Progeria research: Substance from broccoli can moderate defects

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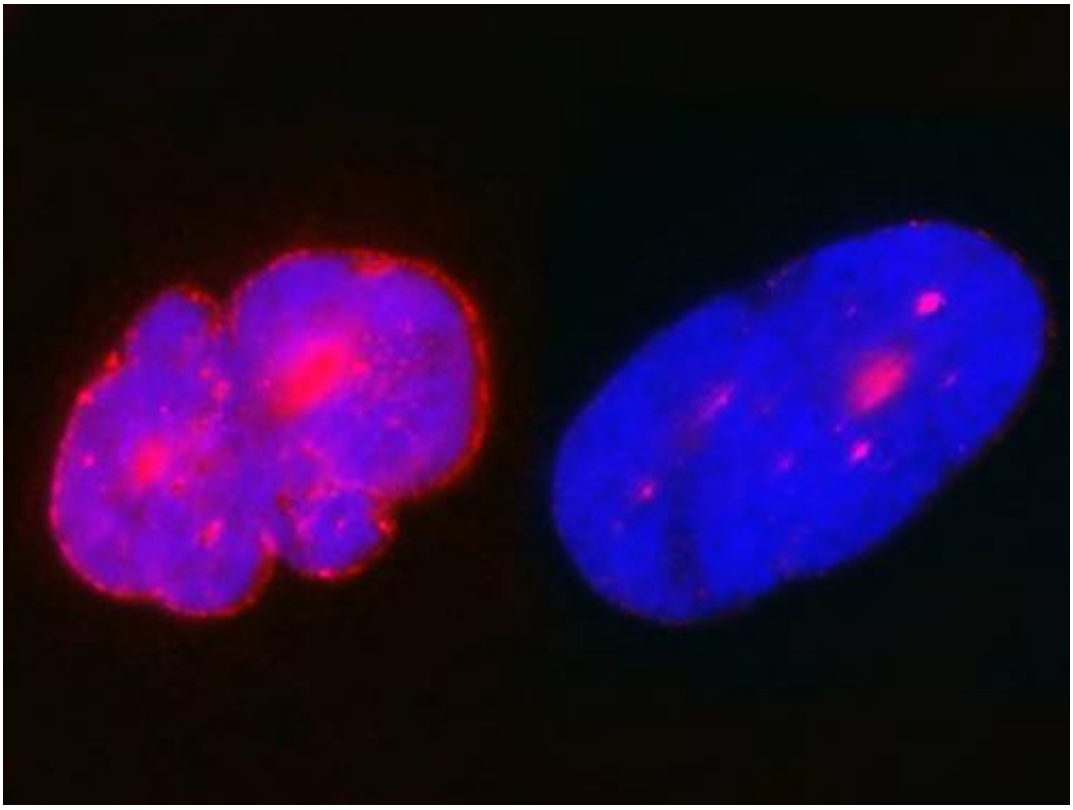

The image shows two cell nuclei containing human DNA (blue). Because of the large quantity of progerin (red), the nuclei in the cells of HGPS patients (left) are deformed in comparison to nuclei with very low levels of progerin (right). (Photo: K. Djabali / TUM The image shows two cell nuclei containing human DNA (blue). Because of the large quantity of progerin (red), the nuclei in the cells of HGPS patients (left) are deformed in comparison to nuclei with very low levels of progerin (right). Credit: K. Djabali / TUM

Children who suffer from Hutchinson-Gilford Progeria syndrome age prematurely due to a defective protein in their cells. Scientists at Technische Universität München have now identified another important pathological factor: the system responsible for removing cellular debris and for breaking down defective proteins operates at lower levels in HGPS cells than in normal cells. The researchers have succeeded in reactivating protein breakdown in HGPS cells and thus reducing disease-related defects by using a substance from broccoli.

Most Hutchinson-Gilford Progeria Syndrome (HGPS) patients carry a mutation that produces a defective form of the protein lamin A. This defective protein is referred to as progerin. Normal lamin A is a key component of the matrix surrounding the DNA in the cell nucleus and plays a role in gene expression. By contrast, the defective form, progerin, is not functional but is nevertheless continuously synthesized. The result is that progerin accumulates in the nucleus and causes the cell to "age". Consequently, HGPS patients develop classic diseases of old age such as atherosclerosis, osteoporosis, heart attacks and strokes. The disease is therefore regarded as a possible model system for the natural aging process in cells.

A window on the cell nucleus

In order to find out which specific metabolic pathways are affected by the mutation and the defective protein, Prof. Karima Djabali and her team from the TUM School of Medicine and the Institute for Medical Engineering conducted a comparative study of diseased and healthy tissue cells in which they investigated the composition of proteins in the cell nuclei and looked for differences.

However, initially they were struck not by a difference but by a common characteristic: they found that both healthy and diseased cells contained the defective protein form progerin, albeit not at the same amounts.

"Progerin is also produced in healthy cells, probably as a byproduct. A well-functioning cellular waste disposal system can break down these small quantities of progerin," says Djabali. The scientists found, however, 10 to 20 times more progerin in the nuclei of diseased cells - a huge backlog of debris that needs to be removed.

Debris removal disrupted in HGPS cells

The scientists observed though that the cellular debris removal systems, known as proteasome and autophagy no longer functions sufficiently in HGPS. These two degradation systems are made of very large protein complexes responsible for breaking down defective or excessive proteins. In HGPS cells, some of these essential components are produced at lower levels. "These errors in the cellular debris disposal system enhance the effect that progerin accumulates and causes cell damage within a short time," explains Djabali. In total, the researchers found more than 28 proteins with a broad range of functions that are faulty in the cell nuclei of HGPS patients - all resulting from a single mutation in the lamin A gene.

Substance from broccoli as a new therapeutic approach?

The scientists then combed the literature in search of substances that activate the proteasomal activity and autophagy and could therefore counteract the accumulation of progerin. In their quest, they found a substance in broccoli called sulforaphane that activates protein degradation in cells. The scientists treated the HGPS-cells with the substance and found that significantly less progerin accumulated within the cells. Moreover, DNA damage and nuclear deformations, other effects of the disease, were also reduced in treated than in untreated cells.

"Of course our experiments are very basic, but every active substance and every new approach brings us a step closer to a treatment for HGPS patients. It could also help us develop anti-aging strategies in the future," explains Djabali.

More information: Gabriel D., Roedl D., Gordon L. B. and K. Djabali, Sulforaphane enhances progerin clearance in Hutchinson-Gilford progeria fibroblasts, *Aging Cell*, 2014.
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