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CELL SCIENCE AT A GLANCE

ARTICLE SERIES: CELL BIOLOGY AND DISEASE

Cancer cell behaviors mediated by dysregulated pH dynamics at a glance

Katharine A. White[1], Bree K. Grillo-Hill[2] and Diane L. Barber[1,*]

ABSTRACT

Dysregulated pH is a common characteristic of cancer cells, as they have an increased intracellular pH (pH_i) and a decreased extracellular pH (pH_e) compared with normal cells. Recent work has expanded our knowledge of how dysregulated pH dynamics influences cancer cell behaviors, including proliferation, metastasis, metabolic adaptation and tumorigenesis. Emerging data suggest that the dysregulated pH of cancers enables these specific cell behaviors by altering the structure and function of selective pH-sensitive proteins, termed pH sensors. Recent findings also show that, by blocking pH_i increases, cancer cell behaviors can be attenuated. This suggests ion transporter inhibition as an effective therapeutic approach, either singly or in combination with targeted therapies. In this Cell Science at a Glance article and accompanying poster, we highlight the interconnected roles of dysregulated pH dynamics in cancer initiation, progression and adaptation.

KEY WORDS: Cancer, Metabolism, Metastasis, Migration, pH, Proliferation

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Introduction

In normal cells, intracellular pH (pH_i) is tightly regulated to near-neutral values by ion transport proteins resident in the plasma membrane (Boron, 2004). The activity of these transporters is regulated not only by changes in pH_i as a homeostatic mechanism but also by intra- or extra-cellular cues, such as oncogenes (Grillo-Hill et al., 2015; Reshkin et al., 2014), growth factor signaling (Counillon and Pouyssegur, 1995; Clement et al., 2013; Meima et al., 2009; Counillon et al., 2016), metabolic burden (Odunewu and Fliegel, 2013; Wu and Kraut, 2014), hypoxia (Reshkin et al.,

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2014) and osmolarity (Lacroix et al., 2008; Counillon et al., 2016). In cancer cells, pH_i is increased compared to normal cells (~7.3–7.6 versus ~7.2), while extracellular pH (pH_e) is decreased (~6.8–7.0 versus ~7.4; see poster). This reversed pH gradient in cancer cells is an early event in cancer development (Reshkin et al., 2000) and increases during neoplastic progression (Cardone et al., 2005). The higher pH_i in cancer cells is paradoxical, considering that metabolic acids are generated through increased metabolism and proliferation; however, an increased pH_i is maintained in cancer cells through the increased expression or activity of plasma membrane ion transporters and pH_i regulators, including the Na^+-H^+ exchanger 1 (NHE1) (Cong et al., 2014; Reshkin et al., 2014), carbonic anhydrases (CAs) (Zheng et al., 2015; Gallagher et al., 2015), monocarboxylate transporter 1 and 4 (MCT1 and MCT4, respectively) (Counillon et al., 2016), and Na^+-driven HCO_3^- exchangers (Parks and Pouyssegur, 2015; Lee et al., 2016; Gorbatenko et al., 2014). The dysregulated pH of cancer cells enables cellular processes that are sensitive to small changes in pH_i, including cell proliferation, migration and metabolism. These global cell biological effects are produced by the pH-sensitive functions of pH sensors: proteins with activities or ligand-binding affinities that are regulated within the narrow cellular range of pH_i dynamics.

