Researchers find acidic pH microenvironments in tumors aid tumor cell survival

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Researchers at Moffitt Cancer Center and colleagues at the University of South Florida and Wayne State University have discovered that tumor cell survival relies on adaptation to acidic conditions in the tumor microenvironment. Their research investigating the effects of acidity on breast and pancreatic cancer cell lines revealed the importance of autophagy in acidic microenvironments and suggests that a successful treatment strategy might be based on this autophagic dependence.

The study appears as the cover story for the Aug. 15 issue of *Cancer Research*, a publication of the American Association for Cancer Research.

"Cancer progression is a multistep process strongly influenced by the physical properties of the tumor microenvironment," said Robert J. Gillies, Ph.D., corresponding author of the study and chair of Moffitt's Department of Cancer Imaging and Metabolism. "Both low oxygen and high acidity can be cytotoxic. Our research suggests that adaptation to these stressful conditions involves autophagy allowing cancer cells to survive, proliferate and eventually metastasize to secondary sites."

According to the authors, not much is known about cell survival mechanisms under acidic conditions, but it has been demonstrated that acidosis can alter gene expression leading to cell types that are adapted for growth and survival in low pH conditions. Identifying low pH

survival mechanisms would "give further insight into tumor progression and potentially introduce novel therapeutic strategies," researchers said.

In this study, the researchers tested cancer cell lines under acidic conditions to learn more about autophagy and cellular adaptation. They noted that normal cells in the acidic environment can respond to acidic stress by increasing cell death pathways, thus introducing the need for survival and adaptive mechanisms by cancer cells.

The researchers also noted that their experiments were carried out under atmospheric oxygen levels and they found that the cell's stress response could lead to chronic autophagy even when nutrients and oxygen were in adequate supply.

"We found that cells subjected to transient and chronic low pH growth conditions demonstrate elevated markers for autophagy and are dependent on this process for prolonged survival in acidic environments," explained Jonathan W. Wojtkowiak, lead author of the study and postdoctoral fellow at Moffitt. "A hallmark of cancer is the ability of cancer cells to evade apoptosis. Autophagy supports this by playing a tumor promoter and survival role under certain circumstances during different stages of tumorogenesis."

Their study demonstrated the importance of autophagy in low pH-adapted breast and pancreatic cancer cell lines and the dependence of these cells on autophagy for survival to acidic tumor microenvironment. According to the researchers, they identified a potential therapeutic strategy of using an autophagy inhibitor, one that does not affect cells under neutral conditions.

More information: cancerres.aacrjournals.org/con …/72/16/3938.full.pdf

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