Scientists uncover the nuclear life of actin

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A key building block of life, actin is one of the most abundant and highly conserved proteins in eukaryotic cells.

First discovered in muscle cells more than 70 years ago, actin has a well-established identity as a cytoplasmic protein that works by linking itself in chains to form filaments. Fibers formed by these actin polymers are crucial to muscle contraction.

So it came as a surprise when scientists discovered actin in the nucleus. Labs have been working for the past few decades to figure out exactly what it's doing there.

A new study published this week in *Nature Structural & Molecular Biology* reveals that actin has a new and fundamental nuclear function, and that surprisingly, it accomplishes this task in its single-molecule (monomeric) form – not through polymerization.

Senior author of the study Xuetong "Snow" Shen, Ph.D., associate professor in The University of Texas MD Anderson Cancer Center Department of Molecular Carcinogenesis, has been fascinated by the mystery of nuclear actin. In collaboration with researchers from Colorado State University, his lab developed a unique model system to nail down actin's function in the nucleus by studying the actin-containing INO80 chromatin remodeling complex.

In 2000, as a postdoc at NIH in Carl Wu's lab, Shen identified actin as a component of the INO80 complex, adding to the growing list of evidence that actin indeed has a life in the nucleus. However, how actin actually works in the nucleus remains fuzzy due to lack of clear experimental systems.

"Our model system opened up a new opportunity to look in depth at the function of nuclear actin as it relates to gene regulation, genome stability, and ultimately cancer," Snow said.

A nuclear role for monomeric actin

Because yeast have only a single actin gene, the authors reasoned that studying INO80 in yeast cells would allow a direct assessment of the protein's nuclear function. In contrast, mammals have at least six forms of actin coded by separate genes, making their study more difficult.

The researchers used both genetic and biochemical methods to dissect actin's role in the INO80 complex. The INO80 complex normally functions in the nucleus to rearrange chromatin ¬– the intertwined proteins and DNA that are packaged into chromosomes – regulating the expression of many different genes.

The authors found that a mutant form of actin impairs the ability of INO80 to function correctly, implicating actin in the process of chromatin remodeling – an exploding field of research with applications in cancer diagnosis and treatment.

In the cytoplasm, actin functions primarily as a polymer. Cytoplasmic actin is a component of the cytoskeleton and the muscle contractile machinery, and is essential for cell mobility, including cancer metastasis. Actin inside the INO80 complex is arranged in a clever way such that it cannot polymerize; instead, actin's monomeric form appears to interact with chromatin.

"Our study challenges the dogma that actin functions through polymerization, revealing a novel and likely a fundamental mechanism for monomeric nuclear actin," Shen said.

New findings for an ancient complex

Because actin and several of the other INO80 components are so highly conserved, even in human cells, this mechanism likely represents an ancient, fundamental role of actin, which has been preserved through evolution.

Shen's group is now teasing out the exact mechanism by which nuclear actin interacts with chromatin. They also hope to extend the results to human cells and to identify potential ways by which nuclear actin could be involved in cancer.

Chromatin is critical for maintaining the delicate balance between gene activation and repression, Shen said. "Disrupting this regulation can lead to cancer, and it remains to be seen whether nuclear actin has a role in this process."

Provided by University of Texas M. D. Anderson Cancer Center

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