A Generation Gap in Cellular Ph

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Cells of the budding yeast Saccharomyces cerevisiae divide asymmetrically: proteins, organelles, and other cellular components are not distributed equally between the mother cell and its daughter (bud). During replicative aging, mother cells produce a finite number of daughter cells before ceasing reproduction. Replicative aging is also asymmetric: mother cells age but daughter cells are rejuvenated. Previous studies have identified a number of asymmetric phenotypes (that is, differences between mother and daughter cells) that are proposed to contribute to the aging of mother cells. In a new study published in *eLife*, postdoctoral fellow Dr. Kiersten Henderson in the lab of Dr. Dan Gottschling (Basic Sciences Division) uncovered asymmetric inheritance of the plasma membrane Pma1, which leads to increased cellular pH in mother cells. This study suggests that asymmetry of cytoplasmic pH is an important factor in both replicative aging and daughter cell rejuvenation.

The authors previously found that the acidity of the vacuole, a lysosome-like organelle, is asymmetric between mother and daughter cells: lysosome acidity decreases in mothers but is restored in daughter cells (Hughes and Gottschling, 2012). Here, the authors further characterized vacuole acidity in budding daughter cells. They found that mother cells, regardless of age, produced a majority of buds with acidic vacuolar pH. Furthermore, re-acidification of buds was found to occur before cytokinesis, indicating that whatever factor is responsible for the asymmetry of vacuolar pH must also be asymmetric between mothers and daughters before cytokinesis occurs.

As one of the major regulators of vacuole acidity is the vacuolar proton ATPase (V-ATPase), the authors analyzed the distribution of V-ATPase in mother and daughter cells, but found that V-ATPase was not obviously asymmetric. Previous work by the authors identified the plasma membrane proton ATPase Pma1 as being asymmetrically retained in mother cells. Pma1 is similar to V-ATPase in that it moves cytosolic protons across membranes, but while V-ATPase pumps protons into the vacuole, Pma1 pumps protons out of the cell. As Pma1 increases cytoplasmic pH, the authors speculated that it might reduce vacuole acidity.

Analysis of Pma1 distribution revealed that it was asymmetrically distributed, with higher levels at the plasma membrane of mother cells. Notably, Pma1 asymmetry was established prior to cytokinesis,

when vacuolar pH asymmetry is established. Pma1 levels also increased during aging, and high levels of Pma1 were correlated with reduced vacuole acidity. Overexpression of Pma1 in newborn daughter cells drastically reduced vacuole acidity, while reduction of Pma1 activity in aging mother cells restored the acidity of a substantial number of vacuoles.

The authors' previous work (Hughes and Gottschling, 2012) showed that delaying the decrease in vacuole acidity through overexpression of V-ATPase extends replicative lifespan. As their current results suggested that high levels of Pma1 antagonize vacuolar acidity, they tested whether loss of Pma1 function might also impact lifespan. Indeed, reduction of Pma1 activity increased replicative lifespan by ~30%. Analysis of the mechanism of lifespan extension through reduced Pma1 activity suggested that that it is mostly, but not entirely, due to increased vacuole acidification.

Analysis of Pma1 function revealed that, consistent with its function in pumping protons out of the cell, cytoplasmic pH increased with age. Additionally, cytosolic pH in mother cells was measurably higher than in their attached buds. Pma1 overexpression experiments revealed that the inherently asymmetric distribution of Pma1 between mothers and daughters causes cytoplasmic pH asymmetry prior to cytokinesis.

In summary, this study identified increased cytoplasmic pH as a major contributor to replicative aging, and that pH asymmetry between mothers and daughters is an important component of daughter cell rejuvenation. Interestingly, other work has shown asymmetry of cytosolic pH in plant and algae cells and of Pma1 distribution in fission yeast and pollen tubes, suggesting that cytoplasmic pH asymmetry is a conserved aspect of asymmetric cell division. However, much work remains to be done. "We don't know how proteins like Pma1 are partitioned asymmetrically between mother and daughter cells," said Dr. Henderson. "We'd like to identify the mechanisms that cause asymmetric inheritance of these proteins."

Henderson KA, Hughes AL, Gottschling DE. 2014. Mother-daughter asymmetry of pH underlies aging and rejuvenation in yeast.*eLife* 3:e03504.

See also: Hughes AL, Gottschling DE. 2012. An early age increase in vacuolar pH limits mitochondrial function and lifespan in yeast. *Nature* 492:261-265.

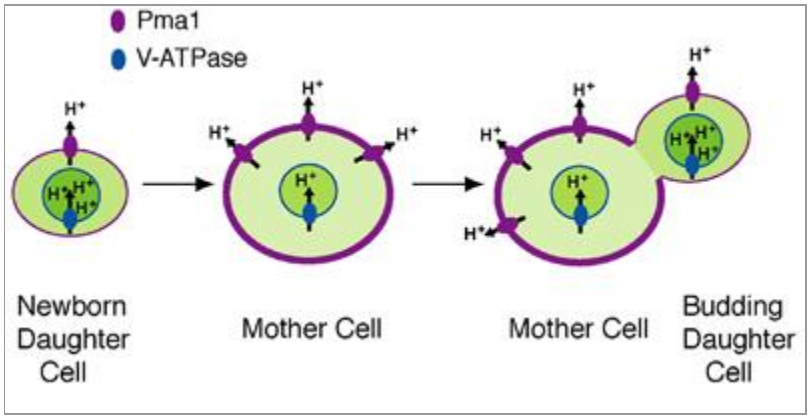

Image modified from the publication.

A model for the effects of increased Pma1 levels and asymmetry during aging on cytoplasmic and vacuolar pH. In newborn daughter cells, Pma1 levels are relatively low, with a correspondingly low cytoplasmic pH leading to high vacuole acidity. As mother cells age, Pma1 levels increase, leading to increased pumping of protons out of the cell with a corresponding increase in cellular pH and decrease in vacuole acidity. When a new daughter cell buds off from an old mother cell, it does not inherit high levels of Pma1 and thus has a low cytoplasmic pH and high vacuole acidity.