Protein lifetime and the stability of cell structures

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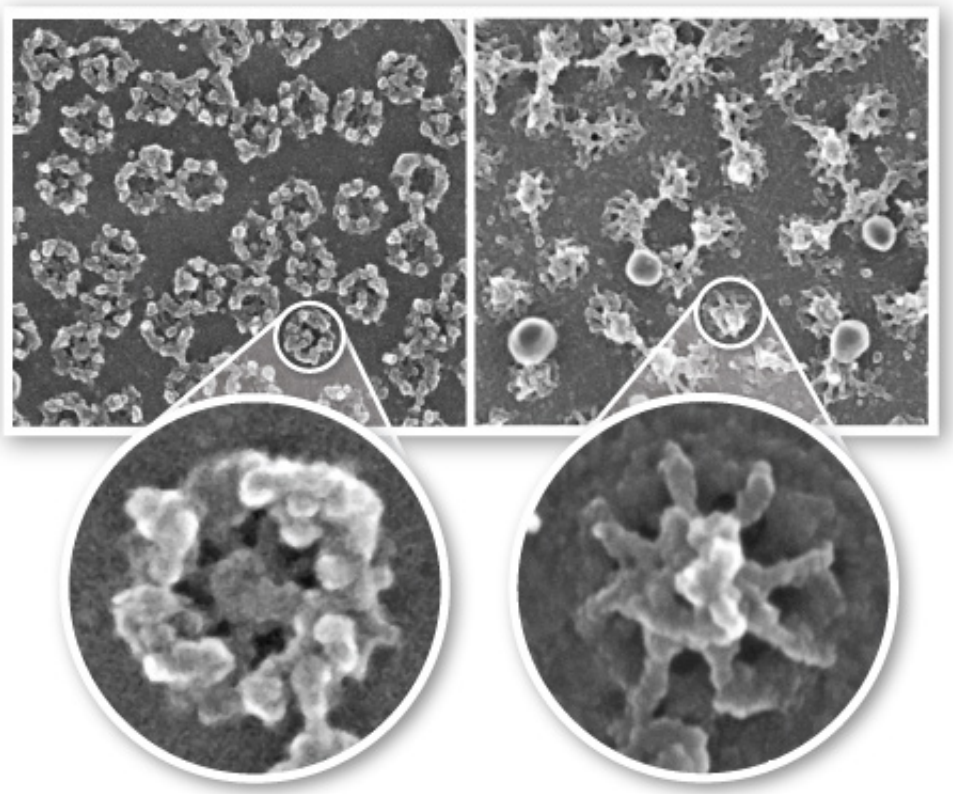

Some Nuclear pore complex proteins can last for the lifetime of the cell. Credit: learn.genetics.utah.edu

(Phys.org) —The ability of a cell to move, replicate, and recast itself according to the needs of the organism which it serves, comes at it price. The extreme flexibility of cells takes its origin from the constant

turnover of nearly every component with which they are made. There are a few exceptions to this general principle for a few protected regions like, for example, the lens of the eye, or the collagen matrix within the extracellular space. In a new paper published in *Cell*, researchers show that certain components of the pore complex that controls the flow of components out of the nucleus, escape the normal turnover cycle, and may persist for the lifetime of the cell.

Extracellular proteins, like crystallins of the lens, or components of cartilage, accumulate damage over time that compromises their function. Clouded vision or stiff joints are the familiar result. Inside cells however, an intricate accounting system exists whereby proteins are stochastically festooned with sequential markers for degradation—much like a trainee might predictably progresses through the colored ranks of Karate. In yeast, it has been reported that the average protein half-life is just 90 minutes, while for mammals it may be more like 1 or 2 days.

An exception to this rule is our DNA, which owes its long life to dedicated repair mechanisms that patch up damage. For proteins however, no such sequence-level mechanisms are known to exist. The histone proteins that bind DNA have also been observed, in some cases, to be exceptionally long-lived. Measuring these lifetimes reliably, particularly for the older generation, requires some special experimental considerations.

The researchers used a method called pulse-chase labeling, which requires feeding newborn rats a diet containing exclusively the 15N isotope as the *pulse*. A normal 14N diet, the *chase*, was begun after 6 weeks, and the animals then sacrificied at various times over the ensuing year. The cellular components were then fractionated and mass spectrometry was used to comprehensively identify long-lived proteins in the brain.

The lifespans of a few components of the nuclear pore complex (NPC) were particularly striking. The NPC contains multiple copies of over 30 different subvarieties of the nucleoporin (Nup) family alone. Two particular subcomplexes of Nup proteins, which serve as scaffold components, where found to resist degradation. The researchers also measured translation levels of these and 11,000 other proteins to measure synthesis levels concomitantly. Every long-lived protein was found to also be actively involved in translation.

Unlike other large protein complexes, such as ribosomes or proteasomes, the NPC apparently does not turnover as an entire complex. Instead individual subcomplexes are exchanged at specific rates as new copies are synthesized. What mechanisms might administer this exchange, if any, are as yet unknown. The researchers found, in particular, that 25% of those proteins within a certain complex (Nup205), have not been replaced after a year. Together with the histone H3.1 protein, that stat earns them the title of most persistent mammalian intracellular protein.

The authors speculate that disassembly of entire NPCs might not be practical for the cell because dismantling these key components could jeopardize the integrity of the nuclear envelope. Important nuclear substructure, possibly including epigenetic depots critical for transmitting information beyond the lifetime of an individual cell might then be compromised. They also note that long-lived proteins might also be sources of vulnerability within the proteome, particular those that would be exposed to harmful metabolites or chemical interlopers. Identification of these elements may therefore be important in understanding the aging process in postmitotic cells.

More information: Identification of Long-Lived Proteins Reveals Exceptional Stability of Essential Cellular Structures, *Cell*, Volume 154, Issue 5, 971-982, 29 August 2013. DOI: 10.1016/j.cell.2013.07.037

Abstract

Intracellular proteins with long lifespans have recently been linked to age-dependent defects, ranging from decreased fertility to the functional decline of neurons. Why long-lived proteins exist in metabolically active cellular environments and how they are maintained over time remains poorly understood. Here, we provide a system-wide identification of proteins with exceptional lifespans in the rat brain. These proteins are inefficiently replenished despite being translated robustly throughout adulthood. Using nucleoporins as a paradigm for long-term protein persistence, we found that nuclear pore complexes (NPCs) are maintained over a cell's life through slow but finite exchange of even its most stable subcomplexes. This maintenance is limited, however, as some nucleoporin levels decrease during aging, providing a rationale for the previously observed age-dependent deterioration of NPC function. Our identification of a long-lived proteome reveals cellular components that are at increased risk for damage accumulation, linking long-term protein persistence to the cellular aging process.

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