Serendipitous discovery leads to a new understanding of how cells multitask

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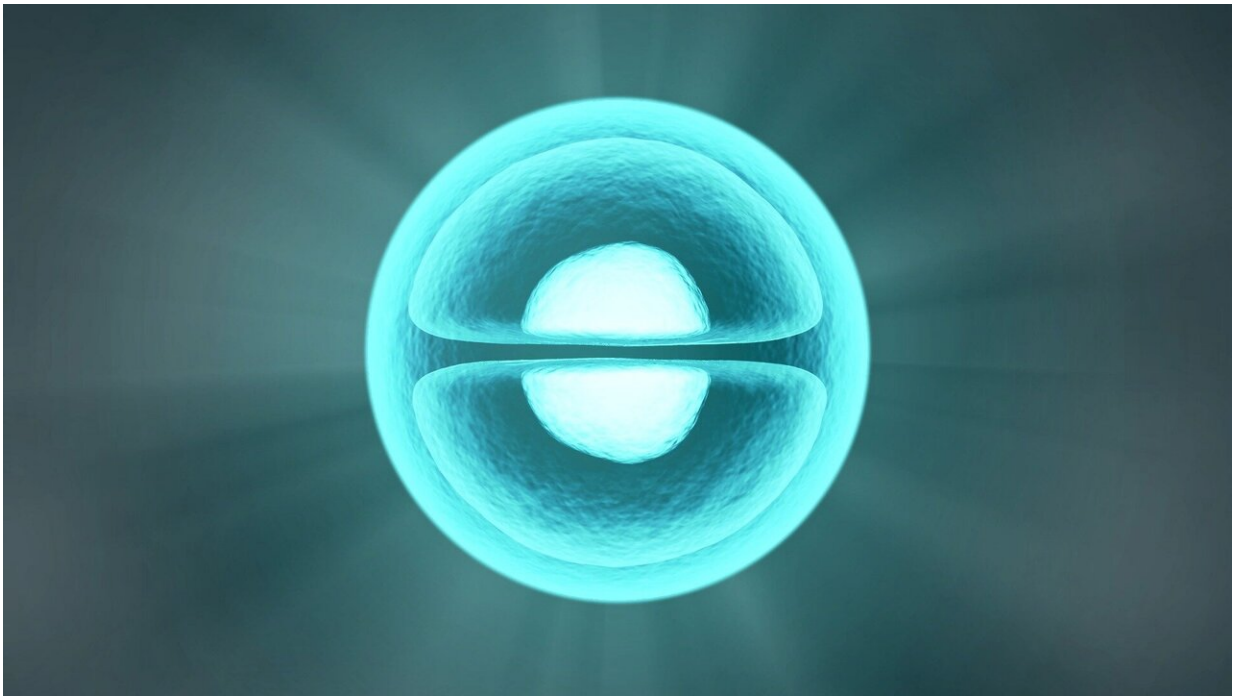

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Quantitative Biosciences Institute (QBI) researchers at UC San Francisco have discovered a new paradigm for how fundamental biological switches, proteins that can be turned on and off to control processes like cell differentiation, cell growth, and transport within a cell, are regulated at the molecular level, specifically by molecules binding at newly discovered sites far away from the main binding site,

and the broader impacts these changes have on a cellular level. This work highlights both a new understanding of how disease mutations may operate and also a possibility for a new class of therapeutic molecules to target switches that often misfunction in disease.

"…it's fundamental curiosity-driven science. But I think what's exciting is that we made new discoveries on something that is a fundamental part of regulatory biology and there is still apparently something really new that changes our understanding of these systems," said Tanja Kortemme, Ph.D., head of the Kortemme Lab at UCSF, Chan Zuckerberg Biohub Investigator, and co-senior author on the research featured in a paper that appears Oct. 13, 2021, in *Nature*.

Typically, Kortemme's lab focuses on the mechanistic details of individual components of a system, or how all the molecular components within a cell work in concert, but QBI's initiative that science should be able to connect ideas from the atom scale to the molecular scale to the cellular scale and ultimately to the level of tissues and organisms is showcased in this project. By collaborating with the co-lead of the study and director of QBI, Nevan Krogan, Ph.D., the team was able to do something methodologically novel, view the entirety of the system at both the molecular (mechanistic components) level and cellular (macro/systems) level. "Science moves so much more quickly when scientists from different disciplines work together. This philosophy manifested the discovery. However, the reward system needs to change where groups and collaborations achieve recognition more than individuals," explains Krogan, and by doing so they serendipitously discovered some surprising new mechanisms.

Multitasking and Sensitivity

Molecular switches, like the GTPase Gsp1 used in the study, a protein that plays an essential role in regulating cell growth and transport of

molecules within the cell, allow complex systems to respond to changes in their environment. However, a single switch may have the job of regulating a wide number of different biological processes simultaneously. So the question is, how does a switch contain all these different properties to do all these different and biologically complex tasks? Until now it was thought that central molecular switches could only be regulated in two distinct ways, when in fact once the molecular and systems-level studies were integrated it was clear that the changes to the protein, Gsp1, were sensed differently as you scaled out from molecular to cellular. "We can explain what happens at the cellular scale through the mechanistic details at the molecular scale by making perturbations at the atom scale [genetic mutations]. This is the dream of seeing direct genotype to phenotype connections," noted Kortemme.

The nuance of regulation here seems to lay in sensitivity, a prediction that was theorized in the 80's and now given experimental evidence that it is operational in a biological system. "Small changes get amplified due to the regulation of the switch," explained Kortemme, "Molecular changes are very small quantitatively but it seems they get amplified in the cellular context. For example, if we measure these effects in a test tube they are small, but then if we measure them in the cellular system they are actually rather dramatic in terms of the consequences on many different biological processes." Explained another way by first authors Tina Perica, Ph.D., and Christopher Mathy, "What might be a simple switch on the molecular level operates like three separate switches on the cellular systems-level. For example, cell division is coupled to how fast the Gsp1 switch turns off, transport processes within the cell sense both the on and off rates of the switch, and yet other processes respond only to the on rate of the switch."

Allostery and Future Implications

Beyond sensitivity, another surprising discovery in the shifting paradigm

of switch regulation, how the switch is turned on, off, and acted upon, was that switches can be regulated from distally located "allosteric" sites, binding sites that are located far away from the main active site but can still affect the function of the switch. This new result allowed the researchers to perturb the system far away from the active site and still have widespread effects on many functions within the cell. Broadly, this might help explain specific disease mutations wherein a mutation away from the active site has profound consequences on function.

The team discovered four new allosteric sites in this project located at positions 34, 141, 147, and 157 in Gsp1. This is important because while these new allosteric sites have implications specifically for GTPase regulation, other central molecular switches will likely also contain distally located allosteric sites which could be targets for future drug development. Continued research with a multi-systems approach seemed to excite Kortemme as she added, "This might mean we could find not only new biological mechanisms but also a completely new class of [molecular] switch regulators as drugs that are much more selective if we know the location and presence of these distally located allosteric sites."

More information: Tina Perica et al, Systems-level effects of allosteric perturbations to a model molecular switch, *Nature* (2021). DOI: 10.1038/s41586-021-03982-6

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