Researchers discover how to map cell-signaling molecules to their targets

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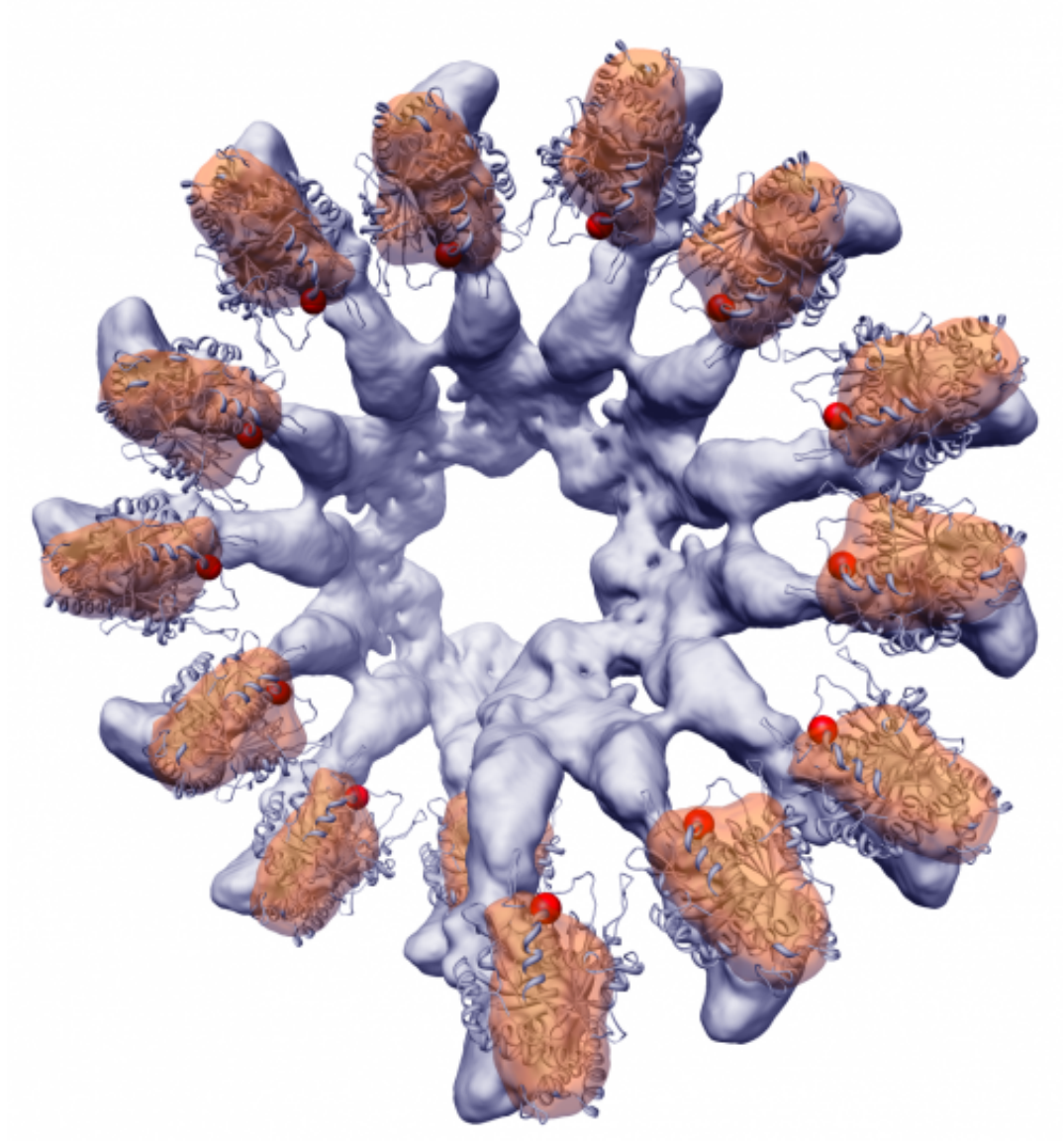

This image shows a mitotic spindle hub (the orange and grey hub-and-spoke structure) primed by Cdk-Clb3 signaling (red). Credit: Conrad Hall, McGill

A team of University of Montreal and McGill University researchers have devised a method to identify how signaling molecules orchestrate the sequential steps in cell division. In an article published online today in the *Proceedings of the National Academy of Sciences*, the scientists explain how they could track the relationship between signaling molecules and their target molecules to establish where, when and how the targets are deployed to perform the many steps necessary to replicate an individual cell's genome and surrounding structures.

Breakdowns in individual steps in these processes are a hallmark of a number of diseases, including cancers. The method outlined in the *PNAS* paper could provide a valuable tool to researchers seeking to better understand these processes.

"How living cells divide and how this process is accurately achieved are among the deepest questions scientists have been addressing for decades," said Dr. Stephen Michnick, co-senior investigator and a University of Montreal biochemistry professor. Co-senior investigator Jackie Vogel, a biology professor at McGill, said, "We know what are the main players in cell division – molecules called cyclins and a common actuator molecule called Cdk1 – but it has proved a vexing problem to figure out precisely how the cyclin-Cdk1 partners deploy target molecules to orchestrate everything that must happen and in precisely the right order to assure accurate cell division."

The University of Montreal and McGill team worked out a method to identify interactions between cyclin-Cdk1 (cyclin-dependent kinase 1) complexes and their targets in living cells. Cdk1 is a signaling protein that plays a key role in cell division – it has been studied extensively in

yeast, because of yeast's rapid reproduction, and is found in many other living organisms including humans. "It is a simple method that could be performed in any laboratory, unlike existing methods that are much more labor- and skill-intensive," said Dr. Michnick.

"The method also picks up cyclin-Cdk1 interactions that traditional methods don't," added Dr. Vogel. "For instance, we study the assembly of a massive molecular machine called the mitotic spindle, a structure that orchestrates the coordinated separation of two copies of the genome between the two new cells that emerge from division. We'd been chasing, for over a decade, an elusive link between a specific cyclin called Clb3-Cdk1 complex and a spindle target called gamma-tubulin that we thought could be a key step in building mitotic spindles accurately. All evidence pointed to this interaction, including a massive effort I was involved in to map out cellular communication directed to the centrosome, a molecular machine that organizes assembly of the mitotic spindle. So we teamed up with Dr. Michnick to try the new method and out popped the Clb3-Cdk1-gamma tubulin interaction—just like that." Now, in collaboration with Paul François, a physics professor at McGill, the researchers have been able to use this information to show that the Clb3-Cdk1-gamma-tubulin interaction controls a massive remodeling of the mitotic spindle.

"The tool that we've developed will be available to the scientific community and concerted efforts by many labs may ultimately unlock the mysteries of one of life's most essential processes," said Dr. Michnick.

More information: Dissection of Cdk1–cyclin complexes in vivo, www.pnas.org/cgi/doi/10.1073/pnas.1305420110

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