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Review

A New and Integral Approach to the Etiopathogenesis and Treatment of Breast Cancer based upon its Hydrogen Ion Dynamics

Running title: pH-related breast cancer etiopathogenesis and treatment.

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Abstract: Despite all efforts, the treatment of breast cancer (BC) cannot be considered to be a success story. The advances in surgery, chemotherapy and radiotherapy have not been sufficient. Indeed, the accumulated experience clearly indicates that new perspectives and non-main stream approaches are needed to better characterize the etiopathogenesis and treatment of this disease. This contibution deals with how the new pH-centric anticancer paradigm plays a fundamental role in reaching a more integral understanding of the etiology, etiopathogenesis and treatment of this multifactorial disease. For the first time the armamentarium available for the treatment of the different types and phases of BC is approached here from a Unitarian perspective based upon the hydrogen ion dynamics of cancer. The wide-ranged pH-related molecular, biochemical and metabolic model is able to embrace most the fields and subfields of breast cancer pathology. This single and integrated approach allows to advance a unidirectional program to treatment. Further efforts in this line are likely to first improve the therapeutics of each subtype of this tumor, then every phase of the disease and finally every individual patient.

Keywords: pH and breast cancer; breast cancer etiology; breast cancer etiopathogenesis; breast cancer treatment; pH-centric anticancer paradigm; hydrogen ion dynamics of cancer; cancer proton reversal; MDR integral approach

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1. Introduction

According to IARC, breast cancer (BC) is the most common malignant tumor in humans and the secondary cause of mortality of cancer in women, just behind lung cancer [1]. BC-related morbidity is primarily due to a progressive metastatic process [2]. Many associated risk factors, either genetic, from *BRCA1* and *BRCA2* gene mutations, plus a wide array of other genetic derangements [3], and a multiplicity of environmental factors such as as age, obesity and estrogens, among many others [4] are involved in the onset of BC. In spite of significant advances in therapy, the overall results are not too successful up to the present time, especially in advanced disease [5,6]. This may indicate that a change towards a more comprehensive and perhaps radically different perspective is necessary in order to incorporate more rational and less toxic treatments, and at the same time foster a better understanding of this multifaceted disease. Looking for common mediating mechanisms to the wide array of apparently unrelated factors involved in the etiopathogenesis of BC, while at the same time searching for new therapeutic solutions, the new and all-comprehensive pH-related paradigm has increasingly grown during the last few years, notably after the realization that the intracellular/extracellular pH homeostasis and its deregulation are critical in the control of many cellular, both normal and pathological, microenvironmental processes [7].

The study of the abnormal hydrogen ion (H+) dynamics of cancer started almost five decades ago [8-12]. Since then, a rapid increase in the understanding of the deregulated H+ dynamics in cancer and the cancer-selective proton gradient reversal (CPR) has resulted in a new and increasingly outreaching paradigm, known as the pH-centric anticancer paradigm. This perspective embraces many different aspects of basic, preclinical and clinical oncology, all derived from this H+-related energetic concept that has allowed an intimate acid-base approach to malignancy. Nowadays the pH or H+- related model is already able to unite different fields of science, from the molecular biology to the biochemistry and the metabolism of cancer, having already reached up to the clinical aspects of cancer cells and tissues [13,14]. This perspective has rapidly extended to other different collateral areas of oncological research, incorporating within its range of possibilities some areas so far apart when approached by the old and reduccionist model, such as angiogenesis, environmental carcinogenesis and cancer immunology, and from the initiation and prevention of BC to its metastatic disease and even to the spontaneous regression of cancer [15-20]. In summary, this integral and all-comprehensive paradigm can embrace most, if not all, aspects of cancer and of breast cancer, from etiology and etiopathogenesis to treatment.

The cancer-selective abnormalities of intracellular alkalinization plus extracellular acidification of all types of solid tumors and leukemias (CPR), represents the mirror image of normality and at the same time an upside-down disruption and tip over from normal homeostasis and allostasis [21], normality being exactly the opposite: a more acidic media inside than outside non-cancerous cells [22,23]. As a consequence of the acid-base homeostatic and energetic failure of cellular hydrogen ion (H^+) dynamics, attempts to induce intracellular acidification using proton transport and pump inhibitors (PTIs and PPIs), as well as other intracellular acidifiers of different origins and natures (repurposed drugs), together with tumoral extracellular alkalinizers, has become a valuable therapeutic strategy in seelctive cancer treatment. In this vein, the wide-ranged applications and potential benefits of this approach to the therapeutics of solid tumors in general has been recently published in a full issue containing fourteen reviews addressing the different aspects of the new pH-centric anticancer paradigm [24]. In the same line, we recently published an original review

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dealing with the pH-related possibilities in the treatment of brain malignancies [25]. In order to uncover further pathophysiological and therapeutic applications of this post-traditional and non-main stream approach to cancer, the present basic to clinically-oriented and translational review will discuss the general foundations and integral perspective of the H+-related paradigm now addressed to the etiopathognesis and treatment of BC [21].

2. **Cancer as an acid-base disease**

During the last few years the H+ dynamics of cancer have helped to significantly increase the understanding of human malignant tumors. Nowadays it is well understood and agreed that all malignant cells and tissues have deep-seated evolutionary and thermodynamic pH-related advantages over all normal tissues. This characteristic allows neoplastic cells first to survive in the most hostile conditions, then to grow locally, later to invade neighboring tissues to finally disseminate out of control, overwhelming all the defensive barriers and immune defense mechanisms of the host, through the, so called, "neostrategy of cancer cells and tissues". These signifcant energetic and metabolic disruptions are based on a pathognomonic intracellular alkalinization of cancer cells and, secondarily, to an extracellular and intratumoral acidosis. Both coordinated phenomena are facilitated by overactive membrane-bound proton transporters (PT) and pumps (PP) extruding mechanisms, inducing an inversion of the normal cells/surrounding tissues pH gradient (pH_i to pH_e), or CPR, across cellular membranes. These deregulated pH dynamics determine the cancerous effects on normal cells and tissues, from early tumorigenesis and transformation to proliferation, local growth and a metastatic process that usually ends up with the death of the host. The metabolic reprogramming confers to cancer cells and tissues other important thermodynamic advantages, such as enhancing their resistance to hypoxia but also to cancer therapy. Finally, these dynamic chnges allow malignant cells and tissues to avoid the pro-apoptotic intracellular acidification (IA) that would normally result in a selective cancer cell death as the successful outcome of treatment.

