Medicine / Healthcare, Drug discovery

Molecular mechanism of adaptation of cancer cells to acidic environments

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Abstract

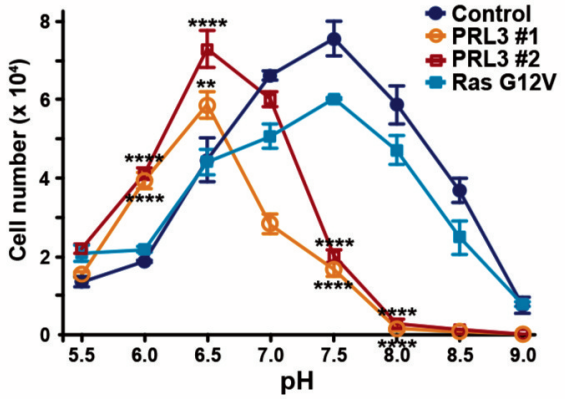
Cancer cells have a unique energy metabolism that consumes large amounts of glucose to produce lactic acid, which acidifies the microenvironment surrounding cancer cells. However, it has long been unclear how cancer cells survive and proliferate in an acidic environment that is harmful to normal cells. We found that PRL, a molecule that is specifically expressed in malignant cancer tissues such as colorectal cancer metastases, enables cells to selectively proliferate in acidic environments. In cells expressing high levels of PRL, lysosomal exocytosis, in which lysosomes fuse with the cell membrane, is activated, and H^+ stored in the lumen of lysosomes is expelled, maintaining the intracellular pH at an appropriate level even in an acidic environment. Furthermore, cancer cells that lost their ability to proliferate selectively in an acidic environment by inhibiting lysosomal exocytosis were also strongly inhibited from forming tumors in vivo, indicating the importance of this adaptation phenomenon to acidic environments in tumorigenesis.

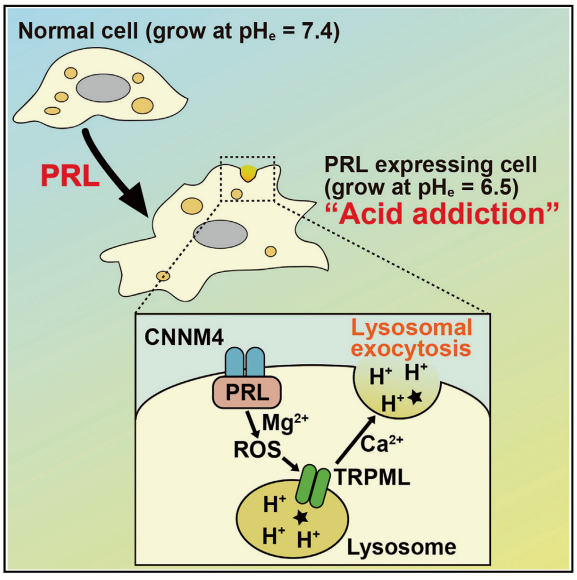
Background & Results

Cancer cells have a unique energy metabolism that consumes large amounts of glucose to produce lactic acid, which acidifies the microenvironment surrounding cancer cells. However, it has long been unclear how cancer cells survive and proliferate in an acidic environment that is harmful to normal cells. We have been analyzing the function of PRL, a molecule that is specifically expressed in malignant cancer tissues such as metastases of colorectal cancer, and have reported the Mg^{2+} transporter CNNM as a direct target of PRL. Here, we found that PRL-expressing cells can hardly proliferate at physiological pH 7.4, but proliferate selectively in acidic environments such as pH 6.5, which is typically observed in cancer tissues. We performed various analyses, including comprehensive gene knockout screening using CRISPR/Cas9, to elucidate the molecular mechanism underlying this phenomenon, and found that lysosomal exocytosis, in which lysosomes fuse with the cell membrane, is activated. The activation of lysosomal exocytosis maintains the intracellular pH at an appropriate level even in an acidic environment by secreting a large amount of H^+ stored in the lumen of the lysosome. Since it was known that the Ca^{2+} channel TRPML, which is localized at the lysosomal membrane, is essential for this lysosomal exocytosis to occur, we knocked out this molecule and found that the cells were unable to actively proliferate in acidic environments when PRL was overexpressed. Furthermore, even in cancer cells whose tumorigenicity in vivo was increased by high PRL expression, TRPML knockout inhibited their growth in acidic environments and greatly reduced their tumorigenicity. These results indicate that the activation of lysosomal exocytosis plays an important role in the adaptation of cancer cells to acidic environments and tumorigenesis, and reveal the response mechanism of cells to acidic environments, a prominent characteristic of the cancer microenvironment.

Significance of the research and Future perspective

Tissue acidification is well known as a characteristic of the microenvironment surrounding cancer cells, along with hypoxia, and thus, clarifying the molecular basis of the adaptation phenomenon is an important achievement of this study. The clarification of the molecular mechanism that is the key to the growth of cancer cells in vivo may lead to the development of new diagnostic and therapeutic agents that target this mechanism.





Patent
Treatise Funato, Yosuke; Yoshida, Atsushi; Hirata, Yusuke et al. The oncogenic PRL protein causes acid addiction of cells by stimulating lysosomal exocytosis. Developmental Cell. 2020; 55: 387-397. e8. doi: 10.1016/j.devcel.2020.08.009. Epub 2020 Sep 11
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