Circulation: Scientists Discover the Cause of Accelerated Atherosclerosis and Premature Death in Progeria

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Hutchinson-Gilford syndrome (HGPS, also known as progeria) is a very rare genetic disease that affects fewer than 400 people in the world and for which there is no effective treatment. HGPS is characterized by early aging accompanied by the development of atherosclerosis. Patients die at an average age of 14 years from a heart attack or stroke, processes triggered by the rupture of unstable atherosclerotic lesions. Now, scientists at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) and the CIBER de Enfermedades Cardiovasculares (CIBERCV), led by Dr. Vicente Andrés, have generated the first genetically modified mice with accelerated atherosclerosis induced by the protein progerin, which causes the development of HGPS. The research team found that the main cause of accelerated atherosclerosis and premature death in these mice was alterations in the smooth muscle cells lining the blood vessels. The results of the study, published today in Circulation, identify vascular smooth muscle cells as a possible therapeutic target for combatting the premature atherosclerosis in progeria. The study was conducted in collaboration with Dr. Carlos López-Otín of the University of Oviedo and Dr. Jacob Bentzon at the CNIC.

Age is the main risk factor for cardiovascular diseases, which are the principal cause of death and disability in the world. This is in large part a consequence of the progressive population aging in
modern societies. In HGPS, cardiovascular deterioration and aging are accelerated by the 
accumulation of an anomalous protein called progerin, produced as a consequence of a point 
mutation in the LMNA gene. Children with HGPS are heterozygous for this mutation and show 
symptoms of premature aging, including loss of hair and subcutaneous fat, osteoporosis, joint 
stiffness, and wrinkled and mottled skin.

There is currently no effective treatment for HGPS and knowledge is very limited about the 
mechanisms underlying the accelerated atherosclerosis in this disease. This situation is in large part 
due to the lack of specific animal models. Now, using mice with the disease-causing LMNA mutation 
and expressing progerin in all tissues, the researchers from the CNIC, CIBERCV, and the University of 
Oviedo have generated the first animal model of progeria that features premature atherosclerosis, 
the main cause of death in children with HGPS. The team also analyzed mice that express progerin 
only in specific tissues implicated in the development of atherosclerosis in order to identify the cells 
responsible for cardiovascular disease in HGPS.

Plaque rupture

Atherosclerosis is characterized by a progressive thickening of the artery wall and a narrowing of the 
blood vessel due to the growth of the atherosclerotic plaque. Rupture or erosion of the plaque can 
trigger a heart attack or stroke. These serious complications normally occur after atherosclerosis has 
been progressing for several decades, but are tragically brought forward in patients with HGPS. 
According to first author Dr. Magda Hamczyk, “we found that smooth muscle cells in the arterial wall 
die early in the development of disease in the progeroid mice, and this induces an anomalous 
accumulation of lipoproteins in the vessels. This significantly increases the formation of 
atherosclerotic plaques, and the loss of smooth muscle also destabilizes the plaques and promotes 
plaque rupture in more advanced stages.” Co-author Dr. Ricardo Villa-Bellosta added that “plaque 
rupture can cause a myocardial infarction and lead to the death of the animal.”

These results also identify the vascular smooth muscle cells as a potential target for treatments to 
combat premature atherosclerosis in HGPS. According to Dr. Vicente Andrés, “this new animal model 
is allowing us to advance knowledge of the molecular and cellular mechanisms that cause 
cardiovascular disease and accelerated aging in progeria, an indispensable goal for the development 
of new therapies for patients with this severe disease.” Moreover, progerin is detected in cells and 
tissues of individuals not affected by HGPS, as part of normal physiological aging, which shares many 
features with premature aging in progeria. “Research into progeria can therefore help to identify 
mechanisms underlying normal aging and promote a healthier old age.”

and Death in a Mouse Model of Hutchinson-Gilford Progeria Syndrome. Circulation. 
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