levels, cytochrome c expression and mitochondrial content. Carracedo *et al*. (62) identified a metabolic function for PML (pro-myelocytic leukemia), a pro-apoptotic and growth inhibitor tumor suppressor, acting as both a negative regulator of PGC1α acetylation and a potent activator of PPAR signaling and fatty acid oxidation in breast cancer cells. Also, this gene was overexpressed in a subset of breast cancers and was enriched in triple-negative cases.

Regarding PGC-1β, Chang *et al*. (63) revealed that PGC-1β and PPRC1 are expressed in several breast cancer cell lines, unlike, PGC-1α which was expressed only in a few breast cancer cell lines and expression of PGC-1β correlates with expression of ERRα. Their data suggests that PI3K and its downstream target Akt are important for the expression of PGC-1β in HER2-positive cells. Also, induction of MAPK and PI3K, important pathways induced in HER2 overexpressed cells, in non-amplified HER2 breast cancer cell, led to PGC-1β up-regulation. Expression regulation of PGC-1β in breast cancer is regulated by c-MYC in response to Her2/IGF-1 activation. Eichner and colleagues (64) identified that PGC-1β and its intronic miRNA (miR-378*) are co-regulated by HER2 overexpression, as knock-down of HER2 expression in SKBR3 cells led to decreased PGC-1β and miR378 expression. Therefore, it is clear that breast cancer cells display several mechanisms to promote their survival involving several redox-signaling pathways and modifying their metabolism.

Exploiting the DNA Oxidative Damage and Repair in Breast Cancer

The DNA repair machinery: an overview. For the successful evolution of metazoan organisms, it was necessary for an alternative way to produce high levels of energy to be

created. In the course of this process, energy generation, as ATP molecules, became possible through the mitochondrial respiratory chain. However, in contrast to this advantage, the generation of harmful sub-products derived from this metabolism. This disadvantage is called oxidative stress (1). Since long, it is known that the main players of oxidative stress are the ROS (65). These molecules show high affinity to cell macromolecules, such as proteins, lipids, RNA and, especially, for DNA. The source of such RS can be, as mentioned, endogenous or exogenous. This last one is principally induced by drugs, pollutants, tobacco, xenobiotics and radiation. In this field, RS generation yields harmful products that cause cellular injury, becoming the first step for cancer development. On the other hand, RS can also be favorable for cancer treatment, when they are purposefully induced by chemicals or by ionizing radiation.

The cellular consequences of RS are primordially-dependent on their direct and indirect effect (66). Direct effects are characterized by direct DNA damage whereas indirect effect is associated with the sub-products generated by the stressors. As an example, the ionizing radiation can directly affect the DNA, promoting disruptions in the DNA structure, or can also yield RS by water radiolysis. The majority of RS products are nucleophilic radicals that have high affinity by DNA structure, promoting breaks or nitrogen base alterations by radicalar chemical reactions. Chromosomal abnormalities such as breaks, deletions and translocations were the first consequences of RS reported in cells exposed to stressors. Next, it was found that RS were also able to induce punctual DNA alteration, mostly transversion, translesion, single- and double-strand breaks (67-69).

To overcome this situation, cells are endowed with a class of molecules specialized in keeping DNA safe of lesions. DNA is a cellular macromolecule where all genetic information is organized, stored; therefore, this valuable molecule should keep safe from any kind of injury. To this purpose, cells present a class of proteins specially working for maintaining DNA free of errors by repairing it in case of damage. These proteins are known as DNA repair proteins that is shared in the sensing, signaling and creating a scaffold for recruitment of DNA damage effector proteins. Sensing proteins detect DNA lesions and start the signaling according to the type of lesion. At the same time, signaling proteins also cross-talk with the cell-cycle to induce arrest of cell division, allowing for the correction of DNA damage. These effector proteins are sub-divided in accordance to the types of lesions in Direct DNA Damage Reversal (DDR), Base Excision Repair (BER), Nucleotide Excision Repair (NER), Mismatch Repair (MMR), Homologous Recombination (HR), Non Homologous End Join (NHEJ), DNA damage tolerance pathway (TSL) (70).

Although there exist several DNA repair pathways, the BER is thought to be the principal defense against DNA damage caused by RS (69, 71, 72). The main DNA damage reported as driven by RS is the nitrogen-base modification. These damages can be divided in four classes: 1) Oxidation: generating 8-oxoguanine, 5-hydroxicytosine, thymidine glycol, FapG; 2) Alkylation: creating 3-methyladenine, 7-methylguanine; 3) De-amination: inducing formation of hypoxanthine from deamination of adenine and thymine made from deamination of 5-methylcytosine; and 4) incorporation of Uracil in DNA or formed by deamination of cytosine (70). These nucleotide alterations have extreme significance in cell biology, because they alter the normal pattern of complementary base pairing, causing alterations of a gene sequence and consequently dysfunctional codification of coding or non-coding gene products. Therefore, DNA alterations can represent a mutagenic event. BER are implicated in a pathway for recognition and removal of altered DNA nitrogen bases mainly performed by the action of DNA glycosylases, DNA nuclease enzymes, polymerases and ligases. The BER performs DNA repair by two distinct ways, known as short-patch (SP-BER) and long-patch (LP-BER).

In mammalians, the first step of BER pathway is coordinated by at least 12 DNA glycosylase enzymes, depending on the type of the lesion (UNG1, 2, SMUG1, TDG, OGG1, MPG/AAG, MBD4/MED1, NEIL1, 2, 3, NTHL1 and MUTYH). After recognition of the damaged site, such DNA glycosylases remove the damage in bases generating abasic sites (AP-site), that can be apurimic or apirimidinic, depending on several points, such as the class of nitrogen bases, the AP-site represented hemi-acetal or aldehyde formation. For removing DNA damage, nucleases are recruited. APE1 is the main protein involved in this process. As mentioned before, two distinct BER pathways can be triggered. The DNA repair will be directed to SP-BER if the lesion affects only one base or to LP-BER if two or more bases are damaged. The proteins involved to filling the piece of removed DNA in SP-BER is compound by Polβ, Polδ, Polε, RFC, FEN1, PCNA, whereas to LP-BER are Polβ, XRCC1. The repair ends with action of ligases proteins, which LIG1 are committed with both BER pathways and LIG3 that are committed with LP-BER (73).

DNA damage in breast cancer. Naturally, the maintenance of DNA integrity is one of the ways leading to cell survival and, for this reason, evolutionary events selected special classes of the cellular machinery dedicated to DNA surveillance. If DNA damage is highly extensive and cannot be repaired by this DNA repair system, the cells will probably trigger cellular mechanisms to induce its death. In this fight for survival, the cells allow for minimal mutational alterations in the DNA sequence. As a consequence, accumulation of DNA errors has been considered the main basis for the development of numerous diseases, especially cancer. There are several pillars for explaining the cellular malignant

transformation, but genomic instability is the most accepted hallmark for cancer development (74).

Some cancers have a markedly intrinsic relationship with the malfunctioning of DNA repair proteins; in most cases this is due to mutations/polymorphisms in specific genes such as in colorectal cancer (mutation in MGMT, MUTYH, MLH1, MSH2); skin cancer (XPD, XPB); pancreatic cancer (RECQL1); leukemias (FANCJ) and breast cancer (BRCA1, BRCA2, PIF1) (75-78). Among existing cancers, the breast cancer remains poorly-explored in the field of DNA repair knowledge.