As previously mentioned, the new acid-base approach to cancer has extended side-ways to the point that it can now integrate under its wide-ranged perspective most, if not all, areas of cancer research and treatment, namely:

a) pH and the Warburg effect [26-32].

b) pH abnormalities in the etiology and etiopathogenesis of BC and other tumors [21,33-38].

c) pH and cancer molecular biology, biochemistry and metabolism [31,39,40].

d) pH, proton transporters (PTs), proton pumps (PPs) and their inhibitors (PTIs and PPIs) [14,32,36,38,41-55].

e) pH and voltage gated sodium channels (VGSC) [56-61].

f) pH, tumor growth and invadopodia [61,63].

g) pH, cancer growth and the metastatic process [63-68].

h) pH and aquaporins [69-71].

i) pH and drug resistance (MDR) [72-86].

j) pH and environmental carcinogenesis [16,17].

k) pH and cancer immunity [19,20,62-64].

l) pH, nanodrugs and liposomes [65-70].

m) pH and apoptosis [21,71-74].

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n) pH and repurposed drugs in cancer treatment [21,75-77].
o) pH and photodynamic therapy in cancer [78,79].
p) pH and the spontaneous regression of cancer (SRC) [80-86].
q) pH, evolution and cancer metabolism [87-91].
r) pHi acidification and reverting cancer proton reversal (CPR) in cancer treatment [21,23,48,92].
s) pH and microenvironmental acidosis in cancer growth and dissemination [21,22,93-97].

3. All phases of breast cancer are weaved into each other to conform a single, all-comprehensive and progressive, Unitarian multistage.

All the above mentioned oncological fields and subfields have in common a pivotal characteristic: namely, the aberrant pHi/pHe regulation of hydrogen (H^+) ion dynamics [98], an abnormality that it cannot be more opposed to the acid-base normality of non-cancerous cells and tissues. In a recent publication on brain malignancies, a large myriad of known etiological and etiopathogenic factors from many different natures and origins, all known to cause different human malignancies, have been considered [21,25]. Importantly, all the carcinogenic factors listed in that review, but also in other previous reports of this group, act via a universal mediating mechanism, namely, an increase of cell pH scoondary to the stimulation of the activity of NHE and/or other H^+-related membrane-bound PTs and PPIs (Figure 1).

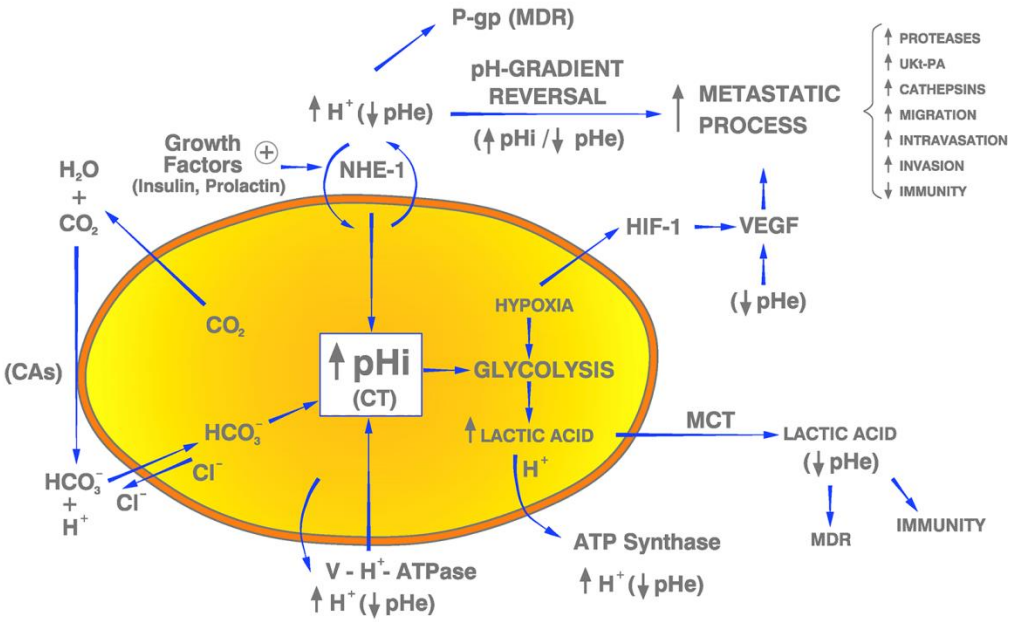

Figure 1. PTs and PPs involved in the carcinogenicity of breast cancer and other malignant tumors. pHi: intracellular pH; CT: cell transformation; pHe: extracellular pH; PTs: proton transporters; PPs: Proton pumps; NHE-1: Na+/H+ antiporter; H^+; hydrogen ion, CAs: carbonic anhydrases; MCT: monocarboxylate transporters: P-gp: P-glycoprotein; V-H+: Vacuolar ATPase; MDR: Multiple drug resistance.

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The nature and evolution of cancer and breast cancer progression allows to accept that the deep-seated pH deregulations and/or highly disrupted H^+-dynamics of malignancy are a fundamental factor behind a predetermined, progressive and staggered strategy of cancer growth and dissemination ("the selective neostrategy of cancer cells and tissues"). This process starts with cell transformation and is closely followed by local growth and invasion under a highly hostile acid-base tumor microenvironment (TME). These initial phases ae followed by neoangiogenesis, which favors metastatic dissemination and drug resistance. Each one of all these closely interrelated periods of the natural evolution of cancer is not separated at all from the previous or later ones, but conform a Unitarian and dynamically active process that can even be considered a preprogrammed strategy. In spite of this, the understanding posed by the pH-anticancer perspective has the potential to offer the possibility of applying therapeutic methods in a unique direction and in all the phases of the malignant process, either in BC or in other solid tumors, in order to interfere with each and all cancer hallmarks using different procedures synergically acting in the same direction, from prevention to the treatment of advanced disease.

4. pH/NHE, microenvironmental acidosis and immunity, insulin, prolactin, estrogens, genetic abnormalities and growth factors in promoting breast cancer.

4.1) pH/NHE, H^+ extrusion and/or intracellular alkalization in the etiology and etiopathogenesis of breast cancer.

In addition to NHE overexpression, H+ extrusion from cells can also be mediated by a cohort of other membrane-bound proton transporters, pumps and ion channels [14,21]. On one hand, these actors participate in keeping pHi normal to elevated, so preventing low pHi-mediated apoptosis. Such factors are carbonic anhydrases (CAs), mainly CAIX and CAXII, vacuolar H^+-ATPase proton pumps, voltage gated sodium channels, sodium bicarbonate cotransporters, monocarboxylate transporters (MCTs), $Cl^-/HCO3^-$ exchangers and ATP-Synthase [14,99]. Different types of acid extruders like NHE1, NBCn1 and MCT4 are expressed in human mammary tumors, promoting growth of at least triple negative BC (TNBC) through synergistic and different mechanisms of action [41]. Paradoxically, the Na^+/H^+ exchanger regulatory factor 1 (NHERF1) presents a dual activity, either oncosuppressant or pro oncogenic in invasive BC, depending of the cellular location of its activity [100]. Also, NHE1 and NBCn1 drive cell cycle progression in human BC cells, while their knocking down reduces proliferation and progression [55]. TME acidosis is also associated to pain in bone metastasis in BC [101]. Importantly, although one or more of these H^+-extrusion systems substanciallly applies to all malignancies, a complete selective mapping of which PTs and PPs are overexpressed in each particular tumor is unfortunately still missing.

