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that areas with aggressive tumor contained low *PTEN* levels and high NEDD4-1. They concluded that NEDD4-1 could promote cancer development by down-regulating *PTEN*.

The second study by Dr. Pier Paolo Pandolfi of Memorial Sloan Kettering Cancer Center and colleagues found that the ubiquitination of *PTEN* by NEDD4-1 also regulates another important aspect of *PTEN*, its cellular localization.

PTEN has been found mostly in the cytoplasm but has been known to also be in cell nuclei. While the cytoplasmic function of *PTEN* is now quite well understood, its nuclear functions have been elusive. Looking at a family with an inherited *PTEN* mutation that caused them to have the cancer-susceptibility condition, Cowden Syndrome, researchers found that the patients' colon cancer strikingly lacked nuclear *PTEN*.

The Pandolfi and Jiang labs showed that the *PTEN* mutation in these patients prevented the addition of ubiquitin by NEDD4-1, providing a molecular mechanism for the detrimental effect of the mutant *PTEN* protein. They showed that the single ubiquitin tagging is necessary to import *PTEN* into the cel nucleus where it is protected from degradation and cancer is initiated.

According to the researchers, the uncovered key role of *PTEN* degradation provides a new therapeutic strategy. Since ubiquitination has both positive (single tag) and negative (repetitive tagging) effects, a class of drugs, the proteasome inhibitors, that selectively blocks the degrading effects of ubiquitination, should now be studied as possible treatments for cancers with *PTEN* mutations.

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