Although breast cancer had named the gene name, BRCA – BReast CAncer gene, due to its relationship between mutation and risk of cancer development (79, 80), the majority of breast cancers occur sporadically (81).

The discovery of the relationship between oncogenes and cancer development was fundamental to interpret, at least in part, the first steps for the malignant transformation (82, 83). However, evidence has reported that only forced oncogene expression or direct mutation in tumor suppressor genes is not sufficient to trigger cellular reprogramming and induce the cancerous phenotype. Recently, several steps have been considered as hallmarks to cancer development (74). Among these, the tumoral microenvironment has received a special focus, highlighting the inflammatory process. In this scenario, the mesenchymal-end inflammatory cells which filled the tumor microenvironment seem to be responsible for creating a RS-enriched niche, which has been reported as responsible for inducing new mutations.

One of the first evidence regarding the connexion between RS and breast cancer was reported by Werts and Gould (84). The authors performed experiments that re-inforced the concept concerning the involvement of free radicals as crucial players of the multi-step carcinogenesis. Such experiments allowed for establishment of an inverse-correlation between the activity of superoxide dismutase (SOD), a detoxifying anti-oxidant enzyme, and the risk for breast cancer development. In the same period, a larger-scale study indicated that the antioxidant activity superoxide dismutase and glutathione peroxidase was elevated in breast cancer tumors in comparison with normal healthy tissues (85). These findings pointed out that increased oxidant conversion enzymes could protect tumors against some RS effects. This hypothesis was strengthened by other studies (86-89).

Several risk factors have been elected for breast cancer development, such as parity, aging, alcohol consumption, obesity, dietary fat and sedentary life style. Among these factors, the great majority are linked to increase of oxidative stress (90). For instance, obesity is intrinsically associated with breast cancer incidence (91). Obesity alters the systemic metabolic profile, favoring the generation of RS, which elevates the probability of oxidative DNA lesions (92). Associated to this fact, obesity also induces leptin and insulin-like growth factors, which in the estrogen-responsive breast cells constitutively trigger the activation of signaling pathways linked to cancer, like STAT3, MAPK and PI3K. These pathways induce cell proliferation, aggressiveness phenotype and apoptosis inhibition (93-94).

Ageing is known as a risk factor for cancer development - including breast cancer- and is intrinsically-associated with RS increase. In part, this correlation may be due to loss or reduction in the activity of the antioxidant machinery. On the other hand, during life the DNA is a constant target of RS, provoking a cumulative effect (95). This fact has been extensively considered one of the main factors for breast cancer development (96). *In vitro* experiments have demonstrated that RS may also be the responsible trigger for inducing the early occurrence of the hereditary breast cancer (97).

Besides the pathophysiology of breast cancer, the polymorphisms in the DNA repair genes (as well as its mutations) also shown to be responsible for error-prone DNA lesions driven by RS. Population and meta-analysis studies have investigated the relationship between BER polymorphisms and the risk for breast cancer in different populations (as summarized in Table I). The most known and extensively studied genes in inherited breast cancer are *BRCA1* and *BRCA2* (79, 80). The mutational status of such genes can confer up to 80% probability for breast cancer appearance. Both genes have been related to several cellular and molecular processes, but they are mainly involved in DNA repair and genome maintenance. These two proteins are involved in the DNA repair by the homologous recombination (HR) pathway (70). BRCA2 protein presents the same functional protein of the Fanconi's Anemia (FA), known as FANCD1 (98). Individuals harboring the FA syndrome exhibit bone marrow failure and increased cancer predisposition. These clinical characteristics are associated with the deficiency in repairing DNA lesions by HR (99). Although primarily described in breast cancer, *BRCA1/2* gene mutations have been linked to ovarian, prostate, endometrial and pancreatic cancers (100).

The relationship between the BRCA pathway and RS is poorly-explored. Existing data indicate that BRCA/FA-deficient proteins are correlated with low SOD expression levels and, consequently, with an increase of RS levels. Recently, some findings suggested a role for BRCA1 in controlling the expression and functionality of BER genes (101). In addition, BRCA/FA-mutated individuals accumulate DNA aberrations due to both harmful RS effects and low BER ability to act, inducing tumors earlier (102).

Regarding sporadic breast cancer, the primary evidence of BER activity on repairing the oxidative DNA damages was found during the investigation of variant DNA polymerase-beta (Polβ). Polβ variants can present 87 base pairs gene deletion that have been associated to breast cancer and other tumors due to malfunction of the BER pathway (103, 104).

Experimental studies on this issue have focused on breast cancer-exhibiting resistant phenotypes, and APE1, MPG and Polβ expression have been reported as predictors of breast cancer resistance (105, 106). Moreover, the permanent RS generation established inside breast cancer cells may create a microenvironment chemically-favorable to fight against the exogenous RS derived from radio/chemotherapy (107).

Thus, the gain with the energetic metabolism for organism development was accompanied by the side-effects caused by the RS generated in this process. Furthermore, the anti-oxidant machinery is not completely effective in pathological conditions to ensure for the surveillance of the DNA. Changes in life-style and increase of life span have run fast, propitiating the accumulation of DNA damages and cancer formation. In this scenario, the main challenge for researchers is in fact to comprise how breast cancer originates. This answer will help to interpret cancer biology and to improve the development of promising therapies against this disease.

Oxidative Stress Metabolites Can Exert Modulatory Effects on the Breast Cancer Environment: Clinical Insights

Recent findings have increased remarkably our understanding concerning the modulatory side of the products generated by RS action on cancer cells. Studies focusing on nipple aspirate fluid (NAF) have added enough information to suggest a paradigm shift of our understanding over the role of oxidative stress metabolites in human breast cancer. Breast cancer is a disease that develops in the ductal and lobular epithelia; this is the main reason why the NAF analysis is so relevant to map the metabolic activity of breast parenchymal network. NAF-based studies represent a promising strategy in the field of biomarker discovery, since it can be easily obtained non-invasively and represents the real picture of the breast microenvironment and its metabolic activity (6, 7).

The secretory nature of the breast glands allows for concentration of several kinds of pro-carcinogenic and growth factors that can profoundly impact on breast cell morphology and metabolism. Morphological studies have demonstrated that the epithelial cells recovered from breast cancer NAF present a cluster presentation in association with abundant inter-cellular tight and gap junctions when compared to normal non-cancerous NAF (119). Such junctions could seal the epithelial cells, increasing their exposition to bioactive molecules that mediate the malignant transformation of the breast.