4.2) A universal mechanism as the possible final mediating cause of breast cancer.

It has been recently demonstrated that H^+ efflux alone is sufficient to induce dysplasia and potentiate growth and invasion by oncogenic Ras. Furthermore, it has been shown that inhibiting H^+ efflux induced cell death in invasive primary tumor mammary cells [34]. In the same line, most striking results have been obtained by the group of Fliegel, showing that NHE-mediated H^+

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extrusion has a carcinogenic effect by itself on breast cells [36]. The same alteration also plays a fundamental role in the metastatic process and in multiple drug resistance (MDR) [37,38,102,103]. In these studies, NHE1 hyperactivity and/or a high pHi act as an early and decisive driver in BC carcinogenesis and also in most, if not all, other human malignancies [33,104]. Moreover, the elevated pHi is also the main responsible actor for the secondary acidification of the extracellular/intratumoral microenvironment (TME). Importantly, H+ extrusion alone has been implicated in the transition and progression from precancerous ductal carcinoma *in situ* to invasive BC. Of note, the precancerous lesion already shows a higher than normal proton export rate [36,38,102]. Indeed, the invasive BC cells show a higher pHi and a higher production and exportation of H^+ into the TME than noninvasive cells [36,97,105]. (Table 1).

Mechanisms	Summary	References
H+ extrusion and/or elevated pHi	H+ extrusion from cells is sufficient to induce transformation, growth and invasion in BC and other tumors. NHE-mediated H^+ extrusion by itself has a carcinogenic effect on breast cells and increases MDR.	[21,23,25,33-38,44,52,72 ,92,99,102,105-109]
Tumor microenviromental (TME) acidosis, immunity and MDR	Acidity of the TME disrupts the body immune defense mechanisms towards malignant tumors, locally and systemically. This allows a relentless and uncontrolled tumor progression. TME also has an essential role in the progression of inflammatory BC. Thus, TME is a novel therapeutic target in breast cancer.	[19,20,22,62-64,90,93-95, 101,110-124]
Insulin (INS) and IGF-1	INS and INS-resistance have a direct effect in raising pHi and are associated to breast cancer carcinogenisity and progression. Over-expression of insulin/insulin-like growth factor-1 is associated with a decrease in the life span of women with BC.	[31,35,125-133]
Prolactin (PRL)	PRL stimulates growth, motility and invasiveness of BC cells through NHE1 activation, in this way contributing to the metastatic process of human BC, so becoming another therapeutic target.	[134-137]
Estrogens	Estrogens play a crucial role in breast tumorigenesis by promoting cell proliferation and decreasing apoptosis. ER- cells are considered to have a higher expression of NHE activity and are preferably associated to CA-IX over CA-XII. Inhibition of CA-IX improves the prognosis of the disease.	[4,138-142]

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Ion channels	NaV1.5-Na^+channels associate with NHE-1 to be overexpressed in BC, stimulating the formation of invadopodia, so facilitating local growth and the metastatic process.	[21,56,57,59-61,143-145]
PTs, PPs, and Growth factors	NHE1-overexpression is stimulated by a myriad of factors, which, either alone or in combination, induce a carcinogenic elevation of pHi as the oncogenic response of cells of many different origins and locations. Carbonic anhydrases (CAs) also have an important role in the pathogenesis of BC, mainly in hypoxic conditions. NHE1 levels are significantly higher in BC tissue than in adjacent normal tissue, and also in resistant BC cells when compared to sensitive cells.	[21,25,37,41,46-50,52,55 ,73,108,146,147]

Table 1: pH-related and unrelated mechanisms in the etiopathogenesis and progression of breast cancer. TME: Tumor microenvironment; NHE: Na+/H+ antiporter: CAs: Carbonic anhydrases; ER+: Estrogen positive cells; ER-: E·strogen negative cells; PTIs: Proton transport inhibitors; PPIs; Proton pump inhibitors.

4.3) Tumor microenvironmental (TME) acidosis and immunity.

There is a direct effect of tumor interstitial acidosis in hindering the antitumor immune response of the organism, another negative effect of the CPR. A complete review of the mechanisms by which tumor acidity disrupts the body immune defenses, locally and systemically, have been published by Huber et al. [19] (Table 1). These authors have shown how the acidity of the TME disrupts the immune defense mechanisms against malignant tumors, locally and systemically (Figure 1), allowing a relentless and uncontrolled tumor progression. Similar conclusions have been reached by other groups, relating aerobic glycolysis and lactic acid production with tumor invasion and even with drug resistance [110]. For all these reasons, the TME has been targeted by different methods in order to decrease, control and, if at all possible, revert, tumoral extracellular acidity both in animals and humans with different malignant tumors. To this end, dietary lipids, PPIs or large daily amounts of sodium bicarbonate or other buffers have been used [95,148], occasionally with good results. These positive and antimetastatic effects are secondary to the fact that acidity blocks T-cell activation and impairs tumor immunity [62]. Therapeutically-wise, controlling TME acidity corrects T-cell dysfunction and allows to improve the efficacy of many other T-cell-based anticancer treatments [20,111,113]. A similar situation arises in lymph nodes, where activated T-cells are inhibited by acidosis [63].

Most importantly, seminal research in this area by Marches et al. demonstrated that the anti-IgM-mediated induction of cell death in human B lymphoma cells is dependent on NHE1 inhibition and subsequent intracellular acidification. These seminal findings do not appear to have been properly followed, in spite that represent a synthesis of three different fields of oncology research: biochemistry, molecular biology and cancer immunity under one wide-ranged embracing unit [64].

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4.4) Insulin (INS) and breast cancer.

After all the experience accumulated on the carcinogenic effects of Na^+/H^+ overstimulation and/or an elevated pHi, it can be concluded that any factor that up-regulate this antiporter may have a carcinogenic activity on its target cells (Table 1). Insulin (INS), through its stimulating effects on glycolysis, is one of these metabolic factors [31,131]**.** INS presents a direct effect in raising pHi, which is probably related to its known tumor-stimulating properties [130]. This is reasonable since hyperinsulinemia and obesity have been associated with an increased incidence of BC [125,126] (Table 1).

