The editome of the ageing brain: towards the understanding of age-related neurodegenerative

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Next generation sequencing technology allowed for unprecedented insight into the workings of the brain on the level of RNA - diverse molecules that carry information required for the operational activities of the brain.

For the first time, instead of looking at how the brain makes and uses RNA messengers one at a time, next generation technology has allowed us gaze into the entire universe of the many different kinds of RNA molecules the brain produces; in different brain regions during different brain activities and when an individual suffers from a neuropsychiatric disorder.

We have come to appreciate the incredible diversity and complexity of these molecules that were initially thought to be simply carriers of transcribed information from the genome, like copies of different passages written in the great genome blueprint.

It was later found that these RNA messengers are a lot more than simple copies. What was discovered is that RNA molecules can be decorated with chemicals that enable them to carry more information than what is simply encoded in the genome. Further, in some RNA molecules the hard-wired, safeguarded genomic information can be re-written or “edited” with the help of proteins called “editors” that have the ability to change single letters encoded in the genome text.

We believe that one kind of such editing, called A-to-I editing, plays an important role in the cognitive capacities of the brain and this was explored in this project funded by SIEF.

In particular, we were interested in an enigmatic "editor" protein that enables A-to-I editing in RNA molecules, called ADAR3. ADAR3 evolved in the vertebrate lineage but it has been debated what exactly its role is, especially taking into consideration there are two other kinds of "editor" proteins that seem to be responsible for much of the detected A-to-I editing.

Through using different molecular techniques we "deleted" the ADAR3 editor in all cells of mice and found out that the mice lacking ADAR3 were struggling with learning and memory tasks compared to mice that had the ADAR3 editor. In addition we used next-generation sequencing technology to look at the effect this has on the RNA molecules in the mouse brain. The mice lacking ADAR3 showed changes in the produced abundances of some kinds of RNA molecules compared to mice that had functional ADAR3. Thus we have uncovered that the ADAR3 editor has a role in learning and memory. Interestingly, the deletion of ADAR3 did not seem to alter much of the A-to-I editing and we are continuing our research, looking deeper at the precise function of ADAR3 and how it is involved in cognition.

Another area of interest where the brain's cognitive capacities are altered is ageing. Not much is known about how A-to-I editing changes as mammalian brains age and whether age-related changes in A-to-I editing contribute to cognitive decline in old age. Again we used next generation sequencing technology to look at the diversity and abundance of RNA molecules in the aged mouse brain as well as how A-to-I editing changes as the brain ages.

We found that a lot of RNA molecules become more abundant when the brain ages and others become less abundant and importantly, many of these RNA molecules follow exactly the same pattern in young and in aged human brains, implying a degree of evolutionary shared brain ageing mechanism amongst mammals. We also found that A-to-I editing occurs more frequently on some kinds of RNA molecules during ageing. Although we don't fully understand the biological reason for

intensifying of the editing with age and if and how it affects cognition, our findings combined with similar findings by other researchers provide evidence that there is a trend for an increase in A-to-I RNA editing with age and that this trend is shared amongst mammals. This is important because it gives us more insight into the mechanism and biological function of A-to-I editing, a process that we are still in our infancy of understanding.

In conclusion, the project funded by SIEF has helped us discover that the ADAR3 editor protein plays an important role in memory and learning. In addition, we have found that the ageing process in the mouse and human brain leaves similar molecular footprints on the level of RNA molecules, altering their abundance and the level of A-to-I editing.