This malignant transformation of the breast is a multi-step process that may enroll oxidative changes in all progression phases. The lipid-rich environment found in the breast propitiates the formation of several metabolites derived from the lipid peroxidation process, with unclear roles in preventing or promoting tumorigenesis. NAF is very rich in lipids, and substances derived from lipid peroxidation found here may present some importance in breast cancer etiology (120). MDA and the 8-epimer of prostaglandin F2-alpha (8-isoPGF2-alpha) are some markers of the *in situ* lipid peroxidation process reported in the NAF of women with breast cancer. Reduced levels of 8-isoPGF2-alpha have been reported in cancerous NAF (121), suggesting a physiological role for the lipid peroxidation process in the breast, since the reduced levels of 8-isoPGF2-alpha may reflect some alteration on the free radical-mediated degradation of the arachidonic acid in breast cancer cells. In fact, augmented levels of group IIa secretory phospholipase-A2 (sPLA2-IIa) are reported in cancerous NAF. Metabolism of arachidonic acid on its bioactive products can contribute to cancer progression, and sPLA2-IIa seems to be involved in this process. It has been demonstrated that the sPLA2-IIa is expressed constitutively in NAF, suggesting a physiological role for such proteins in non-cancerous NAF. Furthermore, enhanced expression of sPLA2-IIa was found within both NAF and epithelial breast cancer cells (122).

The products yielded by the lipid peroxidation process are able to react with protein residues, giving rise to the carbonyl residue, a reliable marker of protein oxidation (123). The carbonylation process causes post-translational modification of proteins that may result in significant cellular dysfunction. Protein oxidative modifications can naturally occur in NAF, but augmented levels of carbonylation in this fluid are reported as a result of oxidative stress generation by *in situ* RS production (7). Furthermore, 8-F2-isoprostanes are negatively-related to this carbonyl content of the NAF, suggesting that the oxidative breast environment further oxidizes this molecule to the end-stages of lipid peroxidation, by forming products that react with proteins and yield the carbonyl formation on NAF.

Evidence supports that some components of the oxidative stress network may regulate the balance between oncogenic and oncosuppressor effects of RS in NAF. High expression of the antioxidant enzyme superoxide dismutase 1 (SOD1) was found in non-cancerous NAF when compared with samples from breast cancer (124). These findings propose a role for SOD1 in NAF redox homeostasis. Up-regulation of SOD1 augments the levels of the hydrogen peroxide, which could impair cancer proliferation and confers an oncosuppressor property to this enzyme. On the other hand, down-regulation of SOD1 favors the accumulation of superoxide anion, resulting in an onco-promoter situation. Thus, SOD1 may reflect a putative switch between such responses in the breast environment.

The inflammatory nature of cancerous NAF have been further associated with high levels of C reactive protein and iron-binding proteins, that are positively correlated (125). Aluminum imbalance, that can also disrupt iron homeostasis, is reported in cancerous NAF, suggesting the accumulation

of this metal on breast tissue (126) that potentially aggravates the pro-oxidant effects of iron disturbance. The disruption of iron homeostasis in cancerous NAF helps to explain, at least in part, the *in situ* pro-oxidant status of breast cancer, because free iron is intimately implicated in the generation of RS.

The presented data reinforces epidemiological findings that implicate chronic inflammation in cancer development and helps to understand the pro-oxidant nature of the breast cancer microenvironment.

The Systemic Mapping of Redox Changes in Human Breast Cancer

Although breast cancer is generally compound by tumor masses ranging from few micrometers to more than 5 centimeters, systemic oxidative changes have been extensively reported in women suffering from this disease. The occurrence of systemic oxidative stress suggests that both the tumor and the host immune response may be the source of RS. Furthermore, these findings indicate that the cancerous patient present profound metabolic modifications that perpetuate even after tumor removal, which helps explain why some individuals present disease recurrence and develop secondary tumors.

Recent studies performed by our group have extensively characterized the systemic oxidative status of breast cancer, demonstrating that women with breast cancer can have distinct oxidative status according to specific disease aspects. The existence of a systemic pro-oxidant status in patients with breast cancer is a well-established fact, and it seems to vary according to disease spreading. The oxidative profiling of the metastatic breast cancer includes reduction in pivotal anti-oxidant defenses such as erythrocytic glutathione, catalase and total anti-oxidant capacity (127). In addition to reduced anti-oxidants, such patients bearing advanced disease also exhibit a high pro-oxidative status marked by augmented ferritin, enhanced plasmatic lipid peroxidation, high levels of circulating NO and increased malondialdehyde/ carbonyl content. A sustained pro-inflammatory status has also been reported, characterized by elevation in C reactive protein levels in all disease stages. TNF-α and IL-1β seems to be the triggering cytokines for this pro-oxidative status found in women with breast cancer. A plasmatic proteomic profiling of advanced breast cancer corroborate such biochemical findings (128). Patients with advanced breast cancer presented up-regulation of TNF-α and the protein of mismatch repair PMS2 in both plasma and tumor samples, suggesting the participation of breast tumors as a source of circulating oxidative markers.

Further studies have demonstrated that this systemic oxidative-inflammatory profile found in breast cancer is dependent on the tumor molecular sub-type (129). Patients bearing luminal tumors are characterized by enhanced TNF-α and TGF-β1 in association with high lipid peroxidation and malondialdehyde. Reduced antioxidant capacity was also reported in luminal patients and strongly associated with age at diagnosis. It is well-established that luminal tumors present a potential for sustained oxidative stress, since the estrogen signaling is constitutively activated in this situation.

A similar cytokine profiling can be found in patients with tumors presenting the human epidermal growth factor receptor-2 (HER2) amplified/overexpressed. Enhanced circulating TNF-α and TGF-β1 is also reported, in association with high IL-12 and suppressed IL-10 levels (129). Interestingly, a recent in-depth analysis of oxidative profiling of patients with HER2 breast cancer suggests that this overexpression seems to attenuate the systemic pro-oxidant status of patients when compared to patients with HER2-negative tumors (130). HER2 patients exhibit decreased malondialdehyde and augmented SOD activity, which favor the accumulation of hydrogen peroxide, potentially enhancing HER2 tumor growth and invasion. This hypothesis may be possible, because HER2 patients also exhibit a significant reduction of systemic glutathione in comparison to HER2-negative patients, indicating its consumption by some RS.

A single systemic oxidative profile was found in patients with triple-negative breast cancer in the study by Herrera *et al*. (129). In contrast to luminal and HER2 tumors, the triple-negative breast cancer established the attenuation on circulating TNF-α and TGF-β1, in association with reduced oxidative changes, as observed by low malondialdehyde and diminished lipid peroxidation in relation to other subtypes. Triple-negative patients further display higher NO levels among subtypes. These findings support that the molecular signature of breast tumors is associated with its capacity on generating oxidative stress at the systemic level. Circulating TGF-β1 seems to be a putative determinant of poor survival in breast cancer and acts as a redox sensor by preserving the glutathione content (131).

The interest in understand the inflammatory environment of breast cancer and its systemic impact on the systemic status of patients has added new players to the game. Recent studies investigated on the role of the metabolic cytokine adiponectin in breast cancer. The imbalance on circulating adiponectin has been reported as a poor prognosis factor in breast cancer. However, all evidence was obtained from studies that investigated this parameter in pre-obese and obese cohorts, producing confounding conclusions regarding this metabolic parameter. Our group recently investigated adiponectin profiling in non-obese women diagnosed with invasive breast cancer (132) and highlighted its anti-inflammatory potential against the pro-oxidant systemic status of breast cancer.