Cancer cells are also associated with INS insensitivity (resistance), due to high oxidative stress, especially during malignant transformation, and this could be an earlier event of carcinogenesis [127]. Recently published data show that behind the effect of INS on resistance appears to be an abnormality of the pH/NHE-1 signaling pathway [128] with NHE-1 over-expression as the first known key event of transformation in carcinogenesis [23]. Moreover, microenvironmental acidification and even systemic metabolic acidosis in cancer are linked with INS resistance [149,150], both phenomena being a reflection of the metabolic complications of cancer, the latter in advanced and disseminated disease [151-153]**.** For these reasons, some antidiabetic drugs like sulfonylureas, known to act by stimulating the pancreatic secretion of insulin, may have a negative impact on cancer growth [154-157]. In contrast, other antidiabetic agents, like Rosiglitazone and Metformin, show promising anticancer properties as INS-sensitizing agents [158,159] (Table 2). From a clinical perspective, it has also been shown that over-expression of INS/INS-like growth factor-1 gene is associated with a decrease in the life span of women with BC, while their deletion improves life span and may also decrease tumorigenesis [129,132,133]. Finally, recently published data have shown that insulin resistance might be a secondary effect of an abnormal NHE-1 signaling pathway [128] (Table 1).

4.5) Prolactin and breast cancer.

The role of prolactin (PRL) in the pathogenesis and progression of human BC is generally accepted [135]. Through NHE1 activation, this hormone stimulates growth, motility and invasiveness of BC, and in this way contributes to the progression of the disease in a similar fashion that estrogens do [99,134] (Table1). From a therapeutic perspective, we agree with these authors that, only considering this effect of PRL, NHE-1 inhibitors could play both a preventive, therapeutic and adjuvant role in the treatment of BC, as it has already been suggested for other tumors [21].
Furthermore, there seems to exist a pro tumoral and synergistic interaction between PRL and growth hormone (hGH) in stimulating the growth of certain tumors, BC among them [136]. In this vein, Clevenger et al. have advanced that antagonists of PRL/PRL receptor interaction can be useful in the treatment of human BC, either alone or in combination with traditional antiestrogenic agents like tamoxifen, letrozole, etc. [135]. For all these reasons PRL inhibitors like bromocriptine, should be taken into account as part of the armamentarium of repurposed drugs in BC therapy, even as a drug sensitizer (see section on repurposed drugs) [137].

4.6) Estrogens and breast cancer.

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Human BC is an heterogeneous disease classified in three major subtypes based on the expression of estrogen and progesterone receptors and human epidermal growth factor receptor-2 [160,161]. Among these BC subtypes, triple-negative BC results in a higher risk of metastatic dissemination and early death (Table 1).

Estrogens frequently plays a crucial role in breast tumorigenesis by promoting cellular proliferation and decreasing apoptosis [138]. Interestingly, a recent study discussed why tumor express ER+ and not ER- [139]. One of the suggested explanations was that while ER+ tumor cells are highly vascularized, ER- cells are better characterized by a higher expression of:

a) NHE1 activity.

b) Higher Hypoxia-inducible Factor activity (HIF).

c) Carbonic Anhydrases (CAs): CA-XII) expression relies on estradiol activity [140]. Therefore, ER+ is more likely to be associated with CA-XII rather than with CA-IX, while CA-IX is more frequently associated with ER- rather than with ER+ cells [141]. It had been shown that a selective inhibition of CA-XII, improves the prognosis of the disease [142]. Although estrogens are growth factors, their effects or relations with the H+ dynamics of BC cells have not been well established, apart from the fact that ER- BC cells seem associated with NHE1 activity [145] (Table 1).

4.7) Ion Channels.

It has been previously shown that ion channels are an important factor in the etiopathogenesis of cancer and neurodegenerative diseases, both pathologies staying at opposite ends of a pH-related metabolic spectrum [21]. It is also been demonstrated that NaV1.5-Na+ channels are in a close and direct association with NHE-1, both being overexpressed in BC, where they contribute together to degrade the tumoral microenvironment, stimulate the formation of invadopodia and foster the metastatic process in a similar manner that CPR does [58-60,106,144] (Table 1). Furthermore, ion channels are activated at low microenvironmental tumor pH in BC and other tumors, thus promoting cell proliferation and migration. In this context, ion channels became relevant therapeutic targets [143].

4.8) PTIs, PPIs and Growth factors.

NHE1-overexpression is stimulated by a myriad of factors, all of which induce a pathological and carcinogenic elevation of pHi as a response in cells of many different origins and locations [25] (Table 1). Hence, the possibility of a cause-effect relationship between *BRCA1* and *BRCA2* genetic mutations in BC and pH/NHE1 and/or other PTs upregulation has been recently pointed out by these authors. Among hormones, growth factors and cytokines that have been shown to be pro-tumoral, either in BC or in other solid tumors, are estrogens, human growth hormone (hGH), prolactin, insulin, EGF and its receptor, VEGF, PDGF, certain interleukins and sex steroids, some of which up-regulate NHE1 (Figure 1) [21]. To this already extensive list, PPs should be added, as well as certain oncogenes, virus and gene products such as Bcl-2 [108], a dysfunctional p53 and many chemical products known to play a role in carcionogenesis [71,73]. Other carcinogenic NHE-related factors are chronic hypoxia and hypoxia inducible factor (HIFα) [146], even high glucose loads stimulate Na+/H+ activity [147]. It can be concluded that if so many unrelated etiopathogenic factors

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of so many different natures and origins are known to be carcinogenic, the up-regulation of any of of them or several ones in a synergistic combination with other stimulators in the same direction, indicates that the pHi/pHe abnormalities so induced may exert their effect through the same acid-base intracellular (IC)/extracellular (EC) deregulated dynamics, which suggests the existence of a universality of phenomenon involved in human carcinogenesis and etiopathogenesis, BC being no exception to this rule [25].

4.9) NHE1-related genetics of breast cancer.

The Na+/H+ exchanger isoform 1 (NHE1) is nowadays recognized as one of the most important factors involved in BC etiology and etiopathogenesis [34,36-38,102]. NHE1 has been found to be produced from the *APNH* gene located on chromosome 1p35-36, whose deletion has been blamed to be involved in the development of different tumors, BC among them [162]. Also, other genes have been described to have a role in the genetic abnormalities behind BC metastasis [3]. These authors have screened 4,200 target genes and discovered 133 and 113 migratory modulators of Hs578T and MDA-MB-231 cells, which are predictive of BC progression and bad prognosis. Other genetic mutations, like *BRCA1* and *BRCA2*, are known to be strongly associated with familial breast and ovarian cancers [163]. The possibility that these two genetic abnormalities can be dependent on NHE1 hyperactivity has been recently proposed, however no factual evidence is available at the present time that can ascertain such cause-effect relationship at the present time [25]. Finally, other pathways known to be involved in the pathogenesis of BC seem to act via different mechanisms and linked to other genes [164]. It is important to realize, as we have previously advanced, that genetic aberrations, in order to exert their role on cellular metabolism, have to do it through the mediation of the microenvironmental changes they secondarily induce, and not directly on their own [165].

