New insights into the regulation of PTEN tumor suppression function

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The PTEN tumor suppressor gene controls numerous biological processes including cell proliferation, cell growth and death. But PTEN is frequently lost or mutated; in fact, alteration of the gene is so common among various types of human cancer that PTEN has become one of the most frequently mutated of all tumor suppressors.

Now, a study led by researchers at Beth Israel Deaconess Medical Center (BIDMC) and Harvard Medical School provides important new insights into PTEN regulation. Reported in the August 20 advance on-line issue of *Nature,* the findings define a pathway that maintains PTEN in the nucleus and offer a novel target for enhancing this gene's tumor suppressive function.

"Our laboratory recently discovered that even when PTEN is produced normally by a cell, it has to be properly localized within the nucleus in order to maintain its full tumor suppressive abilities," explains senior author Pier Paolo Pandolfi, MD, PhD, Director of Basic Research in BIDMC's Cancer Center and Professor of Medicine at Harvard Medical School. "Indeed, it's been demonstrated that in a variety of cancers, PTEN has broken away from the nucleus. With these new findings, we now understand how this happens."

Examination of the abnormal blood cells of acute promyelocytic leukemia (APL) led to the discovery that PTEN had become loosened from the nucleus.

"From there, we observed that the loss of another tumor suppressor known as PML [whose mutation is a main cause of acute promyelocytic leukemia] was at the root of PTEN's escape from the nucleus," adds the study's first author Min Sup Song, PhD, a member of the Pandolfi laboratory. Further investigations revealed that PML was blocking the function of an enzyme known as HAUSP, which under normal circumstances, serves to direct PTEN out of the nucleus.

"We discovered that this pathway is disrupted through the loss or mutation of PML, as well as through unchecked HAUSP expression, either of which can force PTEN from the nucleus and prevent its ability to act as a tumor suppressor," notes Pandolfi.

"The modulation of the PML-HAUSP pathway offers us an exciting and unique approach to enhancing the tumor suppressive actions of PTEN," he adds. "Because PML is known to be 'druggable,' we believe that in cases of APL, modulation of PTEN function can be achieved with drugs already being used for the treatment of human cancers, including interferon and all trans-retinoic acid."

Source: Beth Israel Deaconess Medical Center