

Anti-inflammatory drugs and the Dark Knight

The neuron is probably the most famous actress if we talk about research for neurodegenerative diseases. We normally think that the brain is only a complicated and static net of connected neurons that we have to protect. However, the brain is something dynamic and plastic with a lot of actors and actresses on the stage. Besides the famous neurons, there are other cells in the brain, maybe supporting actresses and less famous but they may be crucial in the development of neurodegenerative diseases such as Alzheimer's or Parkinson's disease. These cells are called glial cells or glia. There are different types of glia: oligodendroglia, astroglia and microglia. All of them are involved in important tasks in the brain. Oligodendroglial cells, for example, have an important role in the transmission of the electrical information of the nerves since they protect the nerve fibers as electric wires. The astroglia is like a scaffold of the neuronal tissue, but also is in charge of the maintenance, homeostasis and repair tasks. However, the cells that keep the law and order in the cerebral parenchyma are the microglial cells. They are very small cells and with big number of processes. They can be found in the entire brain and they can move through the neuronal tissue. Recent studies performed *in vivo*, have demonstrated that microglial cells are moving constantly and detect any change around them due to the plasticity of their prolongations. The mechanisms driving these movements towards the altered areas are not well known, but their task is crucial for tissue repair. They are able to detect degenerative neurons, broken blood vessels and other specific alterations. In addition, they can remove debris and tissue fragments as a result of their phagocytic capacity, working like a real garbage-truck in the cerebral town.

Some neurodegenerative diseases show specific and local microglial activation in the brain. In Alzheimer's disease, amyloid plaques are invaded and rapidly encircled by active microglia. Similarly, remnant dopaminergic neurons of Parkinson's disease patients are also surrounded by active microglia. Their exact function is not fully understood but suggests that neuronal degeneration induces chemotactic signals that may activate and attract surrounding microglial cells towards the damaged areas. But the question is: Are these cells good police officer? Are they doing their real task of surveillance? Are they repairing the tissue and reestablishing the order?

Recent studies about the role of microglial cells are some how contradictory. Some reports suggest that they are good cops, keeping the order in the brain parenchyma, shielding the tissue or vascular lesions and repairing damaged areas. However, other studies have demonstrated that microglial activation could be also deleterious for the surrounding tissue.

The fact that active microglia is present in the brain of patients with Alzheimer's or Parkinson's disease have suggested that microglial activation could be harmful for the tissue and induce neuronal death. In fact microglial activation is always related with local inflammatory processes. Microglial cells are able to secrete specific molecules, called proinflammatory cytokines, such as interferon-gamma, that release them to the parenchyma that could induce neuronal death in the tissue. In fact, some experimental studies have demonstrated that the blocking of inflammatory processes induced by

microglial cells can protect from neurodegenerative processes. Some anti-inflammatory drugs administered to animals seem to be very effective against neurodegenerative processes. Aspirin, as well as COX-2 inhibitors, like ibuprofen, seem to protect neurons at the same time that they inhibit microglial activation.

On the other hand, epidemiological studies have demonstrated that people that have regularly taken anti-inflammatory drugs have less chance to suffer Parkinson's disease.

However, we still have a long way to go to determine whether the administration of anti-inflammatory drugs will be beneficial for patients with neurodegenerative diseases. All these data, suggest that local inflammatory processes produced by microglia could be a two edges sword as happened in the last sequel of Batman: by one side repairing alterations and protecting is good but too much inflammation could be an overkilling for the remnants neurons. The immune system is conceived to protect and defend from toxic invasions and external pathogens, however, as it happens in some autoimmune diseases, the immune system could function against the entire organism itself inducing irreversible damages. In the case of Parkinson's and Alzheimer's disease, this microglial activation could be protective and restoring but if they mistake their target, if the cops shoot indiscriminately, local inflammation could have negative consequences on the tissue.

An extensive research on these filed is very important. In our laboratory, we are trying to decipher the role of glial cells in neurodegeneration, how they interact with neurons and which mechanisms are involved in the local neuro-inflammation. In addition, we are testing different anti-inflammatory drugs in animals and we think that will be crucial to step forward potential clinical treatments and the design of specific drugs, targeting specific molecules and specific areas with safety and without side effects. In summary, to know better the mechanisms that trigger the well doing of microglia in the brain parenchyma, being always a good cop, able to restore the law and order in the complex city of the brain.