In this article and accompanying poster, we describe our current understanding of how the dysregulated pH of cancer enables pH-dependent cancer cell behaviors – with a focus on pH_i dynamics. We refer generally to cytosolic pH_i, but the pH of various organelles is distinct from cytosolic pH (for review, see Casey et al., 2010) and cytosolic pH can be different in distinct parts of the cell, such as at lamellipodia (Stock et al., 2007) and invadopodia (Beaty et al., 2014). While the decreased pH_e of cancer cells will be briefly discussed – as it relates to pH_i and its role in enabling cell migration – detailed reviews on how decreased pH_e alters cell-matrix remodeling can be found elsewhere (Stock and Schwab, 2009; Brown and Murray, 2015; Yamamoto et al., 2015; Hashim et al., 2011). Where known, we discuss the role of specific pH-sensors in the pH_i-dependent cell process and molecular mechanisms for pH sensing. Particular emphasis will be given to how the increased pH_i of cancer cells enables their increased proliferation, their ability to evade apoptosis, their migration and invasion, metabolic adaptation, and tumorigenesis. Finally, we briefly present recent advances in limiting cancer progression that were made by inhibiting ion transporters in order to lower pH_i, both in clonal cells and animal models, and will propose new views on how altered pH_i dynamics may enable adaptive mutations in cancer.

Proliferation and cell survival

From the early work of Pouyssegur and colleagues (Pouyssegur et al., 1984), a higher pH_i has been recognized as being a permissive, although not obligatory, signal for increasing cell proliferation. Subsequent work showed that the pH_i-dependent proliferative response in cancer cells can be generated by distinct ion transport proteins, including NHE1 (Lauritzen et al., 2012), Na^+-driven bicarbonate transporters (Boedtkjer et al., 2013; McIntyre et al., 2016) and the H^+/K^+-ATPase proton pump (Goh et al., 2014). Additionally, pH_i-dependent proliferation has recently been confirmed *in vivo* (Grillo-Hill et al., 2015).

Although increased pH_i acts downstream of growth factor signaling, precisely how it enables proliferation remains to be determined. In normal interphase cells, a transient increase in pH_i at the end of S phase in the cell cycle promotes the G2/M transition (Putney and Barber, 2003) (see poster). Blocking this transient increase in pH_i attenuates cyclin B levels and maintains the inhibitory phosphorylation of Cdk1 at Tyr15 (Cdk1-pTyr15) (Putney and Barber, 2003). Yet, how the constitutively higher pH_i in cancer cells regulates cell cycle progression remains to be determined. One clue comes from a gene array profile of fibroblast cell lines (Putney and Barber, 2004), which showed that a prolonged higher pH_i increases the levels of cyclinB1, increases the levels of Cdc25 phosphatase that dephosphorylates inhibitory Cdk1-pTyr15, and decreases the levels of Wee1 kinase that phosphorylates Cdk1-Tyr15. Collectively, these expression changes increase the amount of active Cdk1, thus promoting G2/M entry and transition.

Additionally, apoptotic cells have a decreased pH_i (Gottlieb et al., 1996) (see poster). Programmed cell death is triggered by release of cytochrome c from mitochondria, which subsequently activates catabolic enzymes including caspases. Regulated pH dynamics are also observed during this crucial time, with alkalization of mitochondrial matrix pH and subsequent cytosolic acidification (Matsuyama et al., 2000).

Importantly, decreased pH_i has been observed in both apoptosis mediated by death receptors and mitochondria (for review, see Lagadic-Gossmann et al., 2004). In death-receptor-mediated apoptosis, decreased pH_i is caspase-dependent (Liu et al., 2000) and precedes DNA fragmentation (Gottlieb et al., 1996). In apoptosis mediated by mitochondria, decreased pH_i precedes cytochrome c release from the mitochondria (Matsuyama et al., 2000) and occurs even when caspase inhibitors are used (Zanke et al., 1998), which suggests that decreased pH_i is an early signal for caspase activation in apoptosis. Supporting this idea, cytochrome-c-mediated activation of caspases requires cytosolic acidification, with highest caspase activity at pH 6.3–6.8 (Matsuyama et al., 2000). It has also been shown that constitutively increased pH_i blocks apoptotic signaling as measured by downstream effects on DNA degradation (Perez-Sala et al., 1995). Although pH_i dynamics clearly plays a role in apoptosis, more studies are needed to understand which ion transporters are crucial for pH_i regulation during apoptosis and whether increased pH_i inhibits responses to different apoptotic signals. Another unresolved question is whether pH_i dynamics regulates any non-apoptotic cell death pathways.

