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New study finds arginine deprivation may be a useful strategy for treating bladder cancers

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With few treatment options available to patients with advanced bladder cancer, investigators are looking for novel molecular targets. In a study published in The *American Journal of Pathology*, researchers report that more than 90% of all bladder cancers are deficient in argininosuccinate synthetase 1 (ASS1), an enzyme necessary for arginine synthesis, and patients with tumors having low ASS1 expression have shorter survival. Treatment with the arginine-degrading enzyme ADI-PEG 20 inhibited tumor growth in ASS1-deficient cells both in vivo and in vitro, suggesting a new therapeutic approach to bladder cancer is possible.

"There is a major unmet need to identify additional therapies for bladder cancer patients that includes agents that can target both conventional urothelial carcinoma and less common subtypes of bladder cancer. Our findings suggest that arginine dependency in bladder cancer may be a useful mechanism to selectively target a subset of these cancers using ADI-PEG 20, although further investigation into the mediators of this effect and the role of combination therapy, including chemotherapy, to enhance efficacy is required," explained lead investigator Donna Hansel, MD, PhD, Professor of Pathology, University of California at San Diego (CA).

Using immunohistochemistry on tissue specimens taken from 252 patients who had undergone surgery for muscle-invasive bladder cancer over a 20-year period, investigators found that normal urothelium demonstrated robust ASS1 expression throughout its full thickness.

Although the majority of samples with urothelial carcinoma, small cell carcinoma, and squamous cell carcinoma showed significant reductions in ASS1 expression, moderate-to-intense ASS1 expression was retained in the great majority of those with invasive bladder adenocarcinomas and invasive micropapillary urothelial carcinomas. "This finding suggests that these three major subtypes of bladder cancer, which account for more than 90% of all bladder cancers, may potentially respond to arginine-degrading therapy such as ADI-PEG 20," noted Dr. Hansel.

Using data from The Cancer Genome Atlas Project, the investigators examined survival data after classifying cases according to ASS1 mRNA expression levels. They found that survival was significantly lower in patients having tumors with low ASS1 expression compared to those with high ASS1 expression.

To evaluate the effects of ADI-PEG 20, the researchers compared its effects on cells that were deficient in ASS1 to those that express ASS1. They found that ADI-PEG 20 decreased colony formation and reduced cell viability only in cells deficient in ASS1 but had little or no effect on other cells. To test the effects of ADI-PEG 20 in vivo, mice were injected with ASS1-deficient cells into subcutaneous tissue in the left flank and ASS1-expressor cells into the right flank. The result was that ADI-PEG 20 arrested tumor growth only in tissue containing ASS1-deficient cells.

In addition to bladder cancer, ADI-PEG 20 is currently being evaluated in a Phase III trial for hepatocellular carcinoma and is being assessed for other cancers including melanoma and mesothelioma. "Our results suggest that arginine deprivation may be a useful strategy for treating bladder cancer and show that ADI-PEG 20 functions through a novel signaling mechanism that includes the pathway mediated by the general control nonderepressible 2 kinase that controls autophagy and apoptosis," commented Dr. Hansel.

Arginine is a semi-essential amino acid that is synthesized from citrulline in two steps of the urea cycle. In the first step, citrulline and aspartate are converted to argininosuccinate via the enzyme ASS1. The argininosuccinate is then converted to arginine and fumarate. Arginase and arginine deiminase (ADI) are arginine-degrading enzymes. ADI-PEG 20 is a commercial formulation of ADI that has a longer pharmacokinetic half-life.

More information: "Argininosuccinate Synthetase 1 Loss in Invasive Bladder Cancer Regulates Survival through General Control Nonderepressible 2 Kinase-Mediated Eukaryotic Initiation Factor 2α Activity and Is Targetable by Pegylated Arginine Deiminase," The *American Journal of Pathology*, DOI: 10.1016/j.ajpath.2016.09.004

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