Toxins from diseased brain cells make diseases of the brain even worse

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Sometimes our immune defence attacks our own cells. When this happens in the brain we see neurodegenerative diseases such as dementia, Alzheimer's and Parkinson's disease. But if the the immune defence is inhibited, the results could be disastrous. Researchers at the University of Copenhagen have now discovered one of the molecular combat mechanisms in the brain that gets out of control in these diseases. In time this may enable targeted therapies to slow down the disease without harming the patient.

"In their attempt to recover, diseased brain cells release chemical waste products into the brain", says Associate Professor Frederik Vilhardt from the Faculty of Health and Medical Sciences. "Unfortunately this makes the automated soldiers of the immune defence in the brain retaliate with high levels of free radicals the way they do with infections, and unfortunately they also attack the healthy nerve cells. This starts a vicious circle. We have discovered hitherto unknown facets of the biological mechanism that the immune cells use for creating the free radicals. This may lead to therapies to slow the neurodegenerative diseases."

The many different troops of the immune system include the macrophages. They are like robotic vacuum cleaners on autopilot, constantly removing any foreign bodies they encounter. They do so by ingesting microorganism and cell remains, putting them into a kind of stomach, and then bombarding them with free radicals such as the familiar hydrogen peroxide, which chemically destroys the stomach

content.

The macrophages create their free radicals with a mobile molecular gun battery - known as NADPH Oxidase among scientists - an enzym, which is located on the surface of newborn immune cells. It secretes free radicals to destroy the foreign bodies the macrophage meets, but can also use the free radicals to signal the logistics troops of the immune system: the T-cells. This occurs when the macrophage ingests a virus and needs to warn the immune system that there is a threat.

But normally the radical battery is moved to the inside of the macrophage where it eliminates the virus and other foreign bodies it ingests. So under normal circumstances this immune cell only releases a few free radicals to its environments when it is combatting invading micro organisms. This option may mean life or death in the brain, where nerve cells are extremely sensitive to free radicals.

"This battery is a vital component of a well-functioning immune system", Associate Professor Vilhardt continues. "If the NADHP Oxidase does not work in the macrophages, patients become so ill that they die".

This is because if the macrophages do not remove foreign bodies, the immune system decides instead to encapsulate viruses, bacteria, fungus and parasites in special shells. These granulomata accumulate in the body until they kill the patient before the latter has reached the age of thirty. This disease is known as Chronic granulomatous disease.

"Things have to be in balance", says Associate Professor Vilhardt. "In neurodegenerative diseases such as Alzheimer's and dementia the level of free radicals in the brain is out of balance: it is too high".

New research will target treatment of brain diseases

He and his colleagues have discovered that the high free radical levels arise in the brain because the macrophages react to the waste products o the diseased brain cells by transferring the combat batteries to the surface, and the vulnerable nerve cells become inundated by high levels of free radicals.

"Unfortunately, completely preventing the activity of the macrophage free radical battery is a bad idea, because then it can't kill bacteria and other foreign bodies, and in effect you give the patient Chronic granulomatous disease", he says.

"Instead, we need to persuade the macrophages in the brain to retract the batteries into their insides. Then they will no longer be able to emit free radicals into the brain, but will continue to be able to ingest and destroy the waste products of the diseased nerve cells. This will enable us to inhibit the neurodegenerative diseases. This is the project I and my colleagues are now starting work on".

More information: NADPH Oxidase is Internalized by Clathrin-Coated Pits and Localizes to a Rab27A/B GTPase-Regulated Secretory Compartment in Activated Macrophages has just been published in the *Journal of Biological Chemistry.*

Provided by University of Copenhagen