Most importantly, there is no formal proof of a relationship between H+-dynamics and *BRCA1* and *BRCA2* genetic abnormalities in BC. In the same line, it is most surprising the total lack of information on inflammatory breast cancer (IBC) and its PTs, PPs and H+-dynamics. In spite of the known importance of TME in this aggressive form of BC, the few reviews available on TME in IBC completely ignore these more than possible relationships [166].

5) Hydrogen ion dynamics in multiple drug resistance (MDR) in breast cancer and other malignant tumors: an integral approach to its etiopathogenesis.

Resistance of BC cells to drugs like doxorubicin (DOXO) and paclitaxel (MDR) depends on pH regulation [109,167,168] (Table 2). DOXO resistance is related to a progressive increase of pHi, and could be suppressed by the addition of a P-glycoprotein inhibitors like verapamil [169]. These findings, apart from showing the close relationship of P-gp and pHi, has allowed to conclude that P-gp behaves as a proton (H^+) extrusion pump [116].

Levels of the proton transporter (PT) NHE1 are significantly higher in BC and in resistant cancer cells when compared to adjacent normal tissues and sensitive cells [155]. A proton transport inhibitor (PTI), like cariporide (CP, HOE-642), induces apoptosis in MCF-7/ADR cells *in vitro and in vivo* and is associated with the intracellular accumulation of DOXO and G0/G1 cell cycle arrest. CP also improves tumor growth attenuation and diminishes tumor volume. This strongly suggests that NHE1 should be a promising adjuvant therapeutic target, not only in BC, but also in a wide array of

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other malignant tumors [170]. Other PTs, like the HCO_3^--cotransporter NBCn1 (Slc4a7), show similar effects [43]. Finally, the association of PTIs with proton pumps inhibitors (PPIs) of the omeprazole family offers the possibility of further improving the effects of chemotherapy in metastatic BC [171], as well as in other malignant tumors [172]. Bringing all these findings together, it can be concluded that the association of PTIs and PPIs can have a synergistic effect in overcoming MDR in BC, apart from having a strong antitumoral effect on their own, from prevention to the treatment of advanced disease.

6) pH-related armamentarium in the treatment of breast cancer.

6.1) NHE Inhibitors and/or intracellular acidifiers.

A fundamental therapeutic aim of the pH-related anticancer paradigm is directed to the concerted inhibition of NHE1 and other PTs and PPis in order to induce a progressively deep intracellular acidification (IA), which first would decrease glycolysis, then lead to tumor cell growth arrest, and finally induce selective apoptosis [173-175]. Amiloride (AM) was the first Na^+/H^+ antiporter introduced in medical oncology. AM is a weak and non-specific Na^+/H^+ antiporter inhibitor and still is commercially available as a diuretic (Table 2).

Drug	Summary	References
Amiloride (AM) (and/or liposomal amiloride, proton transport inhibitors (PTIs) and intracellular (IC) acidifiers	AM is a non-specific NHE inhibitor first introduced for human use as a K+ sparing diuretic. It works as antiangiogenic and has proved to be most effective as antimetastatic in transplanted animal tumors. A positive clinical experience in an occasional patient has been reported with its chronic use. The many anti-cancer effects of AM have been fully described. However, its utilization has not entered clinical trials in bedside oncology. (For further details, see text)	[15,21,25,28,45,48,49,52-54,64,73,75,84,97,98,106,113,148,155,162,167,170,172,173,176-186]
Proton pump inhibitors (PPI) and TME alkalization	PPI are useful in the prevention and in overcoming of BC. The clinical utilization of V-ATPase inhibitors is a novel therapeutic measure to counteract the abnormal proton dynamics of BC and other tumors. PPI also benefit from the microenvironmental acidity of tumors. Preclinical and clinical studies also support a direct anti-tumor effect of PPI in BC and other different solid tumors.	[22,52,62,93,95,112,114,171,172,187-199]
Monocarboxylate transport (MCT) inhibitors	Quercetin is a pan-monocarboxylate transporter (MCT) inhibitor and intracellular acidifier. Liposomal quercetin is also available, since gastrointestinal absorption is very limited in the non-liposomal drug form.	[75-77,123,200-202]

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Acetazolamide (AZM)	AZM is a carbonic anhydrase (CA) pan-inhibitor and cell acidifier. CAIX inhibition significantly reduces invasion of BC cells and represents a most promising drug in the treatment of BC, alone or in combination with different NHE inhibitors.	[48, 50,142,186,203-205]
Doxorrubicin (DOXO)	There is a progressive increase in resistance to DOXO by increasing elevations of pHi that is annulled by P-gp inhibitors, while P-gp increases pHi. MDR is characterized by a reversal of the pH gradient (CPR) across cell membranes (cancer proton reversal)	[21,25,75,167-169,182,211]
Paclitaxel	The inhibition of NHE1 is fundamental in the chemotherapy of triple-negative BC metastasis, improving the efficacy of paclitaxel. NHE1 inhibition is fundamental in mediating in paclitaxel-induced apoptosis in BC cells.	[36,38,103,167,183,208,212-214]
Antiestrogens	ER-cells are considered to have a higher expression of NHE activity and are preferably associated to CA-IX over CA-XII. Inhibition of CA-IX improves the prognosis of the disease. The role of Tamoxifen and Letrozole is well established, but no further connections among pH dynamics and antoestrogens have been described.	[4,5,138-142,145,215]
Melatonin (MT)	MT has an antiestrogenic effect and for this reason it should be contemplated in BC therapy. Treatment with MT modulates tumor aggressiveness and increases apoptosis BC cell lines. MT also suppresses tumor aerobic metabolism (the Warburg effect).	[216-226]
Cariporide (CP)	CP (Hoe-642) is a powerful NHE1 inhibitor that, unfortunately, is not available for clinical use in bedside oncology. It induces apoptotic cells death in different malignant tumors.	[21,25,31,170]
Compound 9t (C9t) (Clinically unavailable)	C9t is 500-fold more potent against NHE1 than CP and has a 1400-fold greater selectivity for NHE1 over NHE2. C9t is orally bioavailable, has low side-effects in mice and it presents a significantly improved safety profile over other NHE1inhibitors.	[21,31,181]
Phx-3	Phx-3 is a potent, selective and non-toxic NHE1 inhibitor that triggers apoptosis in a variety of cancer cell lines and is highly effective in some animal tumor models	[21,28,185]

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Repurposed drugs	Phloretin, Lonidamine, Niclosamide Docosaexaenoic acid, Salinomycin and Simvastatin have been reported to be useful in the treatment of BC. Resveratrol has a role as an aromatase inhibitor. (For further details, see text).	[21,77,227-235]
Metformin (MET)	MET has been introduced as an anticancer agent in BC and also induces intracellular hyperacidification in tumor xenograft models. MET has been reported to inhibit insulin and insulin/IGF-1, HIF-1α, Warburg metabolism, gene expression, angiogenesis, cancer migration, invasion and metastasis, apart from reducing the side effects of DOXO. MET has also been reported to act synergistically with chemotherapy and decrease its dosages. It has also been used to target resistant cells in BC and has also been considered to work as a radio-sensitizer.	[236-256]

Table 2. pH-related drugs with present and potential benefit in the treatment of breast cancer.

