Meet CLAMP: A newly found protein that regulates genes

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"This is the last step of these signaling pathways that make the ultimate regulatory decision about whether you are going to turn on a gene or keep it off," says Erica Larschan, right, with graduate students Marcela Soruco, left, and Jessica Chery. Credit: Mike Cohea/Brown University

(Medical Xpress)—A newly discovered protein, found in many species, turns out to be the missing link that allows a key regulatory complex to find and operate on the lone X chromosome of male fruit flies, bringing

them to parity with females. Called CLAMP, the protein provides a model of how such regulatory protein complexes find their chromosome targets.

They say a good man is hard to find. Were it not for a newly discovered protein, the X chromosome of a male fruit fly could never be found by a gene-regulating complex that male flies need to develop and survive. And that case is just one example of what the new finding means. More generally, the research provides biologists with a model of how proteins that govern gene transcription find their targets on chromosomes, a process that's essential to healthy cell function and sometimes implicated in disease.

The new protein, dubbed CLAMP by the Brown University scientists who led the discovery, is found in many species including humans. In fly embryos it turns out to be the missing link that brings together the X chromosome and the transcription complex MSL, which doubles the expression of the chromosome. That process, called dosage compensation, brings male flies up to parity with females who have two X chromosomes (in mammals, a similar process downgrades one of the female Xs to ensure parity). In fact, MSL stands for "male-specific lethal" because without it, and without CLAMP, the male flies would die.

Scientists have long puzzled over how MSL and the X chromosome came together, said Erica Larschan, assistant professor of biology in the Department of Molecular Biology, Cellular Biology and Biochemistry and corresponding author of the study published online July 15 in the journal *Genes and Development*. In fact, she said, they've lacked that understanding about many such interactions in which regulatory complexes govern the expression of genes in chromosomes.

"This is the last step of these signaling pathways that make the ultimate

regulatory decision about whether you are going to turn on a gene or keep it off at a particular time," Larschan said. "It's exciting because this protein has never been studied before."

In the new paper, Larschan, graduate students Marcela Soruco and Jessica Chery, and their team of collaborators describe several experiments that demonstrate how CLAMP binds to key sites on the X chromosome and then brings in MSL to those sites to do its work. They first turned up the protein in a wide sweep of the fly genome published last year. They were looking for possible missing link candidates, but hadn't yet figured out from the more than 100 they found which ones were genuinely promising. That process took years more work.

As they began to look more closely at CLAMP, they recognized that it has seven zinc ion-tipped "fingers" for grabbing, or clamping, onto DNA. They also noticed it also has a configuration elsewhere that seemed made for binding to a large protein complex.

In their experiments, both in flies and on the lab bench, they show that CLAMP binds DNA at specific sites known to be relevant for MSL's interaction with the X chromosome. They also showed that interfering with CLAMP prevents MSL from finding the X chromosome.

Positive feedback loop

Then they found something that amazed them. Rather than acting simply as an intermediate link, CLAMP works together with MSL to create a self-reinforcing feedback loop of activity at the X chromosome.

"That was a really big surprise," Larschan said. "I did those experiments myself. I kept doing it again and again because I was so surprised."

One of the more telling analyses took advantage of the sex-specificity of

the MSL complex. The researchers noticed that while CLAMP would bind to the X chromosome in both male and female flies, it would only progress past a certain degree in the males. The difference is that males have MSL and females don't.

What the researchers determined is that as a male fly embryo develops, CLAMP binds to some initial sites on the chromosome. That facilitates the assembly of MSL at the chromosome. MSL then opens up the coiled up DNA to expose more sites for CLAMP binding, which brings in more MSL.

Larschan speculates that the ability to instigate that kind positive feedback loop, perhaps in the future with a synthetic small molecule drug, could prove therapeutic in any diseases where a regulatory complex and its linking protein isn't operating properly at a chromosome.

"You could theoretically maintain those domains if they were misregulated," she said.

In addition to Larschan, Soruco and Chery, other Brown authors on the paper are Alexander Leydon, Arthur Sugden, Karen Goebel, Jessica Feng, and Peng Xia. Other authors are Eric Bishop, Michael Tolstorukov, and Peter Park of Harvard Medical School; and Tervor Siggers, Anastasia Vedenko, and Martha Bulyk of Brigham and Women's Hospital and Harvard.

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