Researchers discover new cell structures

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Carnegie Mellon University researchers Kris Noel Dahl and Mohammad F. Islam have made a new breakthrough for children suffering from an extremely rare disease that accelerates the aging process by about seven times the normal rate.

Dahl, an assistant professor of chemical and biomedical engineering at Carnegie Mellon, said her work with researchers at the National Cancer Institute of the National Institutes of Health (NIH), the John Hopkins University School of Medicine and the University of Pennsylvania reveals that children suffering from Hutchinson-Gilford Progeria Syndrome (HGPS) have an excessively stiff shell of proteins.

The nucleus in all three trillion cells of the human body contains the DNA genome, which is wrapped with a stiff protein shell called the nuclear lamina. Children with HGPS have a mutation in one of the proteins of the lamina shell. For years, experts have thought this mutation made their nuclei much softer and more likely to be ruptured when cells were under stress.

But in a *Proceedings of the National Academy of Sciences* (PNAS) Journal article to be published this month, Dahl and her colleagues show that the lamina shell in HGPS patients is stiffer than normal. However, stiffer isn't necessarily better. The stiffer lamina did protect the HGPS nucleus from some forces, but under excessive force the HGPS lamina was more brittle and eventually fractured.

"The mutant HGPS lamina is like an egg shell that cracks when

excessive pressure or force is exerted against it," Dahl said. "By contrast, normal lamina resembles the rubbery outer shell of a racquetball, which does not break under stress or force but can assume its original shape even after hard play."

The researchers also think that the stiffer lamina in HGPS patients may be unable to communicate the proper biological signals to the DNA inside the nucleus to help the cell grow, which contributes to the disease.

Islam, an assistant professor of chemical engineering and materials science and engineering, says that the increased stiffness of the lamina may be caused by mutant proteins self-organizing into ordered structures within the HGPS lamina.

"This could make the lamina stiffer and cause fractures in the nuclei," Islam said. The healthy lamina remains disordered and therefore less rigid.

"Once we understand what causes the lamina to stiffen, we can try to reverse or stop the problem," Dahl said. "We think this stiffening mechanism happens over time with increased protein concentration, so we need to determine the tipping point that causes real problems."

When people grow old, the walls of the cell nuclei exhibit similar problems to the HGPS nuclei, like losing their round shape and perkiness. "Our NIH collaborators have also found that the normal aged nuclei show the same structural changes as HGPS," Dahl said.

Source: Carnegie Mellon University