BC: Breast cancer; NHE: Na+/H+ antiporter; MDR: Multiple drug resistance; P-gp: P-glycoprotein; CAs: Carbonic anhydrases; ER+: Estrogen positive cells; ER-: Estrogen negative cells; PTIs: Proton transport inhibitors; PPIs; Proton pump inhibitors. TME: tumor microenvironment.

Seminal research with AM completely inhibited lung metastases in models of animal tumors. Such an effect was initially reported to be secondary to its inhibitory effects on urokinase-type plasminogen activator (UPa) [180]. AM has clearly shown antitumoral, antiangiogenic and antimetastatic effects [257]. It has been shown that when decreasing pHi values with AM , VEGF mRNA expression is inhibited, at least in gastric and leukemic cells [16,177]. AM completely suppresses pulmonary metastases in rat tunors [178]. The antimetastatic effects of AM in tumor models have been known for a long time [180], while an occasional patient with advanced cancer has benefited for its chronic utilization after mainstream chemotherapy had failed [176]. Finally, for a review on the positive effects of AM on basic cell behavior, see [98] (Table 2).

Among the more modern, potent and selective NHE1 inhibitors, cariporide (CP, HOE-642) induces apoptosis through lowering pHi enough to induce apoptosis [179]. CP also decreases angiogenesis and induces selective apoptosis through Na+/H+ exchanger inhibition [170]. Furthermore, CP induces apoptosis by overcoming paclitaxel resistance through NHE inhibition [183], and works synergistically with erlotinib in reducing metastasis in pancreatic cancer [214]. More potent NHE1 inhibitor than CP is the so called "Compound 9t" (C9t). C9t is five hundred times more potent against NHE1 than cariporide apart from having a 1400-fold greater selectivity for NHE1 over NHE2 [181]. Similarly, Phx-3, is a non-toxic NHE1 inhibitor that induces tumor growth regression after leukemic cell transplantation, inducing selective apoptosis through intracellular acidification [28,185]. Finally, all the data available indicates that these new and selective NHE1 inhibitors have a great potential to become potent anticancer agents in patients with different pathologies [170]. Also, after considering all the evidence and data available thorugh the years, it is difficult to understand why AM itself has not managed to find a place in bedside oncology, mainly

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in BC treatment, either as a preventive measure, as a complement of orthodox chemotherapy and/or as an antimetastatic factor. There can be two reasons for this: a) AM is not patentable, and b) In all areas of scientific research and medical life, sometimes the answers that are looked for in the future are waiting hiding in the past (Table 2).

6.2) Proton pumps (PP) and their inhibitors (PPI) in breast cancer.

Over-expression of proton pumps (PP) V-ATPase promotes growth advantages to cancer cells of any origin, further disrupting pH homeostasis [258]. Different publications have enlightened the crucial role of V-ATPase in tumor invasion and chemoresistance in several cancers, including BC. Therefore, as it happens with PTI inhibition, PPI inhibition of V-ATPases has recently become a novel therapeutic avenue for thwarting the highly abnormal H+ dynamics in BC, but also in tumors of other origins and locations [14,93,197] (Table 2). Furthermore, unlike other anticancer compounds, an advantageous property of PPIs is that in order to be activated they benefit from the acidic microenvironment of tumors, therefore possibly increasing tumor selectivity. In this line, pretreatment with PPI strongly enhances the *in vitro* efficacy of chemotherapeutic drugs against human BC cells and other tumors [172,191,198,259,260]. Niikura showed that oral administration of a V-ATPase inhibitor to SCID mice carrying orthotropic BC xenografts resulted in delayed tumor growth and a decrease in bone metastasis [192]. Another *in vitro* report has shown the therapeutic effectiveness of PPI in triple negative BC cell lines [54]. Finally, different preclinical studies support a clear direct anti-tumor effect of PPI independently from cancer histology [193-195,261].

Two studies have been conducted in pets with spontaneous neoplasms using PPis in combination with standard chemotherapy. The first one evaluated the ability of high dose lansoprazole to reverse chemoresistance in dogs and cats with cancers not responding to chemotherapy. In this study, the drug was used off-label with a three day loading dosage of 5 mg/kg followed by a four day maintenance regimen at 1 mg/kg as a chemosensitizer combined with standard veterinary chemotherapy protocols), the results showing a reversal of chemoresistance in 23 out of 34 treated animals (67% response rate) (Table 2). A further study combined PPI with water alkalization and metronomic chemotherapy [187]. The cohort receiving alkalization showed enhanced tumor response, both in terms of the number of responders and the quality of response, when compared to the group receiving metronomic chemotherapy alone.

The application of this strategy to humans has led to the publication of two clinical trials. These studies evaluated the tolerability and effectiveness of high-dose PPI in patients with osteosarcoma or metastatic BC [171,199]. One of these studies showed that the addition of PPI to chemotherapy increased the effectiveness of chemotherapy in osteosarcoma patients. The second trial recruited women with metastatic BC that were randomized to receive either conventional chemotherapy or chemotherapy with alkalization [171]. In the latter study, patients receiving high dosage PPI obtained the highest response rates and the longest survivals. Furthermore, there is a statistically significant survival advantage for women who continued their PPI therapy after the completion of chemotherapy [259]. This *in vivo* data are also supported by *in vitro* investigations showing the effectiveness of PPI in triple negative BC cell lines [54].

An indirect confirmation of the validity of PPI and alkaline therapy as antitumor agents was provided by a published meta-analysis in head and neck tumor patients that found a better outcome for patients receiving PPI [262]. A more recent study describes the outcome of three patients with metastatic colorectal cancer who were refractory to standard chemotherapy and

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targeted therapies. The combination of high-dose rabeprazole (a PPI inhibitor) and metronomic capecitabine overcame drug resistance [263]. Despite of the very small number of patients studied, the association of rabeprazole and capecitabine resulted in long-lasting stable disease with good quality of life and relatively minor side effects. More recent reports have shown that women affected by medical conditions suitable for PPI treatment, e.g. peptic diseases, have a reduced risk for developing BC [52,197]. Both studies were performed in a very large cohort of patients with very convincing results. The data also shows that the beneficial effects of PPI use increases with age, the BC risk being reduced to a greater extent in older PPI users, getting to 83.0% in the 50- to 64-years old cohort. Of course, these data are of particular importance in women with a higher risk of developing BC, like those with a family history of BC, as well as women treated with long term hormone replacement therapy during and after menopause. These studies support the results obtained in women with metastatic BC, particularly those with triple negative BC when exclusively treated with high dosage PPI, while intermittent high dose PPI also enhances the antitumor effects of chemotherapy in metastatic BC [171]. The evidence that the use of PPIs in women with gastric ulcer or peptic disease was associated with a reduced risk of BC acquires a paramount importance. Three more articles recently suggested to reconsider the use of PPIs in cancer therapy [189,264,265]. Their conclusions are highly convincing and important for the treatment of a disease that is becoming an increasing killer worldwide.