Metabolic reprogramming

A metabolic shift to increased aerobic glycolysis and reduced mitochondrial oxidative phosphorylation – often referred to as the Warburg effect – is considered a common feature of most cancers and rapidly proliferating cells (see poster). This metabolic reprogramming confers advantages to cancer cells by enhancing their resistance to hypoxia, thereby allowing a fast conversion of nutrients into biomass to enable cell proliferation, and protecting against damaging mitochondrial reactive oxygen species. Most cancers are confirmed to have increased glucose uptake and lactic acid production. Glycolytic flux increases with alkaline pH_i (Peak et al., 1992; Miccoli et al., 1996; Dechant et al., 2010; Dietl et al., 2010), which has been speculated but not experimentally confirmed to be partly dependent on the pH-sensitive activity of some glycolytic enzymes (Damaghi et al., 2013; Reshkin et al., 2014), including lactate dehydrogenase and phosphofructokinase-1 (PFK-1).

Increased expression or activity of lactate dehydrogenase A chain (LDHA), the glycolytic enzyme that converts pyruvate to lactate, occurs in highly aggressive metastatic cancers and, when suppressed, decreases tumor growth (Fantin et al., 2006; Le et al., 2010; Xie et al., 2014). LDHA post-translational acetylation of Lys5, which decreases LDHA activity, is reduced in pancreatic tumors and, accordingly, tumor growth decreases when endogenous LDHA is replaced by an acetylation-mimetic mutant (Zhao et al., 2013). Post-translational

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modification by protonation or deprotonation also regulates LDHA activity, which increases with physiologically higher pH_i (Read et al., 2001). A computational program called pHinder (Isom et al., 2013) identified two potential pH-sensing regions in LDHA, where residues have predicted pK_a values to be shifted up or down into the physiological range. The first region involves Asp140 (predicted pK_a ~7.4, solution pK_a 3.9), which forms an electrostatic bond with the backbone carbon of His192 in the catalytic site. The second potential pH-sensitive region involves solvent-exposed Lys131 (predicted pK_a ~7.9, solution pK_a 10.5) and a network of residues that are located at the tetramer interface: Arg170, His180 and His185. However, the molecular mechanisms of pH-sensing by LDHA remain to be determined.

Although increased lactate is a well-characterized feature of highly proliferative cancer cells, the pathways for upstream carbon flow in glucose metabolism remain unclear. Activity of PFK-1, the first rate-limiting enzyme of glycolysis, is known to be pH sensitive, with a >10-fold increase between pH 7.0 and 7.4 (Trivedi and Danforth, 1966; Frieden et al., 1976; Andres et al., 1990). However, previous studies suggest conflicting roles for PFK-1 in cancer. PFK-1 shows increased protein expression in a broad range of cancers, suggesting that higher PFK-1 activity enables cancer cell phenotypes (Moreno-Sanchez et al., 2012). By contrast, PFK-1 glycosylation, which inhibits enzyme activity, is also increased in cancer (Yi et al., 2012). Additionally, we found that several somatic mutations in PFK-1 that have been identified in human cancers inhibit its enzyme activity (Webb et al., 2015). As with LDHA, the molecular mechanisms for pH-dependent PFK-1 activity remain to be determined, currently limiting attempts to resolve the significance of pH sensing by PFK-1 and its role in metabolic reprogramming in cancer cells. To facilitate understanding of how pH dynamics regulates PFK-1 activity, we recently resolved the crystal structure of the platelet isoform of PFK-1 (Webb et al., 2015). Based on this crystal structure, pK_a estimates, and molecular dynamics simulations, His208 was identified as a candidate pH-sensing residue. His208 has an upshifted predicted pK_a and is conserved in all three PFK-1 isoforms (liver, muscle, platelet). His208 is located at the bottom of the substrate fructose-6-phosphate (F6P)-binding pocket and, when protonated at low pH_i, might be able to disrupt the pocket and reduce F6P binding (Webb et al., 2015). In addition to pH-regulated PFK-1 activity, a higher pH_i increases the expression of phosphofructokinase-2 (PFK-2) (Putney and Barber, 2004), which generates fructose-2,6-bisphosphate, an allosteric activator of PFK-1. With pH-sensitive enzymes at proximal (PFK-1 and PFK-2) and distal (LDHA) steps of glycolysis, future studies to resolve pH-regulated mechanisms have substantial promise for the development of therapeutic approaches aimed at suppressing metabolic reprogramming and cancer progression.

