A new pathway for halting neuronal death in Huntington’s disease

The body is an extremely complex puzzle in which every piece plays a critical role. Should pieces disappear harmony is compromised. Such is the case with certain neurodegenerative diseases; when neurons suddenly die, the body’s ability to function properly is jeopardized. CNRS¹ and INSERM biologists from the Curie Institute are working to understand how neurons die in one specific neurodegenerative disease: Huntington’s disease. They have just announced the discovery of two new factors capable of blocking cell death induced in Huntington’s disease. They may eventually provide targets for the therapeutic treatment of this type of disease. These discoveries were published in the 7th of June issue of Developmental Cell.

Huntington’s disease, also known as Huntington chorea, is a rare neurological disease that affects one in every 10,000 individuals. The disease’s most striking symptoms, which are usually manifested between the age of 35 and 50 years, include abnormal and involuntary jerky movements of the limbs, head and neck (chorea). Other symptoms include behavioral problems (anxiety, irritability, depression, etc.). As the disease progresses, a slow intellectual deterioration inevitably leads to dementia. Death occurs between 15 to 20 years after the onset of the disease, usually due to complications (pulmonary emboli, pneumonia, or similar infection).

Clinical diagnosis is often long and difficult to establish due to a wide range of symptoms that can easily be confused with other psychological disorders. Diagnosis should be confirmed by MRI scan of the brain or by genetic testing. If a family history of the disease can be established, predictive gene testing can be done on asymptomatic family members. However, this step must be thoughtfully considered beforehand as the disease’s initial symptoms appear relatively late, and at present, there is no treatment that can effectively delay the onset or the development of the disease.

A mutant protein: huntingtin

Huntington’s disease is an autosomal dominant genetic disorder: if one of two parents carry the mutant gene, 50% of their offspring will inherit the mutation and develop the disease. The IT15 gene responsible for the disease, located on chromosome 4, enables the synthesis of the huntingtin protein, whose function has yet to be established. In its normal state, this protein contains repeated tracks of the amino acid glutamine. These repeats can become dangerous: if a threshold of 35 to 40 glutamines is exceeded, huntingtin becomes mutant and induces the disease. The more numerous the repeats, the earlier the symptoms appear.

It has been established that this abnormal expansion of glutamines is responsible for a change in the structure of huntingtin, which by some still poorly understood mechanism provokes neuronal cell death.

A number of other neurodegenerative diseases have also been linked to the same type of mutation. Different, specific regions of the brain are affected in each of these diseases. In Huntington’s disease, it is the striatum neurons (implicated in motor control), which gradually degenerate.

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Under the direction of Frederic Saudou\textsuperscript{2}, a research team ("Intracellular signalling and neuronal death" UMR 146 CNRS/Institut Curie) studying Huntington’s disease, has focused particular attention on the proteins suspected of playing a role in the neuronal death associated with this disease.

A model to understand neuronal death

To shed light on the mechanisms involved when neuronal death is induced by mutant huntingtin, researchers at the Curie Institute developed a cell model that reproduces the disease’s characteristics. The tool had already proved to be ideal as it allowed them to demonstrate that the huntingtin protein had to build up within the nucleus of the cell to induce neuronal death by apoptosis\textsuperscript{3} (see inset on page 3).

Using the same tool, Sandrine Humbert\textsuperscript{4}, a member of Frederic Saudou’s team, has just demonstrated that the proteins IGF-1 and Akt (see opposite) have a protective effect in the cellular model that reproduced the pathological symptoms.

Indeed, IGF-1 and Akt are capable of blocking both neuronal death and the formation of intranuclear aggregates within cells where the huntingtin protein is mutant.

The researchers also discovered how the Akt protein "disrupts the plans" of mutant huntingtin: it chemically modifies it (via a mechanism known as phosphorylation), which leads to a change in both form and function. Once the huntingtin protein is altered by Akt, they noticed that aggregates no longer form in the nucleus and that apoptotic death is prevented. It is therefore a chemical modification that nullifies the negative effects of the mutant huntingtin protein inside the cells.

This is the first time factors that have a direct impact on the protein implicated in Huntington’s disease have been discovered.

Furthermore, Frederic Saudou’s team has demonstrated that the protein Akt has an abnormal appearance in patients suffering from Huntington’s disease. This provides further proof, if any were needed, of the role of Akt in the development of this disease.

The IGF-1/Akt signaling pathway: a therapeutic turning point?

Although these discoveries are still at a fundamental stage, they already point towards promising new treatments for Huntington’s disease. It is conceivable that the IGF-1 or Akt proteins may provide a therapeutic target for "deactivating" apoptosis, thus giving hope to all those afflicted with Huntington’s disease.

Eventually, research into treatments for other diseases like cancer, in which apoptosis plays a key role (see inset on page 3), may also benefit from these discoveries.

Référence

The IGF-1/Akt pathway is neuroprotective in Huntington’s disease and involves Huntingtin phosphorylation by Akt

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\textsuperscript{3} Results published in the journal Cell in 1998 (95, p. 55-66), by Frederic Saudou.
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More information:

Requiem for a cell

In every living organism, cells grow, reproduce, and then die. But there are several ways they die. For example, when a cell is exposed to excessive stress or extreme temperatures (e.g., following a burn or abrasion), it ruptures and dies a violent death. The cell’s contents are widely dispersed, often leading to an inflammatory reaction. This accidental death is called "necrosis."

Apoptosis: programmed cell death

The cells can also "commit suicide," this is known as programmed cell death, or apoptosis. This form of cell death occurs throughout one's life, beginning in the womb. In fact, apoptosis enables the embryo to develop and plays a role in the gradual growth of the body and its organs. Approximately 85% of the neuronal cells that grow inside the embryo’s brain are eventually eliminated. This "cleansing" is essential to prevent a surplus of brain cells that could prove detrimental to the proper function of the brain.

In addition to eliminating excess cells, apoptosis also rids the body of damaged cells that could prove harmful. Damage to a cell's DNA can occur spontaneously or by exposure to a virus or the sun or various chemical compounds. Cells whose genetic material has been significantly altered are quickly eradicated to reduce or eliminate any risk of cancer.

When a cell is induced to commit suicide, it sets in motion a series of protein reactions that passes on this information and provokes various biochemical and morphological changes:
- A class of proteases, called caspases, cleave a certain number of proteins thus rendering them inactive;
- The nucleus shrinks and the DNA is degraded;
- The cytoplasm breaks into small round fragments;
- These fragments are then bundled by the dying cell's outer membrane into small sacks that are subsequently ingested by neighboring cells.

On average, the process of apoptosis takes between 30 and 60 minutes for a single cell.

When apoptosis goes wrong

The slightest anomaly in this process can lead to serious problems for the entire body. This is evidenced by a number of pathologies:
- When apoptosis is prevented, damaged cells are not eliminated, which enhances the risk of cancer.
- Similarly, an accelerated state of apoptosis, which would lead to the abnormal elimination of specific neurons, has been linked to certain neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease and Huntington’s disease.

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**Akt, a pivot in cell life**

Mutant huntingtin induces the formation of intranuclear inclusions in striatal neurons and their death. By direct phosphorylation of huntingtin, Akt protein inhibits mutant huntingtin-induced toxicity.

Mutant huntingtin (red) in the left neuron forms inclusions (yellow) in the nucleus (blue). At the opposite, in the right neuron where mutant huntingtin is modified by Akt, there is no formation of inclusion and no sensitivity to mutant huntingtin.

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