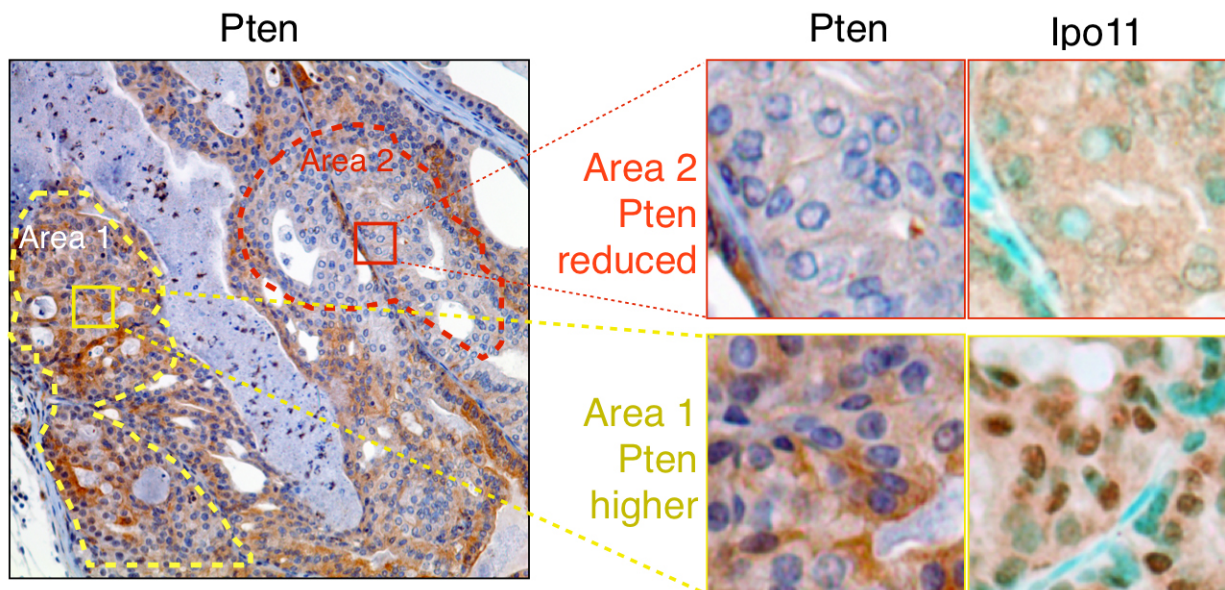


Researchers identify 'Achilles' heel' of PTEN that helps drive prostate cancer progression

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Postdoctoral researchers Muhan Chen, Dawid G. Nowak and others in the Trotman lab at CSHL may have solved a mystery about prostate cancer: why some patients appear to have low levels of the powerful tumor-suppressing protein PTEN and yet have no mutations in the gene that encodes the protein. The answer is implied in this image. In a sample of mouse prostate tissue on the way to becoming cancerous, they show one area in which PTEN protein levels are high (Area 1, yellow dashes) and a nearby area (Area 2, red dashes) where they are low. Where PTEN is low, so are levels of a protein called Importin 11 (Ipo11); where PTEN is abundant, so too is Ipo11. Ipo11 saves PTEN proteins marked for destruction by carrying them into the cell nucleus, perhaps in this way forming a "reservoir" and saving PTEN for future use in the battle against the emerging tumor. When Ipo11 is missing, cancer progression is promoted. Credit: Trotman Lab, CSHL

Researchers at Cold Spring Harbor Laboratory (CSHL) have discovered that a protein called Importin-11 protects the anti-cancer protein PTEN from destruction by transporting it into the cell nucleus. A study they publish today in *The Journal of Cell Biology* suggests that the loss of Importin-11 may destabilize PTEN, leading to the development of lung, prostate, and other cancers.

