UW scientist's cellular studies using frog eggs has cancer connection

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A smiling and very green Kermit looking down from a wall portrait seems to happily give a thumbs—or flipper—up to one of the University of Wyoming's self-described frog guys trying to unravel the mysteries of what in the world regulates cell nucleus size and its cancer implications.

Molecular biologist Dan Levy and his collaborators, using frog eggs, found the concentration of particular proteins—the nuclear lamin—appears to play a part in controlling the size of the cell nucleus. His laboratory is one of a few on campus using frog eggs to untangle cell secrets.

Turns out, there is an important cancer connection. The nucleus of a cancer cell becomes enlarged, and the size is even used to determine the stage of cancer, Levy says. If the basic proteins important for regulating

nucleus size are understood, scientists might be able to apply that to nuclear size changes in cancer and even use it diagnostically or, perhaps, even in a new treatment approach, he notes.

"If we can make the nucleus size small in cancer cells, that might be a way to treat those cancers," says Levy, in the College of Agriculture and Natural Resources.

The research results were in the Nov. 13 edition of The *Journal of Biological Chemistry*, published by the American Society for *Biochemistry* and Molecular Biology Inc.

Anyone wandering into a cell would pass the outer nuclear membrane first, then the inner nuclear membrane. Looking back, the lattice-like nuclear lamina composed of lamins would be seen sitting against the inner nuclear membrane and, like 2-by-4s in a house, provides shape and support. Electron microscope images show the lattice looking like a volleyball net or a woven basket with horizontal and vertical reeds.

Scientists have known the structure is important for providing mechanical structure to the nucleus and had hints lamins might be involved in regulating size.

"The big question was what the contributions of lamin amounts and types are to controlling the size of the nucleus," says Levy, who joined UW in 2011 after working as a postdoctoral fellow in molecular and cell biology at the University of California-Berkeley.

And so, scientists injected frogs with a hormone to induce prolific egg production, spun the eggs in a centrifuge to break the eggs and partition the results, and then extracted the proteins, membranes and cytoplasm. From that, they assemble nuclei in a test tube.

Researchers then add or remove specific proteins, and see how those manipulations affect nucleus size.

Low additions of Lamin B3 caused nuclei to become larger than control cell nuclei.

"That was already kind of cool, that lamins can increase the size of the nuclei," says Levy. "But what we were surprised to see is, if we added more lamins, the nuclei became smaller. To us, that was the most interesting part. We don't totally understand what's causing the reduction in size, but it is very robust and didn't depend on the type of lamin."

The process appears to be the same in human cells. His lab grew tissue cells and found the same results: increase lamins and increase nuclear size; reduce lamins and decrease nuclear size.

He says his lab's next step is to see if the nucleus can be reduced in cancer cells. Ph.D. candidate Lidija Vukovic will conduct the studies.

"I'm pretty excited about the work she's doing," says Levy. "We're mostly frog people, but we are starting to go a little more in this direction."

His lab also will study nuclear size during embryogenesis, or cell division.

Rather than crushed in the centrifuge and made into a protein cocktail, eggs are instead fertilized. The eggs begin rapid cell division, creating huge, single cells, which then divide into smaller cells. The cell nuclei are large early in development and decrease as cells become smaller.

Levy says determining whether or not lamin levels change as the cell moves through division was the real motivation behind the paper.

"There are some changes, but they don't seem to correlate with the size of the nucleus. We don't think it's changes in lamin expression that are regulating the nuclear size," he says. "That's kind of a bummer. That's what we were thinking. But, we still think lamin can affect the size of the nucleus even if they are not the mechanism responsible."

Provided by University of Wyoming