Chemotherapy also exerts profound redox changes in the plasmatic profile of women with breast cancer. The

generation of oxidative stress is one of the main anti-neoplastic mechanisms of several chemotherapeutic drugs, mainly doxorubicin and paclitaxel. We have investigated on the systemic impact of doxorubicin-paclitaxel-based chemotherapy in breast cancer and observed that each of these drugs enrolls distinct ways of oxidative stress generation (133). Patients undergoing doxorubicin chemotherapy present more profound inflammatory and oxidative changes, characterized by reduced TNF-α and IL-1β immediately after chemotherapy infusion (134). Such findings suggest that doxorubicin may directly affect these cytokines by modulating its consumption of degradation. This treatment also impairs the capacity of leukocytes to trigger the oxidative burst for superoxide anion production, indicating an immunosuppressive role for doxorubicin in the early stages of breast cancer treatment.

We also reported on high levels of oxidative stress following doxorubicin treatment. Our data further indicate that the main non-cancerous target of doxorubicin in breast cancer is the erythrocyte, which predispose such cells to the occurrence of pre-hemolytic lesions and may explain in part the quick reduction of circulating red blood cells and hemoglobin levels. In fact, doxorubicin may reach the inside of erythrocytes, since its extrusion is performed after conjugation with glutathione by the RLIP76 transporter (135). In a different manner, paclitaxel treatment in breast cancer seems to impact on the systemic oxidative status more superficially. Patients submitted to paclitaxel chemotherapy present high levels of circulating IL-10 promptly after its infusion, indicating its releasing from the immune surveillance cells. Unlike doxorubicin, the oxidative burst of leukocytes is impaired by paclitaxel treatment. Paclitaxel treatment of breast cancer only affects the lipid peroxidation status of plasma, and this fact may be related with the retention of this drug outside of cells. These data re-inforce the participation of oxidative stress as a pivotal mediator in human breast cancer-related responses.

Conclusion

A summary of the meaning of oxidative stress participation on breast cancer aspects is presented in Figure 1. Altogether, these findings strongly suggest that breast cancer presents a long-lasting oxidative status of mitochondrial dysfunction origin that leads to protein oxidation and lipid peroxidation product formation, increasing the risk for direct DNA damage and injury of the oxidative damage repair mechanisms. On the other hand, RS favor the formation of specific metabolites that may regulate pivotal events in the breast cancer microenvironment. The long-lasting oxidative status may also be implicated in the induction of chemo-resistant breast cancer and may constitute a hypothesis for explaining disease recurrence and secondary tumor development. Oxidative changes seem to be further implicated in disease prognosis, since chemotherapeutic drugs may regulate redox homeostasis through distinct ways.

References

1 Halliwell B and Gutteridge JMC: Free radicals in biology and medicine. New York, Oxford University, 4th edition, 2007.

2 Pani G, Giannoni E, Galeotti T and Chiarugi P: Redox-based escape mechanism from death: the cancer lesson. Antiox Redox Signal *11(11)*: 2791-2802, 2009.

3 Lisanti M P, Martinez-Outschoorn UE, Lin Z, Pavlides S, Whitaker-Menezes D, Pestell RG, Howell A and Sotgia F: Hydrogen peroxide fuels aging, inflammation, cancer metabolism and metastasis: the seed and the soil needs a "fertilizer". Cell Cycle *10(15)*: 2440-2449, 2011.

4 Martinez-Outschoorn UE, Balliet RM, Rivadeneira DB, Chiavarina B, Pavlides S, Wang C, Whitaker-Menezes D, Daumer KM, Linz Z, Flomenberg N, Howell A, Pestell RG, Knudsen ES, Sotgia F and Lisanti MP: Oxidative stress in cancer associated fibroblasts drives tumor-stroma co-evolution: A new paradigm for understanding tumor metabolism, the field effect and genomic instability in cancer cells. Cell Cycle *9(16)*: 3256-3276, 2010.

5 Martinez-Outschoorn UE, Linz Z, Trimmer C, Flomenberg N, Wang C, Pavlides S, Pestell RG, Howell A, Sotgia F and Lisanti MP: Cancer cells metabolically "fertilize" the tumor microenvironment with hydrogen peroxide, driving the Warburg effect: implicating for PET imaging in human tumors. Cell Cycle *10(15)*: 2504-2520, 2011.

6 Manello F, Tonti GA, Pagliarini S, Benedetti S, Canestrari F, Zhu W, Qin W and Sauter ER: The 8-epimer of prostaglandin F (2 alpha), a marker of lipid peroxidation and oxidative stress, is decreased in the nipple aspirate fluid of women with breast cancer. Int J Cancer *120(9)*: 1971-1976, 2007.

7 ManelloF, Tonti GA and Medda V: Protein oxidation in breast microenvironment: nipple aspirate fluid collected from breast cancer women contain increased protein carbonyl concentration. Cell Oncol *31*: 383-392, 2009.

8 Gago-Dominguez M, Castelao JE, Pike MC, Sevanian A and Haile RW: Role of lipid peroxidation in the epidemiology and prevention of breast cancer. 2005. Cancer Epidemiol Biomark Prev *14(12)*: 2829-2839, 2005.

9 Gago-Dominguez M, Jiang X and Castelao JE: Lipid peroxidation, oxidative stress genes and dietary factors in breast cancer protection: a hypothesis. Breast Cancer Res *9*: 201-212, 2007.

10 Gago-Dominguez M, Jiang X and Castelao JE: Lipid peroxidation and the protective effect of physical exercise on breast cancer. Med Hyp *68*: 1138-1143, 2007.

11 Fang J, Nakamura H and Iyer AK: Tumor-targeted induction of oxystress for cancer therapy. J Drug Target *15(7-8)*: 475-486, 2007.

12 Farias J W, Furtado FS, Guimarães SB, Silva Filho AR and Vasconcelos PR: Oxidative stress parameters in women with breast cancer undergoing neoadjuvant chemotherapy and treated with nutraceutical doses of oral glutamine. Acta Cir Bras *26(1-2)*: 82-87, 2011.

13 Halliwell B: Tell me about free radicals, doctor: a review. Journal of the Royal Society of Medicine *82*: 747-752, 1989.

14 Gauthier N, Arnould L, Chantôme A, Reisser D, Bettaieb A, Reveneau S and Jeannin JF: To stimulate or to inhibit nitric oxide production in mammary tumors? Bull Cancer *91(9)*: 705-712, 2004.

15 Glynn SA, Boersma BJ, Dorsey TH, Yi M, Yfantis HG, Ridnour LA, Martin DN, Switzer CH, Hudson RS, Wink DA, Lee DH, Stephens RM and Ambs S: Increased NOS2 predicts poor survival in estrogen receptor-negative breast cancer patients. J Clin Invest *120(11)*: 3843-3854, 2010.

16 Goodpasture, EW: Observations on mitochondria of tumors. J Med Res *38(2)*: 213-224.1, 1918.

17 Cairns RA, Harris I, Mccracken S and Mak TW: Cancer cell metabolism. Cold Spring Harb Symp Quant Biol *76*: 299-311, 2011.