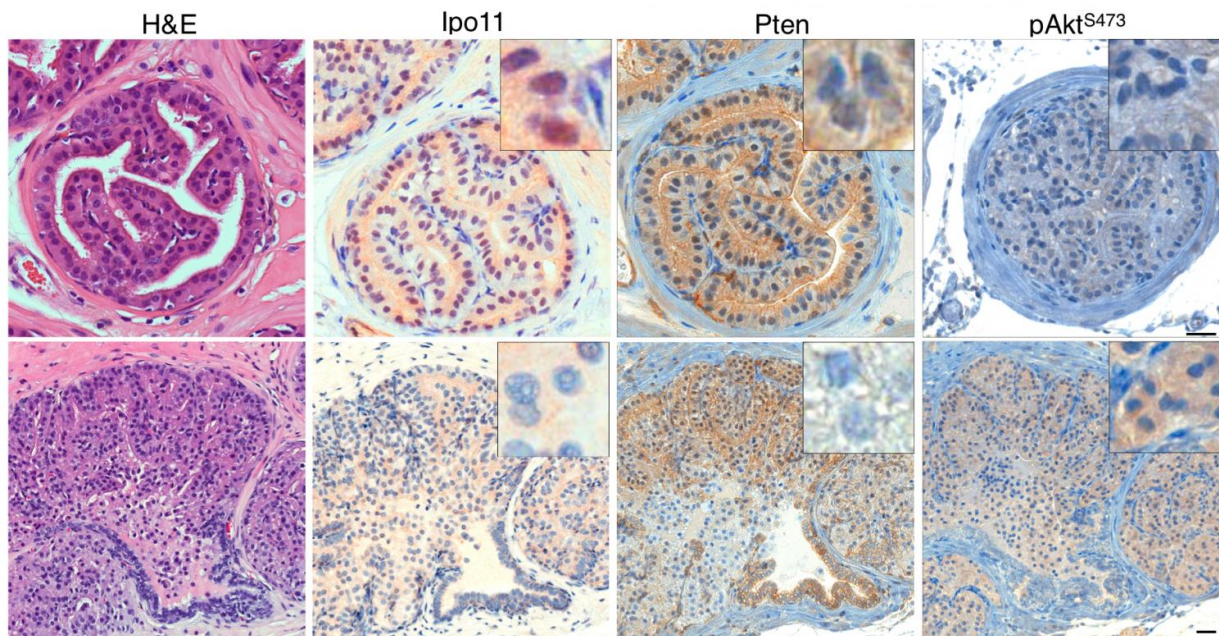
PTEN prevents tumor cells from growing uncontrollably, and mutations in the gene encoding this [protein](#) are commonly found in many different types of cancer. Some patients, however, show low levels of the PTEN protein even though their PTEN genes are normal. CSHL Associate Professor Lloyd Trotman and colleagues discovered that this may be due to defects in Importin-11, which transports PTEN into the nucleus, sheltering PTEN from proteins in the cell's cytoplasm that would otherwise target it for degradation.

Several cytoplasmic proteins—NEDD4-1, NDFIP1, and UBE2E1—combine to tag PTEN with the small molecule ubiquitin. PTEN tagged with multiple ubiquitin molecules can then be recognized and destroyed by the cell's protein degradation machinery. Trotman and colleagues found that Importin-11 protects PTEN from degradation by escorting not only PTEN but also UBE2E1 into the nucleus, thereby breaking up the cytoplasmic ubiquitination apparatus.

Mice lacking Importin-11 showed lower levels of PTEN protein and developed lung adenocarcinomas and prostate neoplasias. Mutations in the gene encoding Importin-11 have been identified in human cancers, and Trotman and colleagues found that tumors from [lung cancer patients](#) lacking Importin-11 tended to show low PTEN levels as well. The researchers estimate that loss of Importin-11 may account for the loss of PTEN in approximately one-third of lung cancer patients lacking this

key anti-cancer protein.

In prostate cancer, loss of Importin-11 predicted disease relapse and metastasis in patients who had had their prostate removed. "We think that the degradation of PTEN after loss or impairment of Importin-11 is a very effective driver of human [prostate cancer](#)," says Trotman. "Our results suggest that Importin-11 is the 'Achilles' heel' of the ubiquitination system that maintains the correct levels of PTEN inside cells."



Cross sections of prostate tissue in healthy mice (top row) and mice in which cancer is beginning to develop (bottom row). Healthy tissue shows regular structures and empty spaces (white in the far left image) called lumen. Cancerous tissue is less organized, and is more densely populated with cells, which are proliferating abnormally. Insets show consistently that when Ipo11 is abundant, so is PTEN tumor-suppressing protein; when PTEN levels are low, so is the protein Importin 11 (Ipo11). Its presence or absence may be a useful diagnostic and therapeutic marker in prostate biopsies. Credit: Trotman lab, CSHL

More information: "The Nuclear Transport Receptor Importin-11 is a Tumor Suppressor that Maintains PTEN Protein," appears in *The Journal of Cell Biology*, jcb.rupress.org/cgi/doi/10.1083/jcb.201604025

Provided by Cold Spring Harbor Laboratory

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