Finally, since PPI are prodrugs requiring activation in the acidic microenvironment of solid tumors they appear particularly suitable to be used as anticancer drugs in the always acidic or very acidic tumor microenvironment [22], this obviously being the case of BC as well. Moreover, while it is not entirely scientifically supported, it appears conceivable that PPI may affect the body pH by buffering the stomach, that is their main target [188].

6.3) Melatonin (MT) in breast cancer.

Melatonin (MT) has been shown to function as an antiestrogenic agent, and only for this reason should be considered for BC treatment [217,221] (Table 2). Sonehara et al., have shown that treatment with MT modulates tumor aggressiveness, increasing apoptosis under microenvironmental acidosis in BC cell lines [222]. Importantly, MT has shown to be a significant antiangiogenic agent by downregulating VEGF expression in human BC cells [216,223]. Previous studies have also indicated that MT suppresses tumor aerobic metabolism (Warburg effect) and cell-signaling pathways that are key for the proliferation and survival of BC cells, as well as for metastasis and resistance to anti-cancer drugs [217,224,225]. Otherwise, traditional oncology has clearly shown that antiestrogens are an effective measure in the treatment of ER+ BC, using either Tamoxifen or Letrozole. MT, as well as resveratrol, also appears to function as aromatase inhibitors, becoming further candidates in the adjuvant treatment of ER+ BC [227]. Beside these mechanisms, MT shows many other anticancer and oncostatic effects in BC [218]. Among them, MT enhances the sensitivity to classical anti-cancer agents [217].

Interestingly, a recent *in vitro* study provides evidence about the positive effects of a novel MT-TMX drug combination in the treatment of BC. It is known that TMX use may eventually lead to resistance. However, this seems to be overcome by the novel MT-TMX conjugates [219].

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Otherwise, an inverse correlation between nocturnal melatonin levels and the development of BC has been confirmed [215,221]. This appears to be related to the loss of the day/night MT circadian rhythm, increasing the risk of BC development in female night workers. In fact, it has been shown that women with BC had lower plasma levels of MT than normal women, and these levels are even lower in nurses working shifts [220].

In summary, it is beyond doubt that MT plays an important role in the prevention and treatment of BC. Although its primary effect seems to be exerted at a mitochondrial level by regulating aerobic metabolism, MT also decreases angiogenesis and proliferation while promoting apoptosis [216,217,222,223,226].

6.4) Cisplatin (CDDP) and pH/NHE in breast cancer.

Cisplatin (CDDP) has been used in the treatment of BC for a long time in different combinations and it continues to be widely used nowadays [208,212,266]. From its first introduction in bedside oncology different mechanisms of action for CDDP have been described [267,268]. An almost completely disregarded issue in bedside oncology hs been the fact that CDDP can significantly modify the intracellular pH of cancer cells inducing cytoplasmatic acidification through a CDDP-mediated inhibition of H+ extrusion secondary to downregulation of NHE-1 [207,208,210,267] (Table 2).

Contrariwise, the activity of NHE-1 and its effect on elevating pHi increases CDDP resistance to treatment [207]. Apart from inducing pHi acidification, CDDP shifts cervical cancer cells from glycolysis to oxidative metabolism, what is accompanied by inhibition of cancer cell growth. In these studies, cancer cells either recover, maintaining an alkaline pHi to survive and proliferate, although at reduced growth rates, or undergo cell death [206].

6.5) pH and MDR in breast cancer: an integrated approach to treatment.

For many years, P-glycoprotein (P-gp) has been held to be the main responsible mechanism for multidrug resistance (MDR) in solid tumors. However, seminal research in this area initially showed that a progressive increase in pHi was correlated with the level of DOXO resistance human in lung tumor cells. This resistance was counteracted upon the addition of verapamil, an inhibitor of P-gp activity [169]. At that time, the fact that P-gp is affected pHi had been already suggested. During the last two decades, increasing attention has been paid to the fact that

pH alterations can be behind fundamental aspects of MDR [114,116,211,269,270]. Recent research has clearly shown that P-gp needs a pH gradient in order to function [271,272]. Nowadays, an integrated mechanism to explain MDR has been recently developed based upon the highly diseased H^+-dynamics of the microenvironment of tumors through changes in the extracellular and intracellular pH (CPR) [93,114,115,167,273]. This new and integral model demonstrates that the CPR of cancer cells and tissues (CPR) and P-gp expression in MDR are related in a direct cause-effect relationship.

In the same line, the therapeutic failure to induce cytoplasmic acidification and/or reverse CPR has also been proposed to be the main underlying factor for MDR, what suggests that MDR and resistance to the induction of the low pHi-mediated therapeutic apoptosis are one and the same

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thing [117]. Furthermore, the expression of P-gp leads to an elevation of pHi [118,274], while intracellular acidification down-regulates the MDR transporter [118,275,276]. Finally, extracellular acidification increases the activity of P-gp, inducing MDR in different cancer cells and tissues [93,114,120]. In summary, all these findings perfectly fit into each other, meaning that the therapeutic induction of a reversion of CPR is the key and fundamental target in overcoming MDR, probably in all malignant tumors. This is in line with all the other integrations made possible if approached through the all-comprehensive pH-centric anticancer paradigm [21,24,119].

6.6) Repurposed drugs in breast cancer treatment.

TME acidification makes BC more aggressive [121,277]. This intratumoral but extracellular acidosis, mainly caused by lactic acid production, is related to an increased aerobic glycolysis (Warburg effect) (Figure 1), and is fundamental in promoting invasiveness of BC cells [122]. On the contrary, chronic administration of sodium bicarbonate to nude mice implanted with human BC reduces the number and size of metastases [95] (Table 2).