Migration and metastasis

Abundant evidence indicates that increased pH_i is necessary for directed cell migration, including the remodeling of actin filaments and cell-substrate adhesions critical for motile cells (Choi et al., 2010; Frantz et al., 2008; Clement et al., 2013; Denker and Barber, 2002; Meima et al., 2009). Decreased pH_e enables cell migration (Stock and Schwab, 2009; Stock et al., 2005) and invasion (Estrella et al., 2013), in part by increasing the activity of acid-activated matrix metalloproteinases (MMPs) that dissolve cell-substrate adhesions (Brown and Murray, 2015; Yamamoto et al., 2015). Evidence suggests that NHE1 is a significant contributor to matrix degradation through local extracellular acidification (Greco et al., 2014) or effects on MMP expression and localization (Lin et al., 2012; Putney and Barber, 2004). Increased pH_i resulting from ion transporter activity has been shown to enable cancer cell migration in oncogene-transformed mammary cells (Lauritzen et al., 2012), in patient-derived glioma cell lines (Cong et al., 2014) and in cervical cancer cell lines that do not exhibit hallmarks of metabolic adaptation (De Saedeleer et al., 2014). Furthermore, increased pH_i due to higher ion transporter activity has been linked to cell invasion phenotypes (Lin et al., 2012; Grillo-Hill et al., 2015). For a detailed review of which specific ion transporters have been linked to normal and pathological migration effects, see (Stock and Schwab, 2015).

During normal cell migration, dynamic changes in pH_i enable both cytoskeletal and focal adhesion remodeling, with increased pH_i decreasing the stability of focal adhesions (Srivastava et al., 2008) and increasing overall cell migratory rates (Choi et al., 2010) (see poster). Importantly, decreasing pH_i or increasing pH_e inhibits cell migration (Parks and Pouyssegur, 2015; Cong et al., 2014; Frantz et al., 2008; Denker and Barber, 2002). We recently described how protonation and deprotonation regulate selective pH sensors involved in cell migration (Schönichen et al., 2013). Through biochemical, molecular dynamics and NMR approaches, we and others have determined the molecular basis for how a higher pH_i increases the activity of guanine nucleotide exchange factors (GEFs) for cell polarity (Frantz et al., 2007), cofilin for actin polymerization and membrane protrusion (Pope et al., 2004; Gorbatyuk et al., 2006; Frantz et al., 2008), and talin binding to actin filaments for focal adhesion remodeling (Srivastava et al., 2008; Gingras et al., 2008) (see poster for structures and mechanisms). These proteins have distinct mechanisms for pH regulation, including the deprotonation of His residues at higher pH_i, which decreases their binding affinity for negatively charged phosphatidylinositolphosphates (PIPs) in the plasma membrane [His843 in the GEF Dbs (also known as MCF2L), and His133 in cofilin] and allosterically regulated conformational changes (His2418 in talin).