18 Warburg O: On the origin of cancer cells: Science *123(3191)*: 309-314, 1956.

19 Ramanujan VK: Metabolic imaging in multiple time scales. Methods, pii: S1046-2023(13)00342-3, 2013.

20 Modica-Napolitano JS, Singh KK: Mitochondrial dysfunction in cancer. Mitochondrion 4: 755-762, 2004.

21 Shijun W, Zhu D and Huang P: targeting cancer cell mitochondria as a therapeutic approach. Future Med Chem *5*: 53-67, 2013.

22 Shaw PG, Chaerkady R, Wang T, Vasilatos S, Huang Y, van Houten B, Pandey A and Davidson NE: Integrated proteomic and metabolic analysis of breast cancer progression. PLoS ONE *8(9)*: e76220, 2013.

23 Sotgia F, Whitaker-Menezes D, Martinez-Outschoorn UE, Flomenberg N, Birbe RC, Witkiewicz AK, Howell A, Philp NJ, Pestell RG and Lisanti MP: Mitochondrial metabolism in cancer metastasis: Visualizing tumor cell mitochondria and the "reverse Warburg effect" in positive lymph node tissue. Cell Cycle *11(7)*: 1445-1454, 2012.

24 Witkiewicz AK, Whitaker-Menezes D, Dasgupta A, Philp NJ, Lin Z, Gandara R, Sneddon S, Martinez-Outschoorn UE, Sotgia F and Lisanti MP: Using the "reverse Warburg effect" to identify high-risk breast cancer patients: Stromal MCT4 predicts poor clinical outcome in triple-negative breast cancers. Cell Cycle *11(6)*: 1108-1117, 2012.

25 Ayyasamy V, Owens KM, Desouki MM, Liang P, Bakin A, Thangaraj K, Buchsbaum TJ, LoBuglio AF and Singh KK: Cellular model of warburg effect identifies tumor promoting function of UCP2 in breast cancer and its suppression by genipin. PLoS ONE *6(9)*: e24792, 2011.

26 Kim S, Kim DH, Jung WH and Koo JS: Metabolic phenotypes in triple-negative breast cancer. Tumor Biol *34*: 1699-1712, 2013 DOI 10.1007/s13277-013-0707-1.

27 Gabrielson M and Tina E: The Mitochondrial transport protein SLC25A43 affects drug efficacy and drug-induced cell cycle arrest in breast cancer cell lines. Oncology Reports *29*: 1268-1274, 2013.

28 Kaipparettu BA, Ma Y, Park JH, Lee T-L, Zhang Y, Yotnda P, Creighton CJ, Chan WY and Wong LJC: Crosstalk from non-cancerous mitochondria can inhibit tumor properties of metastatic cells by suppressing oncogenic pathways. PLoS ONE *8(5)*: e61747, 2013.

29 Yadav N and Chandra D: Mitochondrial DNA mutations and breast tumorigenesis. Biochim Biophys Acta *1836(2)*: 336-344, 2013.

30 Pelletier M, Lepowa TS, Billinghama LK, Murphy MP and Siegel RM: New tricks from an old dog: Mitochondrial redox signaling in cellular inflammation. Seminars in Immunology *24*: 384-392, 2012.

31 Santidrian AF, Matsuno-Yagi A, Ritland M, Seo BB, LeBoeuf SE, Gay LJ, Yagi T and Felding-Habermann B: Mitochondrial complex I activity and NAD+/NADH balance regulate breast cancer progression. J Clin Invest *123(3)*: 1068-1081, 2013 doi:10.1172/JCI64264.

32 Hayes P and Knaus UG: Balancing reactive oxygen species in the epigenome: NADPH oxidases as target and perpetrator. Antiox Redox Signal *18(15)*: 1397-1945, 2013.

33 Graham KA, Kulawiec M, Owens KM, Li X, Desouki MM, Chandra D and Singh KK: NADPH oxidase 4 is an oncoprotein localized to mitochondria. Cancer Biol Ther *10(3)*: 223-231; August 1, 2010.

34 Desouki MM, Kulawiec M, Bansal S, Das G and Singh KK: Cross talk between mitochondria and superoxide generating NADPH oxidase in breast and ovarian tumors. Cancer Biol Ther *4(12)*: 1367-1373, 2005.

35 Choudhary S, Sood S, Donnell RL and Wang HCR: Intervention of human breast cell carcinogenesis chronically induced by 2-amino-1- methyl-6-phenylimidazo[4,5-b]pyridine. Carcinogenesis *33(4)*: 876-885, 2012.

36 Boudreau HE, Casterline BW, Rada B, Korzeniowska A and Leto TL: Nox4 involvement in TGF-beta and SMAD3-driven induction of the epithelial-to-mesenchymal transition and migration of breast epithelial cells. Free Radical Biol Medicine *53*: 1489-1499, 2012.

37 Zhang B, Liu Z and Hu X: Inhibiting cancer metastasis *via* targeting NAPDH oxidase 4. BiochemPharmacol *86*: 253-266, 2013.

38 Antony S, Wu Y, Hewitt SM, Anver MR, Butcher D, Jiang G, Meitzler JL, Liu H, Juhasz A, Lu J, Roy KK and Doroshow JH: Characterization of NADPH oxidase 5 expression in human tumors and tumor cell lines with a novel mouse monoclonal antibody. Free Radical Biol Medicine *65*: 497-508, 2013.

39 Okoh V, Deoraj A and Roy D: Estrogen-induced reactive oxygen species-mediated signalings contribute to breast cancer. Biochimica et Biophysica Acta *1815*: 115-133, 2011.

40 Penney RB and Roy D: Thioredoxin-mediated redox regulation of resistance to endocrine therapy in breast cancer. Biochimica et Biophysica Acta *1836*: 60-79, 2013.

41 Kanchan RK, Tripathi C, Baghel KS, Dwivedi SK, Kumar B, Sanyal S, Sharma S, Mitra K, Garg V, Singh K, Sultana S, Tripathi RK, Rath SK and Bhadauria S: Estrogen receptor potentiates mTORC2 signaling in breast cancer cells by upregulating superoxide anions. Free Radical Biol Medicine *53*: 1929-1941, 2012.

42 Elangovan S, Ramachandran S, Venkatesan N, Ananth S, Gnana-Prakasam JP, Martin PM, Browning DD, Schoenlein PV, Prasad PD, Ganapathy V and Thangaraju M: SIRT1 is essential for oncogenic signaling by estrogen/estrogen receptor α in breast cancer. Cancer Res *17(21)*: 6654-6664, 2011.

43 Xiong Y, Manevich Y, Tew KD and Townsend DM: S-glutathionylation of protein disulfide isomerase regulates estrogen receptor α stability and function. Int J Cell Biol *2012*: 273549, 2012.

44 Ostrakhovitch EA: Redox environment and its meaning for breast cancer cells fate. Curr Cancer Drug Targ *11*: 479-495, 2011.

45 Vurusaner B, Poli G and Basaga H: Tumor suppressor genes and ROS: complex networks of interactions. Free Radical Biol Medicine *52*: 7-18, 2012.

46 Wickramasekera NT and Das GM: Tumor suppressor p53 and estrogen receptors in nuclear–mitochondrial communication. Mitochondrion, pii: S1567-7249(13)00253-5, 2013.

47 Matissek KJ, Mossalam M, Okal A and Lim CS: The DNA binding domain of p53 is sufficient to trigger a potent apoptotic response at the mitochondria. Mol Pharmaceutics *10*: 3592-3602, 2013.