Among the many mechanisms responsible for the regulation of the protoplasmic acid-base balance (Carbonic anhydrases (CAs), Monocarboxylate Transporters (MCT), ATP synthase, V-ATPases and Na+-H+ exchanger isoform 1(NHE1), CAIX appeqars to be a critical mediator for the expansion of BC in hypoxic niches, sustaining the mesenchymal and 'stemness' phenotypes of these cells [204]. CAIX activity affects the uptake and toxicity of anticancer drugs and is associated with a bad prognosis. Also, Erb-2 expression and CAIX activity are associated with bad prognosis [203]. The CA inhibitor Acetazolamide (AZM) enhances DOXO toxicity but reduces melphalan toxicity in BC cell lines that express CAIX, also being a target for anticancer treatment [75]. Furthermore, V-ATPase and MCT4 are both major microenvironmental acidification mechanisms in human BC cell lines [123]. Indeed, MCTs are often upregulated in BC tissue [200], and MCT4 is a clear therapeutic target, at least in certain subtypes of BC [44]. Thus, targeting lactate transport with MCT inhibitors such as Quercetin suppresses BC growth and improves tumor immune response [76,184,201,278]. Other MCT inhibitors such as Simvastatin and Phloretin have also been found active against BC cells [77,228] (Table 2).

Lonidamine was first introduced in 1979 as an antispermatogenic agent. It inhibits L-lactate transport through activity on MCT1, MCT2 and MCT4, causing selective intracellular acidification of tumors. It has been active in metastatic BC patients, but is not commercialized any more [231].
The n-3 polyunsaturated Docosahexaenoic acid (DHA, 22:6n-3), is effective in increasing survival and chemotherapy efficacy in BC patients with metastasis [232], inhibiting NaV1.5 current and NHE-1 activity in human BC cells [233]. The daily doses used in the clinical trials were in the range of 1.800 mg DHA/day, while a single case report showing positive results in a BC patient that only used 480 mg DHA/day as part of a more extensive supplementary cocktail [229].

Drug screening has identified an FDA approved drug, Niclosamide, as an inhibitor of BC stem-like cells [230]. Niclosamide is associated with cytosolic acidification and lysosomal dysfunction [234]. Another group of compounds known to induce cytosolic acidification are the K+ ionophores. These compounds promote the outflow of K+ from the mitochondria as well as from the cytoplasm, mediating an H+/K+ exchange across lipid membrane. The result is the induction of an intracellular accumulation of protons [21]. One such K+ ionophore is the antibiotic **Salinomycin.**

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Promising results from a few clinical pilot studies indicate that Salinomycin is able to induce partial clinical regression of heavily pretreated and therapy-resistant cancers, including BC [235] (Table 2). Finally, for a more complete exposure of repurposed drugs in preclinical and clinical oncology, see [21]

6.7) Metformin (MET).

Boosting glycolysis with mitochondria inhibitors such as Metformin (MET) have also been proposed to be a method to decrease pHi in various cancer cell lines, BC among them [96], alone and/or in combination with the MCT inhibitor Simvastatin [97] (Table 2).
MET has been proposed to be a viable anticancer drug since it induces intracellular hyperacidification in tumor xenograft models through inhibition of Wnt signaling, a feature found to be selective for cancer cells [96]. During the last few years MET has been introduced as an anticancer agent in clinical oncology after it was reported to decrease mortality of BC patients [236,237,246-248], increasing the survival of triple-negative BC patients [248] . MET can act as an anticancer drug through the activity on several glucose transporters [279] known to be in close association with BC [238,239,280,281]. Some of the anticancer-related effects of MET are:

(i) It reduces circulating insulin and insulin/IGF-1 receptor-mediated activation of the PI3K pathway [246].

(ii) MET inhibits the expression of Hypoxia Inducible Factor 1 alpha (HIF-1α) gene expression, increases Pyruvate Dehydrogenase (PDH) gene expression [250] and decreases Warburg metabolism [31]. Besides, HIF-1 is fundamental in tumoral angiogenesis and induces the expression of VEGF in BC [120,146,253,282]. Through this and other mechanisms MET also stimulates cancer growth, including triple-negative BC (TNBC) [255], and in hypoxic conditions inhibits apoptosis and induces cell resistance to cytotoxic lymphocytes and natural killer cells [254,282,283]. Furhermore, also in hypoxic BC tumor cells, the inhibition of different H+-extruding mechanisms has been proposed as a therapeutic strategy, while among them CAIX is considered to represent the most promising target [205].

(iii) As an inhibitor tumor angiogenesis [240,249,251,252] a recent study reveals the impact of MET inhibitory effect on microvasculature [284]. Through this antiangiogenic effect it can also improve tumor prognosis [139,253].

(iv) MET can reduce tumor progression through AMPK inactivation [285,286], in spite the opposite effect has also been reported [287].

(v) MET can inhibit cancer migration, invasion and metastasis in BC and other tumors [209,241,288-290].

(vi) MET is also active via the inhibition of the hedgehog signaling pathway in tumors like BC [242,243].

Finally, MET has not only been used as an anticancer agent on its own, but is also useful as an adjuvant to other cancer chemotherapy agents, notably to reduce the side-effects of DOXO [291].

 doi:10.20944/preprints201911.0331.v1

Moreover, MET has been reported to act synergistically with chemotherapy, also decreasing its dosages [244], and has even been used to target resistant cells in BC and other tumors [245]. Finally, MET has been considered to be a radio-sensitizer agent [256].

7. Conclusions.

If so many unrelated etiopathogenic factors of so many different natures and origins cause cancer, the up-regulation of any or several of them, alone or in a synergistic combination with other stimulators of H+ extrusion indicates that the pHi/pHe abnormalities specifically induced in cancer cells and tissues mediate in the behavior of solid tumors. This also suggests the existence of a universality of phenomenon involved in the carcinogenesis of breast cancer and other solid human tumors. In this contribution, the multifactorial etiological and etiopathogenetic factors in breast cancer are considered all together, which allows to propose an integrated approach to the therapeutics of this disease.

Interestingly, there is a surprising lack of information relating genetic abnormalities like *BRCA1* and *BRCA2* positive tumors and the pH/NHE-related paradigm, as well as on the most likely relationships of inflammatory BC with H+ dynamics, in spite of the known importance of TME in this aggressive form of the disease.

An increasing number of studies have led to conceptualize that any attempts to induce a low pHi-mediated apoptosis can be a cancer-specific therapeutic strategy to treat a wide diversity of human malignant tumors, besides breast cancer. The ultimate goal of this integrated approach is to target the selective molecular and and metabolic-dependant acid-base disruptions specific to cancer cells. Also, the final aim of therapy is to take advantage of the H+-related selective abnormalities that malignant cells and tissues possess over their normal counterparts, in order to exploit such differences in treatment. Finally, the pH-centric paradigm recognizes the selective cancer proton reversal (CPR) of creat cancer as a main therapeutic target. The pending issue nowadays is to find that old Ehrlich´s magic bullet that can selectively reverse CPR, if such a weapon exists. Otherwise, the concerted utilization of some of the measures that we have conceptualized, described and discussed here, is likely to become a useful and integrated alternative in the present and near future to more efficiently treat all forms of breast cancer.

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