THE WISTAR INSTITUTE

Embargoed Until:
THURSDAY, OCT. 2, 2025
11 A.M., EST

Contact:
Darien Sutton
(215) 898-3988
dsutton@wistar.org

Wistar Scientists Discover p53 Can "Read" Cellular Signals to Direct Immune Response, Upending 30 Years of Scientific Consensus

PHILADELPHIA — (OCT. 2, 2025) — Wistar Institute researchers have overturned three decades of scientific thinking about p53, the most important tumor suppressor protein in cancer research. In a study published in *Molecular Cell*, they reveal for the first time that this critical protein, responsible for halting cell division or initiating cell death, changes its binding sites according to specific cellular signals. The findings challenge the long-held scientific belief that p53 always activated the same set of genes regardless of cellular context or outcome. Instead, researchers discovered that p53 can be directed by the enzyme PADI4 to leave some of its usual binding sites and relocate to genes that generate an immune response to attack tumors.

"For 30 years, we joked that p53 was 'dumb' because it couldn't decide what to do in different situations—it just turned on all its target genes whether the cell needed to die or survive, and the cell decided which activity needed to happen," said **Maureen Murphy, Ph.D.,** Deputy Director of the Ellen and Ronald Caplan Cancer Center, Ira Brind Professor & Program Leader of the Molecular and Cellular Oncogenesis Program at The Wistar Institute, and senior author of the study.

"This is the first example of p53 actually reading a signal and deciding where on DNA to bind. It's a completely different mechanism that shows p53 is actually quite smart and, as I suspected, engages the immune system in order to suppress cancer."

The discovery emerged from Murphy's decades-long investigation into genetic variants found in families of African descent who develop cancer at accelerated rates but don't fit typical hereditary cancer patterns. These families carry partially functional versions of p53—called hypomorphic variants—which are understudied and therefore leave patients without clear medical guidance. Murphy and her team hypothesized that studying these semi-functional variants that are associated with cancer, would reveal the key target gene for p53 tumor suppression.

By comparing the function of six p53 hypomorphs to the "normal" or wild-type version of p53, the team identified PADI4 as the only p53 target gene that would typically be activated by wild-type p53 but remained inactive across all six of the hypomorphic variants they tested. They also found that PADI4 doesn't just respond to commands from p53—it actually directs p53's behavior through a process called citrullination. When PADI4 citrullinates p53 (adding chemical tags to specific amino acid residues), it fundamentally changes where p53 goes in the cell's DNA. Instead of binding to its usual genes, the modified p53 relocates to genes associated with ETS transcription factors, which are

known to regulate immune response genes. This gives scientists a whole new perspective on p53's role in responding to cancer.

"P53's real tumor suppressive role appears to be to alert the immune system to come and eradicate the tumor," said Murphy.

The researchers demonstrated this mechanism using advanced genomic techniques, showing that when PADI4 is active, p53 abandons about 30% of its normal binding sites while moving to new locations that activate genes responsible for the interferon response—the cell's primary antiviral and anti-tumor defense system. To do this, Murphy and her team developed new antibodies specific to citrullinated p53 and used cutting-edge techniques including ChIP-seq and CUT&Tag to map precisely where the modified p53 binds in living cells. They confirmed this mechanism in multiple cell lines and validated it in mouse models.

This discovery has important implications for cancer treatment and diagnosis. Since certain hypomorphic p53 variants cannot properly activate PADI4, these patients may not respond as well to immunotherapies that rely on the body's natural immune response to fight cancer. Therefore, Murphy suggests, PADI4 could serve as a potential biomarker to help clinicians guide treatment decisions.

"We might be able to predict whether someone will respond to immunotherapy based on their p53 status and PADI4 function. Instead of trying immunotherapy and finding out it doesn't work, we could direct treatment more precisely from the start. In fact, one of our areas of focus is to identify personalized therapies for people with hypomorphic p53 variants."

Importantly, this discovery represents more than just a scientific advance. It validates Murphy's long-held conviction that studying historically underrepresented populations can lead to breakthrough insights. Some families of African descent have the highest cancer burden of any ethnic group, yet their genetic variants have been largely understudied.

"These families are getting cancer in their 30s and 40s, and genetic counselors are telling them 'sorry, we don't know if this mutation is really responsible for increasing your cancer risk,'" Murphy said of African descent families with hypomorphic p53 variants.

"By studying people who are marginalized and variants that were being ignored, we ended up discovering a fundamental new mechanism of how the most important tumor suppressor actually works."

Co-authors: Alexandra Indeglia, Andrea Valdespino, Giulia Pantella, Sarah Offley, Connor Hill, Maya Foster, Kaitlyn Casey, HsinYao Tang, Anneliese M. Faustino, Alessandro Gardini, and Maureen E. Murphy from The Wistar Institute.

Work supported by: National Health Institutes (NIH) grants R01 CA102184 to M.E.M., F31 CA277953 to A.I., and R50 CA221838 to H.Y.T. Wistar shared resources are supported by the Cancer Center Support Grant P30 CA010815.

Publication information: Targeted Citrullination Enables p53 Binding to Non-canonical Sites, *Molecular Cell*, 2025. Online publication.

###

The Wistar Institute is an international leader in biomedical research with special expertise in cancer research and vaccine development. Founded in 1892 as the first independent nonprofit biomedical research institute in the United States, Wistar has held the prestigious Cancer Center designation from the National Cancer Institute since 1972. The Institute works actively to ensure that research advances move from the laboratory to the clinic as quickly as possible. wistar.org.