**Innate immune memory – microglia as key players**

Memory is the process of storing and retrieving information. In human beings, the brain is the central organ for acquiring memories as it is equipped with the neuronal system, which forms the basis for processing memories.

Apart from the complex neuronal system, a variety of cell populations that possess some kind of memory exist. For example, cells of the adaptive immune system are well-known to develop a very specific immunological memory when exposed to a pathogen. Upon a second encounter with the same pathogen, so-called memory cells elicit an adapted immune response. This natural effect is therapeutically used during vaccinations, protecting against devastating diseases such as hepatitis.

While it was long assumed that this is the only type of immunological memory, recent studies indicate that cells of the very fast reacting innate immune system, which every human is equipped with from birth, have a memory. While innate immune cells were originally believed to always react in the same way, new findings indicate that innate immune cells also show adaptations of their immune response, representing a type of memory as well. Interestingly, recent studies demonstrate that the initial encounter of innate immune cells with a pathogen can either lead to a training effect, meaning an increased immune reaction, or to a tolerance effect, in which the immune cell’s secondary response is suppressed.

Of course, immune cells don’t have a brain to store this memory, but researchers identified a molecular mechanism how cells of the innate immune system retrieve their memories: they suppress or enhance the process of DNA conversion into functional proteins, which happens through chemical modifications of DNA packaging proteins (histones).

In our project we investigated whether immune memory occurs in microglia, the long-lived innate immune cells of the brain, and whether it has consequences for subsequently developing brain pathology. To answer this question, we analyzed a mouse model of Alzheimer’s disease pathology after challenging the immune system with a bacterial component that was injected into the mice’ bellies for one to four days. This substance is known to induce an immediate inflammatory response spreading throughout the whole body including the brain.

Interestingly, after the second injection we measured a strong increase in brain cytokines, small molecules mirroring the presence of an inflammatory reaction. This effect disappeared after the fourth injection. Therefore, by adjusting the number of inflammation inducing injections, the microglia reacted with two differential innate immune memory programs, namely with training after a single injection or with tolerance after four injections.

In a mouse model of Alzheimer’s disease pathology, we found that immune training induced by a single injection of the bacterial component in young adult mice increased much later developing Alzheimer’s specific disease signs (in this case amyloid pathology), while tolerance alleviated pathology. Of note, amyloid pathology, which is the deposition of misfolded proteins in the affected organs, is believed to be the initiating force behind the disease process in Alzheimer’s disease.

In accordance with previous findings, we attributed immune memory in microglia to molecular changes in histone modifications. Importantly, those changes were evident for a period of more than 6 months in a mouse, showing that modifications in histones indeed represent the basis of long-lasting immunological memory also in microglia. These changes subsequently affected the activation of genes and their translation into proteins in microglia. Changes in protein levels then altered important microglial functions (such as eating up aggregated amyloid) and thereby resulted in the observed modulation of amyloid pathology in mice.

Our data in mice indicate that systemic infections, which affect the whole organism, or inflammatory events throughout life could affect the severity neurological diseases occurring much later in life through their memory in microglial cells. What does this imply for humans? Currently, it is still unresolved how similar human microglia are to the microglia of a mouse. However, there is evidence for a connection between inflammation occurring as part of several diseases such as diabetes and neurological diseases such as Alzheimer’s in patients. Recent studies indicate that the number of infections throughout life may speed up progression of developing Alzheimer’s disease much later. Such long-term detrimental effects of systemic inflammation could indeed be mediated by immune memory in microglia in the brain. Thus, identifying microglia as the prominent players of innate immune memory in the brain opens up the possibility of novel treatment options for neurological disease. Thus, future studies will reveal how microglial memory can be targeted to aid in combatting neurological disease.