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Unique Change in Protein Structure Guides Production of RNA from DNA

Gladstone-led study sheds light on critical molecular process

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SAN FRANCISCO, CA—November 7, 2013—One of biology’s most fundamental processes is something called *transcription*. It is just one step of many required to build proteins—and without it life would not exist. However, many aspects of transcription remain shrouded in mystery. But now, scientists at the Gladstone Institutes are shedding light on key aspects of transcription, and in so doing are coming even closer to understanding the importance of this process in the growth and development of cells—as well as what happens when this process goes awry.

In the latest issue of [Molecular Cell](#), researchers in the laboratory of Gladstone Investigator [Melanie Ott, MD, PhD](#), describe the intriguing behavior of a protein called RNA polymerase II (RNAPII). The RNAPII protein is an enzyme, a catalyst that guides the transcription process by copying DNA into RNA, which forms a disposable blueprint for making proteins. Scientists have long known that RNAPII appears to stall or “pause” at specific genes early in transcription. But they were not sure as why.

“This so-called ‘polymerase pausing’ occurs when RNAPII literally stops soon after beginning transcription for a short period before starting up again,” explained Dr. Ott, who is also a professor of medicine at the University of California, San Francisco, with which Gladstone is affiliated. “All we knew was that this behavior was important for the precise transcription of DNA into RNA, so we set out to understand how, when and—most importantly—why.”

The research team focused their efforts on a segment of RNAPII called the *C-terminal domain*, or CTD. This section is most intimately involved with transcription regulation. Previous research had found that CTD’s chemical structure is modified before and during transcription. However, the combinations of modifications as well as precisely how they influence or control transcription remained unclear. So in laboratory experiments on cells extracted from mammals, the researchers took a closer look.

The first breakthrough came when the research team identified a new type of modification, known as *acetylation*, which regulated transcription.

“Our next breakthrough occurred when we pinpointed the precise locations on the CTD where acetylation occurred—and realized it was unique to higher eukaryotes,” explained Sebastian Schröder, PhD, the paper’s first author. “We then wanted to see how this mammalian-specific acetylation fit into the realm of polymerase pausing.”

Now that the team knew *where* the CTD became acetylated, their next goal was to find out *when*. Clues to the timing of acetylation came in experiments where they mutated RNAPII so that CDT was unable to become acetylated. In these cases, the length of polymerase pausing dropped, and the necessary steps for the completion of transcription failed to occur. Additional experiments revealed the elusive timeline of acetylation and transcription.

“RNAPII binds to DNA to prepare for transcription. Shortly after that we see polymerase pausing—at which point the CTD becomes highly acetylated,” continued Dr. Schröder. “Soon after the pause, CTD is then *deacetylated*—the original modification is reversed—and transcription continues without a hitch.”

Polymerase pausing is not unique to mammals—in fact it was characterized in HIV, the virus that causes AIDS, many years ago—but the fact that the CTD becomes acetylated just *before or during* the time when transcription is paused appears to be unique. Drs. Ott and Schröder argue that CTD acetylation is a stabilizer, preparing RNAPII for efficient completion of transcription and slowing down the process to make sure everything is functioning correctly—not unlike the final ‘systems check’ a pilot must perform before takeoff.

These findings offer important insight into the relationship between acetylation and transcription. And given the importance of transcription in the growth and maturation of cells in general, the team’s result stands to inform scientists about a variety of cellular processes. These include, for example, the mechanisms behind stem-cell development and what happens when normal cellular growth spirals out of control, such as in cancer.

“However, there is still much we don’t know about acetylation as it relates to transcription,” said Dr. Ott. “For example, if CTD acetylation is important for stabilizing transcriptional pausing, why do we also see CTD acetylation at non-paused genes, although at different locations? Further, we believe there may be other steps in the transcription cycle that depend upon acetylation. Our most immediate goal is to find them. By doing so, we hope to deepen our understanding of one of nature’s most elegant biological processes.”

Dr. Schröder performed this research at Gladstone while completing his PhD at the University of Heidelberg, Germany. Eva Herker, PhD, Sean Thomas, PhD, Katrin Kaehlcke, Sungyoo Cho, Katherine Pollard, PhD, John Capra, PhD and Benoit Bruneau, PhD, also participated in this research at Gladstone, which was supported by the National Institutes of Health, the National Institute of Environmental Health Sciences, the Boehringer Ingelheim Fonds, the Human Frontiers Science Program and an E.G.G. fellowship.

About the Gladstone Institutes

Gladstone is an independent and nonprofit biomedical-research organization dedicated to accelerating the pace of scientific discovery and innovation to prevent, treat and cure cardiovascular, viral and neurological diseases. Gladstone is affiliated with the University of California, San Francisco.