Cutting off the oxygen supply to serious diseases

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A new family of proteins which regulate the human body's 'hypoxic response' to low levels of oxygen has been discovered by scientists at Barts Cancer Institute at Queen Mary, University of London and The University of Nottingham.

The discovery has been published in the international journal Nature Cell Biology. It marks a significant step towards understanding the complex processes involved in the hypoxic response which, when it malfunctions, can cause and affect the progress of many types of serious disease, including cancer.

The researchers have uncovered a previously unknown level of hypoxic regulation at a molecular level in human cells which could provide a novel pathway for the development of new drug therapeutics to fight disease. The cutting-edge work was funded by the Biotechnology and Biological Sciences Research Council (BBSRC).

Proteins are biochemical compounds which carry out specific duties within the living cell. Every cell in our body has the ability to recognise and respond to changes in the availability of oxygen. The best example of this is when we climb to high altitudes where the air contains less oxygen. The cells recognise the decrease in oxygen via the bloodstream and are able to react, using the 'hypoxic response', to produce a protein called EPO. This protein in turn stimulates the body to produce more red blood cells to absorb as much of the reduced levels of oxygen as possible.

This response is essential for a normal healthy physiology but when the hypoxic response in cells malfunctions, diseases like cancer can develop and spread. Cancer cells have a faulty hypoxic response which means that as the cells multiply they highjack the response to create their own rogue blood supply. In this way the cells can form large tumours. The new blood supply also helps the cancer cells spread to other parts of the body, called 'metastasis', which is how ultimately cancer kills patients.

The scientists have identified a new family of hypoxic regulator proteins called 'LIM domain containing proteins' which function as molecular scaffolds or 'adapters' bringing together or bridging two key enzymes in the hypoxic response pathway, namely PHD2 and VHL. Both of these are involved in down-regulating the master regulator protein called Hypoxia-inducible factors (HIF1). The research has shown that loss of LIMD1 breaks down the bridge it creates between PHD2 and VHL and this then enables the master regulator to function out of control and thus contribute to cancer formation.

Molecular Oncologist, Dr Tyson Sharp, who carried out research for the project at The University of Nottingham's School of Biomedical Sciences, said: "The results from this research represent a significant advancement in our understanding of precisely how the hypoxic response works. It will help researchers develop better drugs to fight cancer and also other human diseases that are caused by low levels of oxygen within our body such as anaemia, myocardial infarction (heart attack), stroke and peripheral arterial disease. Further work in this fascinating area is now continuing at Barts Cancer Institute at Queen Mary University of London and will form the basis of a whole new additional research theme for my group."

Provided by University of Nottingham