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Researchers discover possible strategy against stroke

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Scientists at VIB and KU Leuven have identified the oxygen sensor PHD1 as a potential target for the treatment of brain infarction (ischemic stroke). Despite (minor) improvements in stroke treatment, stroke remains the fourth leading cause of death and the most common reason of severe disability. The impact of stroke is overwhelming for the patient, family and society -representing one of the largest unmet medical needs. Research led by prof. Peter Carmeliet and dr. Annelies Quaegebeur (VIB/KU Leuven) indicates that inhibition of PHD1 offers protection against stroke, via an unexpected mechanism, raising hope for future stroke treatment. The study was published in the leading medical journal *Cell Metabolism*.

The importance of PHD1 in the brain

Of all organs in our body, the brain is unique because it needs the highest levels of oxygen and glucose to function and to survive. The simple reason herefore is that brain cells absolutely rely on oxygen and glucose to generate energy, necessary to function normally. In stroke, reduced blood supply therefore threatens this energy balance, causing neurons to die. The Carmeliet lab discovered that brain cells sense and adapt to a shortage of oxygen and nutrients via PHD1.

The Peter Carmeliet lab observed that mice lacking the oxygen sensor PHD1 were protected against stroke induced by an obstruction of a main blood vessel supplying oxygen and glucose to the brain. Not only was

their infarct size reduced by more than 70 % (which is an unusually large beneficial effect), but mice lacking PHD1 also performed much better in functional tests after stroke.

Peter Carmeliet (VIB/KU Leuven): "These results established for the first time that blocking PHD1 offered large protection against irreparable brain damage when blood vessels can no longer supply vital nutrients to brain cells".

Reprogramming of glucose metabolism - a first in class mechanism

A critical problem when brain cells are deprived of oxygen is that they generate damaging side-products, "oxygen radicals", which kill brain cells. Most previous stroke treatments are unsucessful, because they are based on the principle to target the consequences rather than the cause of these oxygen radicals. The Peter Carmeliet lab focused on a completely new concept, i.e. utilizing the endogenous power of brain cells to enhance the neutralization of these toxic side-products. The researchers now discovered that inhibition of the oxygen sensor PHD1 protects brain cells against these toxic side-products by reprogramming the use of sugar in low-oxygen conditions.

Dr. Annelies Quaegebeur (VIB/KU Leuven): "By reprogramming glucose utilization, neurons lacking PHD1 have an improved capacity to detoxify damaging oxygen radicals, protecting the brain against stroke. This is a paradigm-shifting concept in the field of stroke protection."

Translational potential of PHD1 inhibition for stroke

While further study is necessary, this research identifies PHD1 as a potential therapeutic target for stroke. Prof. Peter Carmeliet (VIB/KU

Leuven): "Similar to genetic loss of PHD1, treating mice with a pharmacological PHD1 blocker protected mice against stroke. This raises the possibility that PHD1 inhibition might be clinically useful, but future research will be necessary to unveil the therapeutic potential in this debilitating disorder.

More information: Quaegebeur et al., Deletion or Inhibition of the Oxygen Sensor PHD1 Protects against Ischemic Stroke via Reprogramming of Neuronal Metabolism, *Cell Metabolism* (2016).

Provided by VIB (the Flanders Institute for Biotechnology)

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