The Problem
The nucleus of a cell has a tight security system, composed of membranes dotted with channels and gates called nuclear pore complexes that only let some molecules through. If the wrong molecules get into the nucleus, they can incorrectly turn genes on or off or botch normal cellular programs. But sometimes the security system of the nucleus malfunctions: cancer cells have been shown to have lapses in their nuclei, as have brain cells associated with neurodegenerative diseases like Parkinson’s. To understand how these leaky nuclei might cause disease—and how to boost these security systems again—scientists first need to understand the normal functioning of nucleoporins, proteins that make up nuclear pore complexes.

The Approach
Martin Hetzer applies molecular biology techniques to pose questions about how nucleoporins mediate what happens inside a cell’s nucleus and why nuclear pore complexes can weaken as a cell ages. Researchers had assumed that irregular nucleoporins associated with some cancers let the wrong molecules in and out of the nucleus, and it’s those molecules that alter genes. But Hetzer was among the first to show that the nucleoporins sometimes have an even more direct role in changing gene expression—fragments of some nucleoporin proteins bind directly to genes. He’s now investigating how common this phenomenon is among nucleoporins and how it drives cancers.

He also studies what allows nuclear pore complexes to stay relatively intact throughout a cell’s entire lifespan. In most individuals, these channels continue to do their jobs even as cells divide many times over. But in some people with neurodegenerative diseases, it appears that the nuclear pores in older cells start letting large filaments into brain cells. Understanding why this happens is the first step to potentially preventing and treating diseases like Parkinson’s.

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 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: http://www.salk.edu/faculty/hetzer.html