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Lysosomal protein relocation as an adaptation mechanism to extracellular acidosis

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Hypoxia, poor vasculature, and increased flux of carbons through fermentative glycolysis leads to extracellular acidosis in solid tumors (Pasteur effect). Cancer cells can maintain the glycolytic phenotype even in the presence of oxygen (Warburg effect) causing further and constant acidification of the tumor microenvironment. In early in situ cancers, acidification and adaptation to acidosis starts in the the periluminal center of the duct, far from vasculature. Adaptation and development of resistance to intraductal acidosis is one of the key issues in cancer development and evolution that leads to selection for a more aggressive phenotype. Evolutionary advantages over non acid-resistant cells (e.g. normal epithelial and stromal cells) are gained, such as being more glycolytic, migratory, and invasive. We have proposed that this acidic environment induces genomic instability and selects for emergence of aggressive clones of cells, leading to genomic diversity that is evident as intratumoral genetic heterogeneity and is a proximal cause of malignancy and resistance.[1] Specifically, the acidified habitat imparts a Darwinian selection pressure that favors cells that constiutively express mechanisms to resist acid-mediated apoptosis. Further, the acidic microenvironment is recapitulated in locally invasive cancers, which provides cancer cells with a selective advantage over the stroma into which they invade. Indeed, an acidic microenvironment stimulates invasion and metastasis, is toxic to non-acid adapted cells and remodels the extracellular matrix, ECM.[2] Further, acidosis promotes angiogenesis via the release VEGF[3] and impairs the immune response to tumor antigens.[4,5] Importantly, neutralizing acidity can inhibit metastasis and augment the response to anti-tumor immune therapies, including checkpoint blockade and adoptive cell transfer.[5]

In our recent paper[6] we investigated the acid adaptations in MCF-7 breast cancer cells using shotgun proteomics. In our experiment, cancer cells were adapted to growth in acidic conditions (media with pH 6.7) for more than 20 passages (>2 months), after which their growth rate in acidic conditions was identical to that of the parental cells at neutral pH. We then used SILAC discovery proteomics to compare the whole proteome of acid-adapted cells to cancer cells grown in normal pH (7.4). The proteomics result reveled a significant upregulation of lysosomal proteins. Prominent among these was LAMP2, a heavily glycosylated membrane protein that functions to protect lysosomal membranes from acid proteolysis, and which is important in the induction of autophagy, which is also stimulated by acid adaptation.[7] LAMP2 upregulation was confirmed in MCF-7 and other cancer cell lines using multiple techniques *in vitro* and *in vivo*. These cells exhibited increased resistance to acid-mediated cytotoxicity, and this resistance was reversed with shRNA knockdown of LAMP2. Immunohistochemistry of breast cancer patient samples revealed increased LAMP2 expression with increased progression from DCIS to invasive and metastatic ductal carcinoma. Surprisingly, in addition to increased expression, we also observed that LAMP2 was highly expressed at the plasma membrane of breast cancer cells, particularly in regions expected to be acidic, such as the center of DCIS. To follow this up in vitro, we observed that acid adapted cells expressed LAMP2 at their plasma membranes using immune fluorescent microscopy. Thus this work identified a previously unknown adaptive mechanism wherein cells chronically exposed to an acidic environment translocate lysosomal proteins to their surface, thus protecting the plasmalemma from acid induced hydrolysis.[6] This is just one of the many strategies that cancer cells use to protect themselves and gain advantages against the emerging harsh conditions in their habitat. This work is also a good example of our work showing how we can fight cancer by harnessing the cancer progress using its evolutionary adaptation mechanisms and vulnerability they gain through these evolutionary adaptations.

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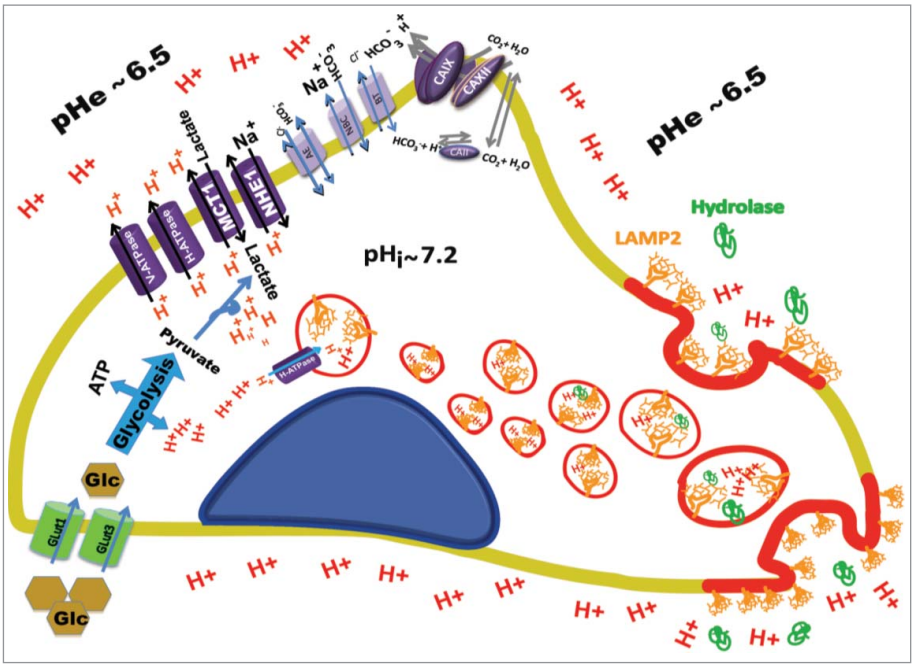

Figure 1. Lysosomes relocate to cell periphery to support lysosomal protein relocation to the cell surface to protect cancer cells against extracellular acidosis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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