48 Diers AR, Vayalil PK, Oliva CR, Griguer CE, Darley-Usmar V, Hurst DR, Welch DR and Landar A: Mitochondrial bioenergetics of metastatic breast cancer cells in response to dynamic changes in oxygen tension: effects of HIF-1a. PLoS ONE *8(6)*: e68348, 2013.

49 Cai Q, Lin T, Kamarajugadda S, Lu J: Regulation of glycolisis and the Warburg effect by estrogen-related receptors. Oncogene *32*: 2079-2086, 2013.

50 Cha Y, Kang Y, Moon A: HER2 induces expression of leptin in human breast epithelial cells. BMB Reports *45(12)*: 719-723, 2012.

51 Hall BA, Kim TY, Skor MN and Conzen SD: Serum and glucocorticoid-regulated kinase 1 (SGK1) activation in breast cancer: requirement for mTORC1 activity associates with ER-alpha expression. Breast Cancer Res Treat *135*: 469-479, 2012.

52 Park SA, Na HK and Surh YJ: Resveratrol suppresses 4-hydroxyestradiol-induced transformation of human breast epithelial cells by blocking I k B kinase b -NF-kB signaling. Free Radical Res *46(8)*: 1051-1057, 2012.

53 Qu Y, Wang J, Ray PS, Guo H, Huang J, Shin-Sim M, Bukoye BA, Liu B, Lee AV, Lin X, Huang P, Martens JW, Giuliano AE, Zhang N, Cheng NH and Cui X: Thioredoxin-like 2 regulates human cancer cell growth and metastasis *via* redox homeostasis and NF-κB signaling. J Clin Invest *121(1)*: 212-225, 2011.

54 Sohn YS, Tamir S, Song L, Michaeli D, Matouk I, Conlan AR, Harir Y, Holt SH, Shulaev V, Paddock ML, Hochberg A, Cabanchick IZ, Onuchic JN, Jennings PA, Nechushtai R and Ron Mittler R: NAF-1 and mitoNEET are central to human breast cancer proliferation by maintaining mitochondrial homeostasis and promoting tumor growth. PNAS *110(36)*: 14676-14681, 2013.

55 Puigserver P, Wu Z, Park CW, Graves R, Wright M and Spiegelman BM: A Cold-Inducible Coactivator of Nuclear Receptors Linked to Adaptive Thermogenesis. Cell *92*: 829-839, 1998.

56 Lin JC, Handschin C and Spiegelman BM: Metabolic control through the PGC-1 family of transcription coactivators. Cell Metab *1(6)*: 361-370, 2005.

57 Scarpulla RC: Nucleus-encoded regulators of mitochondrial function: Integration of respiratory chain expression, nutrient sensing and metabolic stress. Biochim Biophys Acta *1819*: 1088-1097, 2011.

58 Falconer C, Kenny PA, Smart CE, Monteith GR and Roberts-Thomson SJ: Peroxisome proliferator-activated receptor subtypes in mammary gland development and breast cancer. J Cancer Ther Res *1*: 14, 2012.

59 Jiang WG, Douglas-Jones A and Mansel RE: Expression of peroxisome-proliferator activated receptor-gamma (PPARgamma) and the PPARgamma co-activator, PGC-1, in human breast cancer correlates with clinical outcomes. Int J Cancer *106(5)*: 752-757, 2003.

60 Klimcakova E, Chénard V, McGuirk S, Germain D, Avizonis D, Muller WJ and St-Pierre J: PGC-1α promotes the growth of ErbB2/Neu-induced mammary tumors by regulating nutrient supply. Cancer Res *72(6)*: 1538-1546, 2012.

61 Vaughan RA, Garcia-Smith R, Dorsey J, Griffith JK, Bisoffi M and Trujillo KA: Tumor necrosis factor alpha induces Warburg-like metabolism and is reversed by anti-inflammatory curcumin in breast epithelial cells. Int J Cancer *133*: 2504-2510, 2013.

62 Carracedo A, Weiss D, Leliaert AK, Bhasin M, Boer VCJ, Laurent G, Adams AC, Sundvall M, Song SJ, Ito K, Finley LS, Egia A, Libermann T, Gerhart-Hines Z, Puigserver P, Haigis MC, Maratos-Flier E, Richardson AL, Schafer ZT and Pandolfi PP: A metabolic prosurvival role for PML in breast cancer. J Clin Invest *122(9)*: 3088-3100, 2012.

63 Chang CY, Kazmin D, Jasper JS, Kunder R, Zuercher WJ and McDonnell DP: The metabolic regulator ERRα, a downstream target of HER2/IGF-1R, as a therapeutic target in breast cancer. Cancer Cell *20(4)*: 500-510, 2011.

64 Eichner LJ, Perry MC, Dufour CR, Bertos N, Park M, St-Pierre J and Giguère V: miR-378(*) mediates metabolic shift in breast cancer cells *via* the PGC-1β/ERRγ transcriptional pathway. Cell Metab *12(4)*: 352-361, 2010.

65 Evans MD, Dizdaroglu M and Cooke MS: Oxidative DNA damage and disease: induction, repair and significance. Mutat Res *567(1)*: 1-61, 2004.

66 Imlay JA and Linn S: DNA damage and oxygen radical toxicity. Science *240(4857)*: 1302-1309, 1988.

67 Emerit I: Reactive oxygen species, chromosome mutation, and cancer: possible role of clastogenic factors in carcinogenesis. Free Radic Biol Med *16(1)*: 99-109, 1994.

68 Ziech D, Franco R, Pappa A and Panayiotidis MI: Reactive oxygen species (ROS)-induced genetic and epigenetic alterations in human carcinogenesis. Mutat Res *711(1-2)*: 167-173, 2011.

69 Wang D, Kreutzer DA and Essigmann JM: Mutagenicity and repair of oxidative DNA damage: insights from studies using defined lesions. Mutat Res *400(1-2)*: 99-115, 1998.

70 Milanowska K, Krwawicz J, Papaj G, Kosinski J, Poleszak K, Lesiak J, Osinska E, Rother K and Bujnicki JM: REPAIRtoire-a database of DNA repair pathways. Nucleic Acids Res *39(Database issue)*: D788-792, 2011.

71 Storr SJ, Woolston CM and Martin SG: Base excision repair, the redox environment and therapeutic implications. Curr Mol Pharmacol *5(1)*: 88-101, 2012.

72 Lindahl T: Keynote: Past, present, and future aspects of base excision repair. Prog Nucleic Acid Res Mol Biol *68*: xvii–xxx, 2011.

73 Brem R and Hall J: XRCC1 is required for DNA single-strand break repair in human cells. Nucleic Acids Res *33*: 2512-2520.

74 Hanahan D and Weinberg RA: Hallmarks of cancer: next generation. Cell *144*: 646-674, 2011.

75 Minoo P: Toward a Molecular Classification of Colorectal Cancer: The Role of MGMT. Front Oncol *3*: 266, 2013.

76 Mazzei F, Viel A and Bignami M: Role of MUTYH in human cancer. Mutat Res *743-744*: 33-43, 2013.

77 Arends MJ: Pathways of colorectal carcinogenesis. Appl Immunohistochem Mol Morphol *21(2)*: 97-102, 2013.

78 Lord CJ, Ashworth A: The DNA damage response and cancer therapy. Nature *481(7381)*: 287-942012.

79 Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bogden R, Dayananth

P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rosteck P, Lai M, Barret C, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnick MH: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science *266*: 66-71, 1994.

