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ESCRTs Take on a Job in Surveillance

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Nuclear pore assembly can go awry, but how the cell handles defective intermediates has been an ongoing question. In this issue, Lusk and colleagues describe a surveillance pathway during nuclear pore assembly and, in doing so, identify a new role for proteins that function at the endosome and plasma membrane.

Cells eliminate defective products through quality control mechanisms to ensure that biochemical pathways operate smoothly. One well-studied example of quality control is endoplasmic reticulum-associated degradation (ERAD), an intricate process by which secretory and membrane proteins that fail to fold properly within the confines of the endoplasmic reticulum are extruded into the cytosol for disposal by proteasomes (Ruggiano et al., 2014). ERAD is but one way in which cells guard against abnormal accumulations of proteins that might be nonfunctional or could potentially be dangerous. More pathways for quality control, however, remain to be discovered. In this issue of *Cell*, Webster et al. describe a new quality control pathway to eliminate nascent nuclear pore complexes (NPCs) that have failed to assemble properly and, in doing so, they unexpectedly broaden the realm of activities for a protein machinery that was originally discovered to function at endosomes.

Hundreds of NPCs perforate the double-membrane barrier created by the nuclear envelope to form aqueous channels that connect the cytoplasm with the interior of the nucleus. Given their sheer abundance, NPCs are constantly undergoing assembly in proliferating cells (Fernandez-Martinez and Rout, 2009). Humans and other eukaryotes undergo open mitosis during which NPCs are disassembled at the onset of mitosis into their constituent proteins, the nucleoporins. At the end of mitosis, these nucleoporins reassemble into new NPCs in the newly formed nucleus established in each daughter cell. Given that mitosis effectively doubles the amount of nuclear membrane, NPCs must also be assembled with newly synthesized nucleoporins since assembly with recycled nucleoporins is not sufficient to maintain the density of NPCs needed in the nuclei of daughter cells. NPC assembly is even more reliant on newly synthesized nucleoporins in the budding yeast *Saccharomyces cerevisiae*, which has a closed mitosis where the nuclear membrane remains intact, and pre-existing NPCs do not undergo disassembly.

In humans and yeast, defects in NPC assembly can result in aggregates of nucleoporins that decrease nuclear integrity, which is linked to a reduction in cellular replicative lifespan (Fernandez-Martinez and Rout, 2009). In this issue of *Cell*, the study by Webster et al. (2014) shows that in yeast, misassembled NPCs accumulate in a storage compartment they term the SINC, for storage of improperly assembled nuclear pore complexes. SINCs are preferentially retained in mother yeast cells during mitosis. This apparent act of altruism prevents defective NPCs from being passed on to progeny but saddles parental cells with the prospect of decreased NPC utility as they age. Indeed, the accumulation of SINCs in mother yeast cells correlates with a reduction in nucleocytoplasmic transport.

Unexpectedly, defective NPC assembly intermediates can avoid the SINC altogether through a pathway that involves the endosomal sorting complexes required for transport (ESCRTs). As their name implies, ESCRTs were originally identified because of their function at endosomes. In the canonical ESCRT pathway, five distinct protein complexes cooperate in the creation of vesicles that bud into the endosome lumen, and these intralumenal vesicles are destroyed in the interior of the lysosome upon endolysosomal fusion (Figure 1). However, ESCRTs have since been found to operate at the plasma membrane, where they are

