New diagnostic clues found for life limiting lung condition

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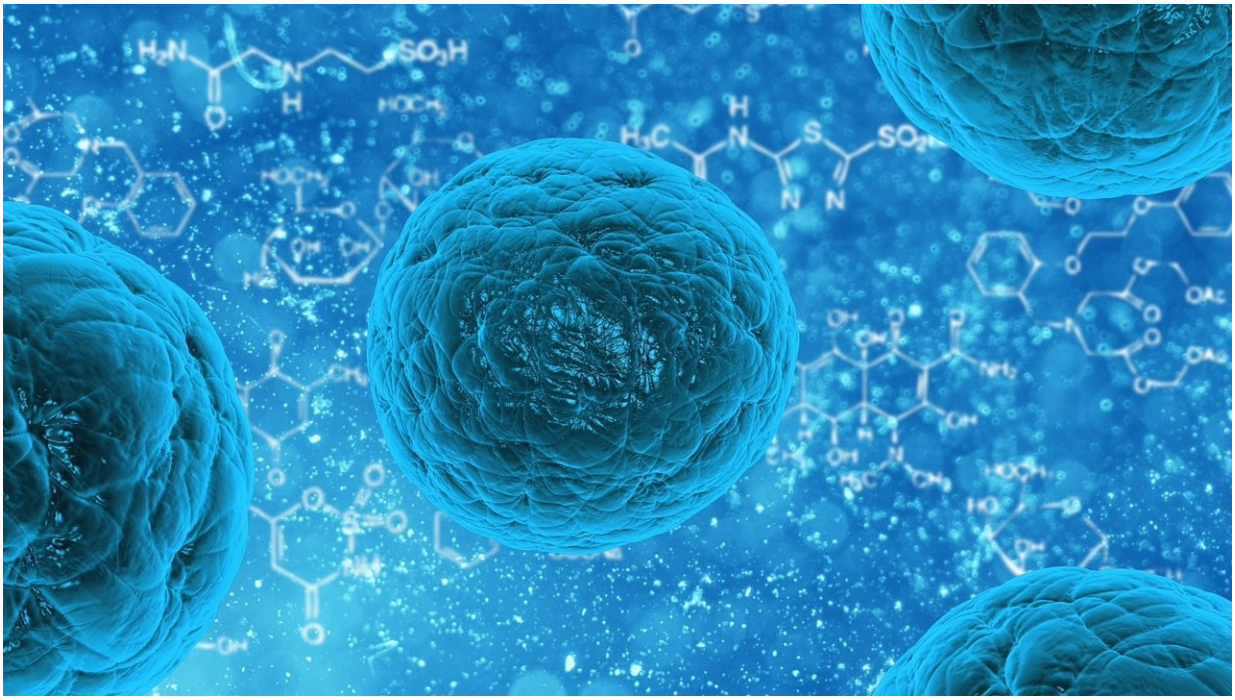

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A new biomarker that could be used to provide earlier diagnosis for a life limiting lung condition has been identified by researchers at the University of Bradford.

Pulmonary arterial hypertension (PAH) affects around 6,500 people in the UK and is caused by a narrowing of the arteries supplying blood to

the lungs. This leads to high blood pressure and, eventually, to heart failure.

PAH can occur spontaneously at any age. There is no cure and current therapies can cost up to £100,000 per patient. Symptoms—including shortness of breath and tiredness—are similar to many other cardiovascular conditions, so it can take up to four years to get a diagnosis.

The new study, published in *Human Molecular Genetics*, identifies a particular protein responsible for a build-up of cells in the blood vessels. It was led by the University of Bradford and includes researchers from the University of Cambridge (UK), Kings College London (UK), University of Dhaka (Bangladesh), Centre for Health Agricultural and Socio-economic Advancements (CHASA, Bangladesh) and Hacettepe University (Turkey).

The study builds on earlier research to investigate the genetic causes of PAH—in particular the mechanism of one faulty gene, known as BMPR-II, which was first identified nearly two decades ago.

Dr. Talat Nasim, in Bradford's School of Pharmacy and Medical Sciences, has previously shown that mutations in BMPR-II are responsible both for two important processes behind the disease. In the first of these, cells forming the wall and lining of the arteries supplying blood to the lungs reproduce excessively; while in the second the mechanism that causes old or unwanted cells to die—apoptosis—is reduced. Together, these processes cause the blood vessels to become narrow or blocked.

Understanding precisely how BMPR-II contributes to each of these processes has taken many years of investigation. In a 2012 study published in *Human Molecular Genetics*, the team showed how BMPR-II

drives the excessive production of cells. The current study focuses on the second challenge—how apoptosis is affected by the faulty gene.

Dr. Nasim explains: "We wanted to find out why the cells are not dying, but instead were building up inside the wall of the pulmonary arteries. To do this, we needed to identify and investigate the proteins that are influenced by this gene."

The team discovered that the faulty BMPR-II gene affected one particular protein called Bcl-x. This, in turn, is responsible for making two different proteins, one of which increases cell apoptosis, and the other one reduces it. These two work in balance in the body to regulate cell death. If BMPR-II is faulty, however, the protein for reducing cell apoptosis is increased—preventing cell death from occurring.

"This protein can be used as a biomarker for accurately identifying PAH in patients," says Dr. Nasim. "This could help us diagnose PAH at an earlier stage, possibly leading to better treatment options for patients. We can also make other services available, such as genetic counselling, to help patients understand the disease and to identify those at risk of developing it."

Co-author, Professor Nick Morrell, from the University of Cambridge, says: "This exciting work adds significantly to our understanding of how inherited forms of PAH are caused, and potentially offers a new way to diagnose the disease early. Early diagnosis and early treatment means better outcomes for our patients."

Co-author, Professor Richard Trembath from Kings College London, says: "PAH remains a challenging condition to manage and the findings reported in the present work offer additional insights as to both the process of development of PAH and ways of monitoring the progression of the disease. Further studies are now required to determine the utility

of this approach."

Dr. Nasim's team has filed a patent for the biomarker and is now investigating whether it could also be a target for new drugs. A number of promising compounds are currently being developed and tested in animal models.

More information: H M Chowdhury et al, BMPRII deficiency impairs apoptosis via the BMPRII-ALK1-BclX-mediated pathway in pulmonary arterial hypertension (PAH), *Human Molecular Genetics* (2019). DOI: 10.1093/hmg/ddz047

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