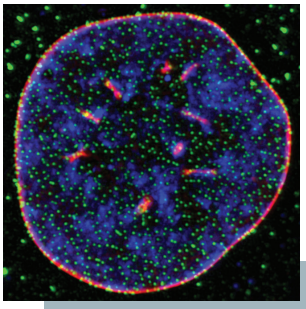

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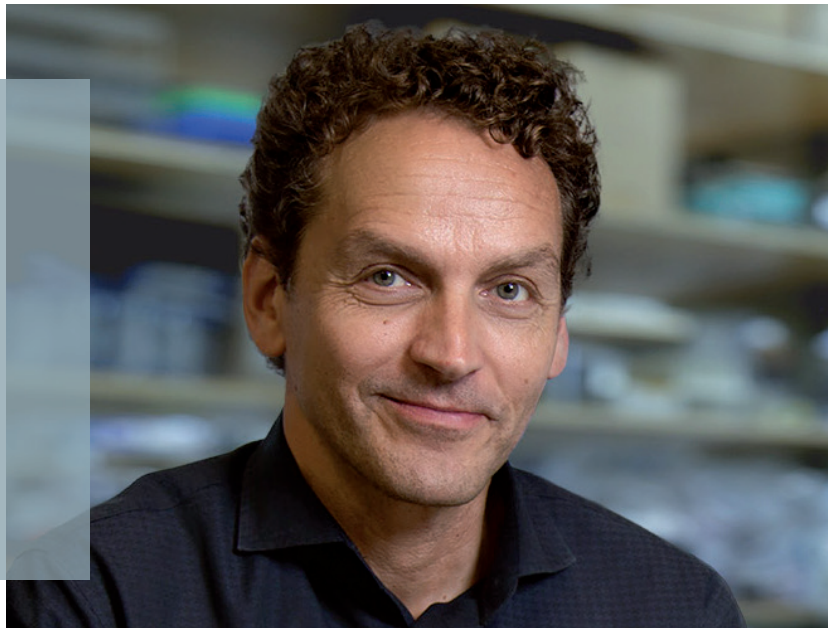

Martin Hetzer

Vice President, Chief Science Officer
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The Problem

The nucleus of a human cell uses a tight security system made up of a protective membrane. This membrane barrier, called the nuclear envelope, is perforated with channels and gates called nuclear pore complexes that only grant some molecules access to the genome. If the wrong molecules get into the nucleus and access the genome, they can incorrectly turn genes on or off or botch normal cellular programs. During aging and under some pathological conditions, the security system of the nucleus malfunctions. Cancer cells have been shown to have lapses in their nuclei, as have nerve cells associated with neurodegenerative diseases like Alzheimer's disease. To understand how the nuclear genome is inherited and maintained and how disrupted nuclei might cause disease—and how to boost these security systems again—scientists first need to understand the normal functioning of proteins that make up the nuclear security system.

The Approach

Martin Hetzer applies genomics, proteomics and advanced imaging biology techniques to pose questions about how the human genome is organized inside a cell's nucleus and why nuclear pore complexes fail to work properly as a cell ages. Hetzer was among the first to show that the nuclear pore proteins play a direct role in changing gene expression during normal and pathological development as well as cancer. The Hetzer laboratory also discovered long-lived proteins (LLPs) in the nucleus, which exhibit no or very little protein turnover in the adult brain. The functional decline of LLPs could be a major contributor to age-related changes in the survival of nerve cells. A focus of his lab is to understand what allows LLPs to stay intact throughout an organism's entire lifespan. In people with neurodegenerative diseases, it appears that LLPs in older cells lead to the decline of the nucleus. Understanding why this happens is the first step to potentially prevent and treat disorders like Alzheimer's disease.

The Innovations and Discoveries

- Hetzer showed that one of the ways nuclear pores manage to stay relatively stable for a cell's long life is by occasionally exchanging just one part of the channel complex at a time for a newer part. Since nucleoporin levels drop as a cell ages, however, Hetzer thinks this maintenance is limited.
- He also looked more broadly at the phenomenon of long-lived proteins (LLPs) in the rat nervous system. Most proteins in the body are replaced when they accumulate damage or begin to degrade. But LLPs—which include proteins that make up nuclear pores—last for a lifetime, Hetzer found.
- Hetzer's lab group recently developed a way to visualize and track micronuclei—small fragments of a cell nucleus. Some types of lung cancer cells, they showed, have especially high numbers of micronuclei, which are formed during mistakes in cell division. The new method will let them further probe how the formation and collapse of micronuclei is linked to cancer progression.

For more information, please visit:
www.salk.edu/scientist/martin-hetzer

Aging, Cancer, Neurobiology, Neurological Disorders, Parkinson's Disease