# Scientists discover a mechanism that can send cells on the road to cancer

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Using a common virus as a tool for investigating abnormal cell proliferation, a team led by scientists at Cold Spring Harbor Laboratory (CSHL) has succeeded in clarifying an intricate series of biochemical steps that shed light on a way that cancer can begin.

The team's findings are the latest in a long and distinguished line of research at CSHL involving adenovirus, a type of virus that causes the common cold in people, but whose genome contains known oncogenes -- genes whose expression can promote cancer under certain conditions.

"Adenovirus carries a number of cooperating genes that modulate cell growth in ways we're interested in," said William Tansey, Ph.D., who, along with CSHL professors Scott Lowe, Ph.D., and Gregory Hannon, Ph.D., is one of the team's co-leaders and corresponding author of a paper to be published April 22 in *Proceedings of the National Academy of Sciences*. Other team members include molecular biologists from Stony Brook University in New York.

## Using a Tumor Virus to Illuminate Function

The team focused on an adenoviral oncogene called E1A, and a protein that it codes for with the same name. "Both have received a great deal of attention over the years," said Dr. Tansey, "and to understand why, it helps to understand why viruses -- in this case, adenovirus, a DNA tumor virus -- is useful to us. We use them as you would use a flashlight, to

illuminate important processes inside the cell that help us understand what goes awry in oncogenesis."

Viruses can't reproduce on their own. A DNA virus like adenovirus is little more than a tiny, double-stranded segment of DNA enclosed within a protein shell. It must find a way to enter the nucleus of a living cell and hijack the cell's reproductive machinery in order to reproduce itself. "It's not adenovirus itself, but the things it does when it enters a cell, that really interest us," Dr. Tansey explained. "By looking, in particular, at the activity of the proteins adenovirus codes for -- proteins like E1A -- we are tapping into a kind of natural growth-control mechanism."

"The utility of DNA tumor viruses for cancer research is based on the premise that they've evolved to target the minimum number of cellular pathways necessary for virus propagation," said Dr. Lowe. When things go awry, understanding how a tumor virus like adenovirus promotes cancer can reveal, in turn, "the most vulnerable pathways and nodes that are linked to tumorigenesis," Dr. Hannon added.

## Commandeering the Cell Cycle

Because a tumor virus needs to commandeer the reproductive machinery of a living cell to survive, it must force the host cell to enter the reproductive, or S-phase, of its cycle. Past research has demonstrated that a protein called E2F is central in the process by which S-phase is activated. When the cell is not reproducing, E2F is known to be inhibited by its binding to another protein, called Rb, or retinoblastoma protein.

"It's this regulated association of E2F and Rb that is one of the primary mechanisms through which cells normally progress into S-phase," Dr. Tansey said. The E1A protein, after binding Rb, is capable of physically pulling it off the E2F molecule. This unleashes the cell to replicate its DNA. And this, in turn, can promote transformations associated with

cancer.

Recently, it's been shown that E1A's cancer-promoting activity is more extensive, also involving a gene-regulating protein called p400. Until the CSHL/Stony Brook team published its current paper, no one knew how E1A's binding with p400 affected the process.

## E1A's Role in Another Oncogenic Pathway

The team knew from prior studies that when the E1A and p400 proteins were bound to one another, cellular growth control was disrupted. The question was why this potentially oncogenic effect occurred. What mechanisms were set in motion by the binding of these two proteins?

They hypothesized that the answer could be found in the activity of yet another protein, called Myc, which Dr. Tansey has spent much of his career studying. Myc is an oncoprotein: one that is important in a great many regulatory processes in the cell, and which, when overexpressed, can cause dysregulation that leads to cancer.

Prior work had shown that when E1A was present in a cell, the potentially dangerous Myc protein was stable -- it did not degrade naturally. In new experiments, Tansey and colleagues found that E1A's stabilization of the Myc protein was accomplished not, as was suspected by some, by directly inhibiting its degradation in a cellular component called the proteosome, which destroys proteins. Rather, E1A stabilized Myc by promoting its binding with p400.

To recap the complex sequence of events: E1A, when present in a cell, binds to p400. That protein, in turn, forms a complex with Myc which accounts for Myc's stability in cells in which E1A is present. Close study showed that "the piece of the E1A protein that was important for stabilizing Myc was the same piece that bound to p400," Dr. Tansey

said. And just as E1A can pull the Rb protein away from E2F, initiating a cascade of pathologies potentially leading to oncogenesis, so does the ability of E1A to bind p400 -- and via that connection to engage Myc -- stabilize that oncoprotein and open the door to tumorigenesis.

“We know now that the interaction of E1A and p400 is very important in terms of regulating cell growth in normal and cancer cells,” Dr. Tansey said. “So we’re taking a cue from the history of work on adenoviruses and we’re leaving E1A behind to concentrate on Myc and p400. For us, now, the next step is to learn more about the p400-Myc connection.”

Source: Cold Spring Harbor Laboratory