GLADSTONE INSTITUTES | NEWS

Contact Press Relations: email: press@gladstone.ucsf.edu | phone: 415 734 5000

Gladstone Scientists Discover Gene "Bursting" Plays Key Role in Protein Production

Findings question earlier studies and shed light on fundamental cellular process

EMBARGOED UNTIL 3PM EDT, October 8, 2012

SAN FRANCISCO, CA—October 8, 2012—Scientists at the Gladstone Institutes have mapped the precise frequency by which genes get turned on across the human genome, providing new insight into the most fundamental of cellular processes—and revealing new clues as to what happens when this process goes awry.

In a study being published this week online in the *Proceedings of the National Academy of Sciences*, Gladstone Investigator Leor Weinberger, PhD, and his research team describe how a gene's on-and-off switching—called "bursting"—is the predominant method by which genes make proteins. By gaining an understanding of this underlying mechanism, this discovery has the potential to vastly help researchers learn what happens at the molecular level when this mechanism is disrupted—such as in cancer or when exposed to a particular drug.

The manufacture, or synthesis, of proteins takes place inside every cell. DNA and genes—which house the instructions for making proteins—are stored within the nucleus of each cell. When a gene is switched on, those instructions are transcribed as a copy onto RNA, another type of genetic material that then directs the protein synthesis. Proteins perform a variety of functions within the cell—from the breaking down and digesting fats to resisting foreign invaders, such as bacteria or viruses. The timing and frequency with which a particular protein is synthesized is crucial to maintaining the health of the cell.

"Much like flicking on a light switch, genes get 'switched on' at specific intervals to initiate the fundamental biological process of protein synthesis," said Dr. Weinberger, who is also an associate professor at the University of California, San Francisco (UCSF), with which Gladstone is affiliated. "Until recently, the process was thought to be continuous—once a gene is switched on, it stays on, churning out protein products at a steady pace like a garden hose. But recently, some studies have suggested the opposite—that DNA produces RNA molecules in rapid-fire 'staccato' bursts. We decided to investigate how common this rapid-fire bursting was across the genome."

In laboratory experiments, Dr. Weinberger and his team inserted a green fluorescent protein, or "vector," into the DNA of Jurkat T lymphocytes—a type of white blood cell that helps maintain a healthy human immune system. From this they generated new cells in which the vector was integrated into any one of thousands of gene segments—with each segment glowing green when it was activated, or "switched on." This allowed the

researchers to see exactly how gene activation occurred across the entire human genome.

“Our analysis reveals support for the “bursting” hypothesis—the genes acted as a sort of strobe light—transcribing RNA in rapid-fire bursts,” said Roy Dar, PhD, a Gladstone postdoctoral fellow and one of the paper’s lead authors. “We observed that the bursting frequency increases until, over time, it reaches a particular threshold. At that point higher protein levels are reached by increasing the size of the bursts, eventually coming to a halt when no more protein product is needed. These results are a huge step towards understanding the basic molecular mechanism behind gene regulation.”

"Dr. Weinberger and colleagues have shown that there is a single rule governing the behavior of all genes in the genome. Their findings in human cells complement and extend similar findings made recently in other organisms,” said Arjun Raj, PhD, assistant professor of bioengineering at the University of Pennsylvania and an expert in imaging single molecules within cells.

The team believes that this new-found understanding of this fundamental biological process—that genomic bursts account for the majority of instances of protein production—holds clues to discovering how the disruption of these bursts could be harmful.

“For example, in certain cancers, genes may be switched on at the wrong times, eventually leading to the formation of tumors,” said Brandon Razooky, a Gladstone and UCSF graduate student and the paper’s other lead author. “This is also a good example of how the basic science being performed here at Gladstone provides a solid foundation with which to prevent, treat and ultimately cure some of the world’s most devastating diseases.”

Michael Simpson, PhD, from the Oak Ridge National Laboratory Center for Nanophase Materials Sciences, is also a senior author on this paper. Funding came from a variety of sources, including the NIH Director’s Common Fund Program (through the NIH Director’s New Innovator Award Program), the National Science Foundation’s Graduate Research Fellowship Program, the US Department of Energy, the Pew Scholars Program in the Biomedical Sciences, and the Alfred P. Sloan Foundation.

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.

###