We have recently identified another mechanism of pH sensing through the focal adhesion kinase (FAK) (Choi et al., 2013). FAK includes a four-point-one protein, ezrin, radixin, moesin (FERM) domain for its targeting to focal adhesions and a kinase domain that catalyses activity of downstream kinases, as well as a linker between these two domains containing Tyr397. Increased autophosphorylation of Tyr397 (to pTyr397) is the first step in FAK activation and requires deprotonation of His58 in the FERM domain that occurs above pH 7.4. In this state, protonated His58 maintains a complex electrostatic network that keeps FAK inactive by rendering Tyr397 inaccessible for autophosphorylation. Neutral His58 disrupts this electrostatic network and concomitant conformational changes then allow autophosphorylation of Tyr397. The established roles of FAK in cancer progression (Sulzmaier et al., 2014) make it a promising target for therapeutics designed to selectively maintain His58 in its protonated state.

Importantly, constitutive increases in pH_i have been linked to increased migration in cancer cell models (Amith et al., 2015, 2016a; Parks and Pouyssegur, 2015; Lin et al., 2012; Cong et al., 2014), and we have recently shown that increased pH_i enables cancer cell invasion in an animal model (Grillo-Hill et al., 2015). Importantly, in these studies, decreasing pH_i inhibits the migration or invasion phenotype, suggesting that lowering the pH_i of cancer cells as part of cancer therapy can limit metastasis.

Tumorigenesis

As we describe above, dysregulated pH_i enables diverse cancer cell behaviors and can be considered a distinguishing feature of cancer.

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This leads to a growing consensus in the field of cancer research that approaches targeting increased pH_i are clinically promising (Neri and Supuran, 2011; Kopecka et al., 2015; Pedersen and Stock, 2013), particularly in cases where other targeted therapies have failed (Gillies et al., 2012; Alfarouk et al., 2015). Supporting this idea, lowering pH_i through genetic knockdown or inhibition of ion transporters reduces cell proliferation and migration (Andersen et al., 2016; Amith et al., 2016a; Le Floch et al., 2011), cell invasion (Yang et al., 2010), and suppresses tumorigenesis in xenograft models (Amith et al., 2015; Lagarde et al., 1988; Sonveaux et al., 2008; Colen et al., 2011; Chiche et al., 2012). Additionally, we have recently shown in *Drosophila* animal models and human clonal cells that, by lowering the pH_i, we can induce synthetic lethality with expression of activated oncogenes – notably Raf and Ras – possibly by limiting the efflux of metabolically generated acids (Grillo-Hill et al., 2015). Moreover, increasing pH_i in the absence of oncogenes is sufficient to induce hyperproliferation and dysplasia (Grillo-Hill et al., 2015; Petzoldt et al., 2013). One strength of using model organisms, such as flies (*Drosophila melanogaster*) and zebrafish (*Danio rerio*), is the ability to use genetic screens to reveal previously unknown signaling pathways and molecular mechanisms that mediate pH-dependent cancer cell behaviors.

Recent work suggests that intratumoral pH_i is heterogeneous, which adds to the complexity of studying and interpreting pH_i dynamics in xenograft and animal models. Hypoxia has been shown to increase pH_i (Reshkin et al., 2014), suggesting that anoxic cells at a tumor center can have a higher pH_i than peripheral cells. However, a recent study of rat brain gliomas found that NHE1 and MCT1 are more abundant at the tumor edge (Grillon et al., 2011), although pH_i was not determined. Furthermore, increased pH_i has recently been proposed to be necessary for epithelial-to-mesenchymal transition (Amith et al., 2016b), and epithelial-to-mesenchymal transition is implicated in initiating metastasis. Finally, we have recently shown that the pH_i in stem cells is lower than in differentiated daughter cells (Ulmschneider et al., 2016), which raises the possibility that tumor-initiating cells have a lower pH_i than neighboring cells. An important new direction will be to measure intratumoral pH_i by using genetically encoded tools, such as tags of pHluorin protein, a GFP variant with near-neutral pK_a (Miesenbock, 2012). Another understudied area is how dysregulated pH in stromal cells contributes to maintaining dysregulated tumor pH and supports or enables tumor growth and progression (see Box 1 for a brief review).