80 Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C and Micklem G: Identification of the breast cancer susceptibility gene BRCA2. Nature *378*: 789-792, 1995.

81 Kenemans P, Verstraeten RA and Verheijen RH: Oncogenic pathways in hereditary and sporadic breast cancer. Maturitas *49(1)*: 34-43, 2004.

82 Bishop JM: Oncogenes and proto-oncogenes. Hosp Pract *8*: 67-74, 1983.

83 Newmark: Oncogene discovery. Priority by press release. Nature *304(5922)*: 108, 1983.

84 Werts ED and Gould MN: Relationships between cellular superoxide dismutase and susceptibility to chemically induced cancer in the rat mammary gland. Carcinogenesis *7(7)*: 1197-201, 1986.

85 Punnonen K, Ahotupa M, Asaishi K, Hyöty M, Kudo R and Punnonen R: Antioxidant enzyme activities and oxidative stress in human breast cancer. J Cancer Res Clin Oncol *120(6)*: 374-377, 1994.

86 Musarrat J, Arezina-Wilson J and Wani AA: Prognostic and aetiological relevance of 8-hydroxyguanosine in human breast carcinogenesis. Eur J Cancer *32A(7)*: 1209-1214, 1996.

87 Mobley JA and Brueggemeier RW: Increasing the DNA damage threshold in breast cancer cells. Toxicol Appl Pharmacol *180(3)*: 219-226, 2002.

88 Malins DC, Anderson KM, Jaruga P, Ramsey CR, Gilman NK, Green VM, Rostad SW, Emerman JT and Dizdaroglu M: Oxidative changes in the DNA of stroma and epithelium from the female breast: potential implications for breast cancer. Cell Cycle *5(15)*: 1629-1632, 2006.

89 Feng JF, Lu L, Zeng P, Yang YH, Luo J, Yang YW and Wang D: Serum total oxidant/antioxidant status and trace element levels in breast cancer patients. Int J Clin Oncol *17(6)*: 575-583, 2012.

90 Afanas'ev I: Reactive oxygen species signaling in cancer: comparison with aging. Aging Dis *2(3)*: 219-230, 2011.

91 Baer HJ, Tworoger SS, Hankinson SE and Willett WC: Body fatness at young ages and risk of breast cancer throughout life. Am J Epidemiol *171*: 1183-1194, 2010.

92 Du F, Virtue A, Wang H and Yang XF: Metabolomic analyses for atherosclerosis, diabetes, and obesity. Biomark Res *1(1)*: 17, 2013.

93 McCormack D, Schneider J, McDonald D and McFadden D: The antiproliferative effects of pterostilbene on breast cancer *in vitro* are *via* inhibition of constitutive and leptin-induced janus kinase/signal transducer and activator of transcription activation. Am J Surg *202*: 541-544, 2011.

94 D'Esposito V, Passaretti F, Hammarstedt A, Liquoro D, Terracciano D, Molea G, Canta L, Miele C, Smith U, Bequinot F and Formisano P: Adipocyte-released insulin-like growth factor-1 is regulated by glucose and fatty acids and controls breast cancer cell growth *in vitro*. Diabetologia *55*: 2811-2822, 2012.

95 Hoeijmakers JH: DNA damage, aging, and cancer. N Engl J Med *361(15)*: 1475-1485, 2009.

96 Kasapović J, Pejić S, Todorović A, Stojiljković V and Pajović SB: Antioxidant status and lipid peroxidation in the blood of breast cancer patients of different ages. Cell Biochem Funct *26(6)*: 723-730, 2008.

97 Hossein R and Houshmand M: Diagnostic algorithm for identification of individuals with hereditary predisposition to breast cancer. Lik Sprava *1-2*: 103-108, 2008.

98 Kennedy RD and D'Andrea AD: The Fanconi Anemia/BRCA pathway: new faces in the crowd. Genes Dev *19(24)*: 2925-2940, 2005.

99 Shyamsunder P, Ganesh KS, Vidyasekar P, Mohan S and Verma RS: Identification of novel target genes involved in Indian Fanconi anemia patients using microarray. Gene *531(2)*: 444-450, 2013.

100 Lee JM, Ledermann JA and Kohn EC: PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies. Ann Oncol *00*: 1-9, 2013.

101 Alli E, Sharma VB, Sunderesakumar P and Ford JM: Defective repair of oxidative DNA damage in triple-negative breast cancer confers sensitivity to inhibition of poly(ADP-ribose) polymerase. Cancer Res *69(8)*: 3589-3596, 2009.

102 Pagano G, Talamanca AA, Castello G, d'Ischia M, Pallardó FV, Petrović S, Porto B, Tiano L and Zatterale A: From clinical description, to *in vitro* and animal studies, and backward to patients: oxidative stress and mitochondrial dysfunction in Fanconi anemia. Free Radic Biol Med *58*: 118-125, 2013.

103 Bhattacharyya N, Banerjee T, Patel U and Banerjee S: Impaired repair activity of a truncated DNA polymerase beta protein. Life Sci *69(3)*: 271-280, 2001.

104 Srivastava DK, Husain I, Arteaga CL and Wilson SH: DNA polymerase beta expression differences in selected human tumors and cell lines. Carcinogenesis *20(6)*: 1049-1054, 1999.

105 Trivedi RN, Wang XH, Jelezcova E, Goellner EM, Tang JB and Sobol RW: Human methyl purine DNA glycosylase and DNA polymerase beta expression collectively predict sensitivity to temozolomide. Mol Pharmacol *74(2)*: 505-516, 2008.

106 Luo M and Kelley MR: Inhibition of the human apurinic/apyrimidinic endonuclease (APE1) repair activity and sensitization of breast cancer cells to DNA alkylating agents with lucanthone. Anticancer Res *24(4)*: 2127-2134, 2004.

107 Mimnaugh EG, Dusre L, Atwell J and Myers CE: Differential oxygen radical susceptibility of adriamycin-sensitive and -resistant MCF-7 human breast tumor cells. Cancer Res *49(1)*: 8-15, 1989.

108 Zheng L, Yang F, Zhang X, Zhu J, Zhou P, Yu F, Hou L, Zhao G, He Q and Wang B: Investigation on XRCC1 genetic polymorphism and its relationship with breast cancer risk factors in Chinese women. Med Oncol *30(4)*: 738, 2013.

109 Al Mutairi FM, Alanazi M, Shalaby M, Alabdulkarim HA, Pathan AA and Parine NR: Association of XRCC1 gene polymorphisms with breast cancer susceptibility in Saudi patients. Asian Pac J Cancer Prev *14(6)*: 3809-3813, 2013.

110 Przybylowska-Sygut K, Stanczyk M, Kusinska R, Kordek R and Majsterek I: Association of the Arg194Trp and the Arg399Gln polymorphisms of the XRCC1 gene with risk occurrence and the response to adjuvant therapy among Polish women with breast cancer. Clin Breast Cancer *13(1)*: 61-68, 2013.

