A window to the brain: olfaction in neurodegenerative diseases

Biomarkers of neurodegenerative diseases reflecting early neuropathological changes are critical for the development of new treatment. Finding ways of detecting the disease even before the appearance of clinical symptoms could help the treatment before irreversible brain damage or mental decline has occurred. Diseases like Alzheimer's (AD) or Parkinson's (PD) have already caused severe brain damage in patients showing the distinctive clinical symptoms. Failures in recent clinical trials for much awaited AD drugs are probably because patients treated were at very advanced stages of the disease. The most effective therapies will have to be administered early on, before symptoms are evident, and well validated biological measures will be needed for both diagnosis and prognosis.

Olfactory dysfunction is a well documented early symptom of neurodegenerative diseases like AD and PD. In Parkinson's disease, for example, about 95% of idiopathic PD patients have olfactory impairments. These deficits can be observed many years (up to 10 years) before any motor or cognitive disturbances become evident. The cause of olfactory dysfunction in these diseases is poorly understood, but it most likely reflects the development of the pathology in the olfactory system.

We have focused our studies at the periphery of the olfactory system, in the olfactory epithelium (OE). The OE lines the inside of the nasal cavity and it's the only nervous tissue that is exposed to the external environment. It is easily accessible in living individuals and can represent a window to the brain. We have studied olfaction in transgenic mice modelling diseases related to tau protein (tauopathies, like AD). These animals show severe olfactory deficits from a very early age, before the appearance of any motor symptoms. We then sequenced the RNA obtained from the olfactory epithelium of these animals and compared it to wildtype control mice. RNA sequencing is a very powerful technology allowing the study of the expression of all genes in the genome. From ~17,000 genes that are expressed in the OE, over 1,500 genes were differentially expressed between mutants and control animals. From these we have found some possible candidate genes that could work as early biomarkers and other groups of genes that could work as markers of disease progression.

We are intending to apply the same technology to different animal models in the hope of identifying disease-specific biomarkers. These initial experiments will serve as an essential proof of principle necessary for future studies on biomarkers in humans.