Box 1. Stromal cells and dysregulated pH

Dysregulated pH can also affect stromal cells including fibroblasts and endothelial cells (for review see Andersen et al., 2014). Metabolic links between tumor cells and stromal cells are well established (for review see Draoui and Feron, 2011). Monocarboxylate transporters (MCTs) have an important role in shuttling lactate produced in tumor cells to stromal cells where it is converted to pyruvate and then processed through oxidative phosphorylation (Koukourakis et al., 2006). Endothelial cells can also take up lactate from the stroma, which can drive angiogenesis (Vegran et al., 2011). Although there are no reports describing a direct measurement of pH in stromal cells *in vivo*, recent work by Hulikova and colleagues has shown that stromal myofibroblasts can act as proton reservoirs, thereby mitigating extracellular acidification, buffering protons, and transmitting acids across a stromal syncytium (Hulikova et al., 2016). Given the complex interactions between cancer cells and stromal cells, more work is needed to investigate the contributions of stromal cells in enabling or maintaining dysregulated pH in cancer cells.

Mapping spatial differences in intratumoral and stromal pH_i could improve our understanding of the heterogeneity of tumor properties and behaviors.

Future outlook for dysregulated pH dynamics and cancer

Recent work suggests that dysregulated pH_i contributes to chemotherapy resistance (Daniel et al., 2013; Alfarouk et al., 2015; Harguindey et al., 2005) and radiotherapy resistance (Huber et al., 2015). Several groups have shown that lowering pH_i by suppressing the expression of ion transporters or using selective inhibitors of ion transporters is sufficient to re-sensitize a chemoresistant cell line (Lauritzen et al., 2010; Zheng et al., 2015) or xenografts (Amith et al., 2015; Nath et al., 2015) to chemotherapeutic treatment. Furthermore, targeting increased pH_i in combination with other chemotherapeutic drugs holds promise as a combinatorial therapeutic approach (see poster). Synergistic inhibition of 3D colony growth and invadopodia formation has been reported in various pancreatic ductal adenocarcinoma (PDAC) cell lines in response to a combination of NHE1 inhibition and erlotinib, an inhibitor of the epidermal growth factor receptor (EGFR) pathway (Cardone et al., 2015). Additionally, based on findings that acidic pH_e attenuates immune response (Lardner, 2001), neutralizing pH_e has recently been shown to improve responses to cancer immunotherapies (Pilon-Thomas et al., 2016).

These promising results, and the variety of cell lines, tumor types and animal models in which inhibition of ion transporters has been successful, suggest that clinical applications are more generally applicable than other targeted therapies. Future work might reveal new combination therapies that use treatments targeted towards a genetic signature or histological identity in combination with general ion transporter inhibitors. Moreover, designing therapeutics that alter the protonation state of pH sensors regulating cancer cell behaviors is a promising, but challenging, future direction.

Finally, ongoing work in our lab investigates a new idea with substantial impact: that some recurrent mutations are adaptive to the increased pH_i of cancer cells. Of particular interest are Arg→His and His→Arg mutations. Arg residues, with a pK_a of ~12, would be constitutively charged; however, His residues have a pK_a of ~6.5 and might be able to titrate between the higher pH_i of cancer cells and the lower pH_i of untransformed cells. One example is the recurrent Arg273His mutation in p53 (also known as TP53). In wild-type p53, Arg273 forms electrostatic interactions with the DNA phosphate backbone, which might be retained by protonated His273 but not neutral His273 (Joerger et al., 2005) (see poster). Other examples include the EGFR-Arg776His mutation for gain in pH sensing, and PIK3CA-His1047Arg for loss of pH sensing. Determining whether changes in the pH-sensitive function of mutant proteins can confer a fitness advantage to the higher pH_i of cancer cells might improve our understanding of how mutations drive cancer phenotypes.

Competing interests

The authors declare no competing or financial interests.

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Cell science at a glance

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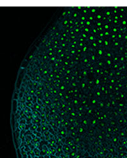

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