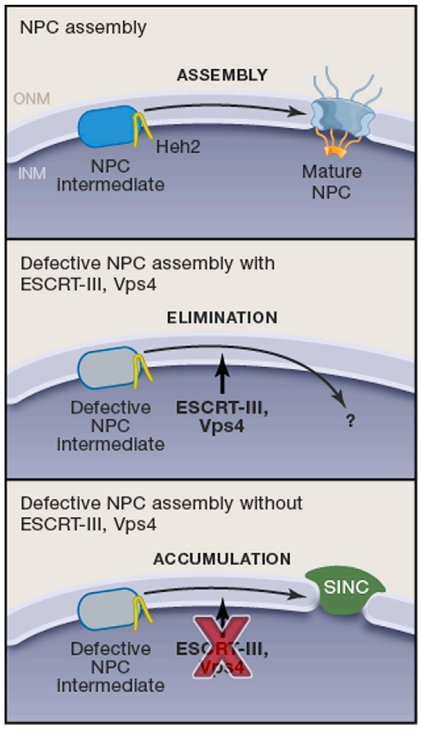

Figure 1. A New Pathway for NPC Assembly Quality Control

ESCRT-III and Vps4 were originally discovered because of their function at endosomes, where they catalyze the membrane scission reaction required for vesicles to bud into the endosome lumen. These intralumenal vesicles carry transmembrane proteins targeted for degradation within the interior of the lysosome. The study by Lusk and colleagues (Webster et al.) shows that ESCRT-III and Vps4 also function at the inner nuclear membrane (INM), where they function with Heh2 to mediate the disposal of defective NPC assembly intermediates. Without ESCRT-III or Vps4 function, defective NPC intermediates accumulate in the SINC. Successful assembly of an NPC intermediate results in the formation of a mature NPC forming an aqueous channel separating the INM and the outer nuclear membrane (ONM).

recruited by retroviruses to bud virions out of infected cells (Garrus et al., 2001) and where they function to separate daughter cells during cytokinesis (Carlton and Martin-Serrano, 2007). Thus, ESCRTs do not restrict their activity to endosomes alone.

Webster et al. now extend the known realm of ESCRT activity to the nuclear envelope by describing a role for ESCRTs in the recognition and clearance of defective NPC intermediates. Specifically, the authors show that a key subunit of the ESCRT-III complex, Snf7, interacts with Heh2, a transmembrane protein resident of the inner nuclear membrane that facilitates the assembly of NPCs (Figure 1). When NPC assembly is genetically disrupted, Snf7 and other members of the ESCRT-III complex colocalize with Heh2 at SINCs. Vps4 is an ATPase that disassembles ESCRT-III subunits from one another so they can undergo further rounds of complex assembly (Babst et al., 2002), and genetic disruption of Vps4 function both increases the number of SINCs and enriches ESCRT-III localization to these structures. The consequences of disrupting ESCRT-III/Vps4 function are manifested as a reduction in nucleocytoplasmic transport, which might explain why these mutations were seen previously to compromise cellular fitness.

The study by Webster et al. thus points to an unexpected role for ESCRT-III/Vps4 in a surveillance mechanism at the inner nuclear membrane (INM) that acts to guard against defects in the assembly of NPCs. However, none of the other ESCRT complexes were found to be involved, so what might ESCRT-III/Vps4 be doing to facilitate this process? Assembly of the ESCRT-III complex and its subsequent disassembly by Vps4 catalyzes membrane scission reactions both at endosomes and the plasma membrane (Hurley and Hanson, 2010), and a similar role for ESCRT-III/Vps4 at the nuclear envelope would imply that defective NPC assembly intermediates are eliminated by a membrane budding pathway. Alternatively, ESCRT-III might somehow guide Vps4 in remodeling misassembled NPCs, which is a plausible scenario given that Vps4 is a member of the AAA family of ATPases, and many AAA proteins disassemble transmembrane protein complexes (Hanson and Whiteheart, 2005). In fact, VCP/p97 (Cdc48 in yeast) is a AAA protein that functions in the ERAD pathway in which misassembled transmembrane proteins are dislocated from the endoplasmic reticulum and degraded by proteasomes (Ruggiano et al., 2014), and proteasome activity was found by Webster et al. to be required for degradation of individual nucleoporins when NPC assembly was stalled. Whether nucleoporins are similarly dislocated from the INM and how these nucleoporins might be transferred from the INM to proteasomes is unknown. What is clear, however, is that the study by Webster et al. has created opportunities to unravel the mechanical details of NPC surveillance and to learn how ESCRT-III/Vps4 functions in this process.

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