Progerin's 'discrimination' may contribute to fatal disease HGPS

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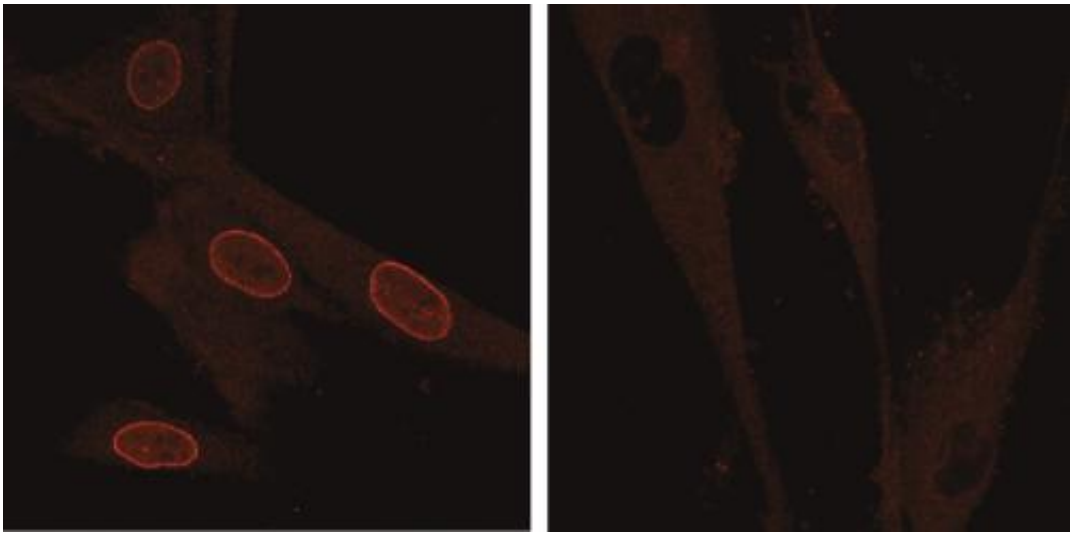

A new study in *The Journal of Cell Biology* suggests that the fatal disease HGPS might result from the selective exclusion of large proteins or protein complexes from the nucleus. One such protein, Tpr (red), accumulates in the nuclei of cells from a healthy person (left), but it remains in the cytoplasm of cells from an HGPS patient (right). Credit: Snow, C.J., et al. 2013. *J. Cell Biol.* doi:10.1083/jcb.201212117

A mutant protein responsible for Hutchinson-Gilford Progeria syndrome (HGPS) bars large proteins from entering the nucleus, according to a study in *The Journal of Cell Biology*.

The culprit in HGPS, a fatal disease that resembles premature aging, is a

protein variant called Progerin. This defective protein impairs cells in many ways, including reducing nuclear levels of the RanGTPase. Ran is crucial for nuclear import and export, as it stimulates unloading of cargo that has just entered the nucleus and loading of cargo that's ready to exit. Progerin also impedes the import of Tpr, which forms the basket-like structure on the inner side of nuclear pores. But the mechanism behind this exclusion wasn't clear.

One possibility is that Progerin disrupts the activity of Tpr's nuclear localization sequence (NLS). To test this idea, a team led by researchers from the University of Virginia replaced Tpr's NLS with the localization sequence from a protein that readily enters the nucleus. The modified Tpr was still locked out, however, suggesting that the effect wasn't related to its NLS.

Tpr is one of the largest proteins to traverse nuclear pores. The researchers found that Progerin also limits the nuclear import of three other hefty proteins. This size effect stems from the reduction in nuclear Ran levels triggered by Progerin. For reasons that are still unclear, large cargoes require more Ran to enter the nucleus. These findings suggest that some cellular defects of HGPS might result from the exclusion of large cargoes, such as multisubunit enzyme complexes, from the nucleus.

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