111 Liu L, Yuan P, Liu L, Wu C, Zhang X, Guo H, Zhong R, Xu Y, Wu J, Duan S, Rui R, Wu T, Nie S, Miao X and Lin D: A functional -77T>C polymorphism in XRCC1 is associated with risk of breast cancer. Breast Cancer Res Treat *125(2)*: 479-487, 2011.

112 Falagan-Lotsch P, Rodrigues MS, Esteves V, Vieira R, Amendola LC, Pagnoncelli D, Paixão JC and Gallo CV: XRCC1 gene polymorphisms in a population sample and in women with a family history of breast cancer from Rio de Janeiro (Brazil). Genet Mol Biol *32(2)*: 255-259, 2009.

113 Mitra AK, Singh N, Singh A, Garg VK, Agarwal A, Sharma M, Chaturvedi R and Rath SK: Association of polymorphisms in base excision repair genes with the risk of breast cancer: a case-control study in North Indian women. Oncol Res *17(3)*: 127-135, 2008.

114 Saadat M, Kohan L and Omidvari S: Genetic polymorphisms of XRCC1 (codon 399) and susceptibility to breast cancer in Iranian women, a case-control study. Breast Cancer Res Treat *111(3)*: 549-553, 2008.

115 Kim KY, Han W, Noh DY, Kang D and Kwack K: Impact of genetic polymorphisms in base excision repair genes on the risk of breast cancer in a Korean population. Gene *532(2)*: 192-196, 2013.

116 Sangrajrang S, Schmezer P, Burkholder I, Waas P, Boffetta P, Brennan P, Bartsch H, Wiangnon S and Popanda O: Polymorphisms in three base excision repair genes and breast cancer risk in Thai women. Breast Cancer Res Treat *111(2)*: 279-288, 2008.

117 Sliwinski T, Ziemba P, Morawiec Z, Kowalski M, Zadrozny M and Blasiak J: Polymorphisms of the DNA polymerase beta gene in breast cancer. Breast Cancer Res Treat *103(2)*: 161-166, 2007.

118 Kang H, Dai Z, Ma X, Ma L, Jin Y, Liu X and Wang X: A genetic variant in the promoter of APE1 gene (-656 T>G) is associated with breast cancer risk and progression in a Chinese population. Gene *531(1)*: 97-100, 2013.

119 Manello F, Tonti GAM, Qin W, Zhu W and Sauter ER: Do nipple aspirate fluid epithelial cells and their morphology predict breast cancer development? Breast Cancer Res Treat *102*: 125-127, 2007.

120 Manello F, Tonti GA and Canestrari F: Nutrients and nipple aspirate fluid composition: the breast microenvironment regulates protein expression and cancer aetiology? Genes Nutr *3*: 77-85, 2008.

121 Manello F, Tonti GA, Pagliarini S, Benedetti S, Canestrari F, Zhu W, Qin W and Sauter ER: The 8-epimer of prostaglandin F(2alpha), a marker of lipid peroxidation and oxidative stress, is decreased in the nipple aspirate fluid of women with breast cancer. Int J Cancer *120*: 1971-1976, 2007.

122 Manello F, Qin W, Zhu W, Fabbri L, Tonti GA and Sauter ER: Nipple aspirate fluids from women with breast cancer contain increased levels of group IIa secretory phospholipase A2. Breast Cancer Res Treat *111*: 209-218, 2008.

123 Niki E: Lipid peroxidation: physiological levels and dual biological effects. Free Radical Biol Medicine *47*: 469-484, 2009.

124 Manello F, Tonti GA, Pederzoli A, Simone P, Smaniotto A and Medda V: Detection of superoxide dismutase-1 in nipple aspirate fluids: a reactive oxygen species-regulating enzyme in the breast cancer environment. Clin Breast Cancer *10*: 238-245, 2010.

125 Manello F, Tonti GA, Simone P, Ligi D and Medda V: Iron-binding proteins and C-reactive protein in nipple aspirate fluids: role of iron-driven inflammation in breast cancer microenvironment? Am J Transl Res *3*: 110-113, 2011.

126 Manello F, Tonti GA, Medda V, Simone P and Darbre PD: Analysis of aluminum content and iron homeostasis in nipple aspirate fluids from healthy women and breast cancer-affected patients. J Appl Toxicol *31*: 262-269, 2011.

127 Panis C, Victorino VJ, Herrera ACSA, Freitas LF, De Rossi T, Campos FC, Colado Simão AN, Barbosa DS, Pinge-Filho P, Cecchini R and Cecchini AL: Differential oxidative status and immune characterization of the early and advanced stages of human breast cancer. Breast Cancer Res Treat *133*: 881-888, 2012.

128 Panis C, Pizzatti L, Herrera ACSA, Cecchini R and Abdelhay E: Putative circulating markers of the early and advanced stages of breast cancer identified by high-resolution label-free proteomics. Cancer Letters *330*: 57-66, 2013.

129 Herrera ACSA, Panis C, Victorino VJ, Campos FC, Colado Simão AN, Cecchini AL and Cecchini R: Molecular subtype is determinant on inflammatory status and immunological profile from invasive breast cancer patients. Cancer Immunol Immunother *61*: 2193-2201, 2012.

130 Victorino VJ, Campos FC, Herrera ACSA, Colado Simão AN, Cecchini AL, Panis C and Cecchini R: Overexpression of HER2/neu protein attenuates the oxidative systemic profile in women diagnosed with breast cancer. Tumor Biol, DOI 10.1007/s13277-013-1391-x, 2014.

131 Panis C, Herrera ACSA, Victorino VJ, Aranome AMF and Cecchini R: Screening of circulating TGF-β1 level and its clinicopathological significance in human breast cancer. Anticancer Res *33(2)*: 737-742, 2013.

132 Panis C, Herrera ACSA, Aranome AMF, Victorino VJ, Michelleti PL, Morimoto HK, Cecchini AL, Simão ANC and Cecchini R: Clinical insights from adiponectin analysis in breast cancer patients reveal its anti-inflammatory properties in non-obese women. Mol Cel Endocrinol *382*: 190-196, 2014.

133 Panis C, Herrera ACSA, Victorino VJ, Campos FC, Freitas LF, De Rossi T, Colado Simão AN, Cecchini AL and Cecchini R: Oxidative stress and hematological profiles of advanced breast cancer patients subjected to paclitaxel or doxorubicin chemotherapy. Breast Cancer Res Treat *133(1)*: 89-97, 2012.

134 Panis C, Lemos LGT, Victorino VJ, Herrera ACSA, Campos FC, Colado Simão AN, Pinge-Filho P, Cecchini AL and Cecchini R: Immunological effects of Taxol and Adryamicin in breast cancer patients. Cancer Immunol Immunother *61(4)*: 481-488, 2012.

135 Awasthi S, Sharma R, Singhal SS, Zimniak P and Awasthi Y: RLIP76, a novel transporter catalyzing ATP-dependent efflux of xenobiotics. Drug Met Disp *30(12)*: 1300-1310, 2002.

Received December 16, 2013
Revised January 10, 2014
Accepted January 14, 2014