Evolution and function of astrocyte-derived extracellular vesicles

Language or abstract thinking distinguish us from our closest living relatives the non-human primates (NHP). The genes that emerge in the human lineage or feature a human-specific activity in the developing brain, shape the newly-acquired abilities of the human mind. Remarkably, the same genes are also often linked to neuropsychiatric disorders, including schizophrenia (SCZ) or Autism Spectrum Disorder (ASD). Regulation of their activity is not yet fully understood.

The brain consists of two main cell types: neurons, which transmit signals, and non-excitatory glial cells. Astrocytes belong to the latter type. For many years astrocytes were perceived solely as neuron-protective cells. However, more recent data revealed that astrocytes control neurogenesis, synapse production and function and therefore participate in cognitive processes. Human astrocytes are bigger and more complex than their NHP or rodent counterparts. Moreover, recent studies have shown that astrocytes, not neurons, are the fastest-evolving cells in the brain. We are in the laboratory investigating the evolution of astrocytes. We have recently uncovered hundreds of genes with pattern of activity unique to the human species.

Proper development and brain functions require coordinated communication between cells. All cells in our body, thus also in the brain, produce extracellular vesicles (EVs)–small, lipid-made structures that carry information at long distances between cells or even organs. The biological cargo transported in EVs includes proteins or nucleic acids. EVs are produced by the “sender cells” and delivered to the “recipient cells”, where they can impact various processes. Non-coding RNAs (miRNA), are a particularly interesting group of cargos, as they can directly control the expression of the genes in the recipient cells. The identity of miRNA in the EVs depends on the sender cell type and is shaped by the developmental stage or disease status of the cell that produces them. Upon delivery to the recipient cell, the miRNAs can control genes implicated in development. Hence, EVs and the miRNAs inside them can impact brain development. Yet, the precise functions of EVs are not fully understood. Addressing how EVs, and the miRNAs they carry, orchestrate neuronal maturation and functions will help to understand human brain development and mental disorders. Furthermore, EVs carrying miRNAs can cross blood-brain barrier. Therefore, they can be used for diagnostic purposes and, in the future, as therapeutic tools.

Provided the profound changes in astrocyte biology in humans, we hypothesize that the cargos of EV produced by astrocytes (including miRNAs) also changed in evolution. We posit that by unraveling how the changed EVs impact neuronal activity we will gain new insights into the mechanisms that orchestrated the emergence of traits specific to our brain. Hence, we propose to compare miRNAs carried by human and chimpanzee astrocytes and identify the miRNA that are specifically present in the human astrocyte-derived EV. We will specifically focus on miRNAs, which can regulate genes linked with neuropsychiatric disorders such as SCZ or ASD.

Our project will take advantage of induced stem cell-based models of astrocytes and neurons. We will obtain the EVs produced by human and NHP astrocytes, and compare the miRNAs carried within them. We will identify miRNAs that are more abundant in the human than the chimpanzee EVs. Then, we will examine the impact of these miRNAs on neuron function. Moreover, we will apply 3D organoid models (so-called “mini-brains”), which mirror early brain development stages, to investigate the role of chosen miRNAs in brain development.

Together, this project will deepen our knowledge about the impact of human-specific, astrocyte-derived, miRNAs on early brain development. It will also identify miRNAs potentially involved in the emergence of SZ or ASD, which in future, might become diagnostic or therapeutic targets. Insights obtained in this project are likely going to change our way of thinking about the mechanisms of brain evolution and their relationship with the diseases of the human mind.