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Sexual differentiation of microglia and neurodegenerative diseases

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Content

Sex plays a role in the incidence and outcome of neurological illnesses, also influencing the response to treatments. In the recent past, our laboratory developed several tools, including cellular and animal models, aimed at investigating the sexual differentiation of microglia and its impact on brain physiology, allowing us to demonstrate that these cells show a sex-specific phenotype that is maintained all-through the life of the animal: in details, while male microglia showed a tendency towards pro-inflammatory activation, female microglia revealed a more neuroprotective phenotype. In culture, the cells maintained the characteristics derived from the sex of origin: morphological analyses revealed that most of the male microglia in culture show ameboid shapes and fewer branching extensions. On the other hand, the shape of female microglia is more complex and ramified (See Figure below). With this in mind, we decided to develop simplified *in vitro* models of selected neurological and neurodegenerative diseases, with the aim of assessing whether microglia could play a role in the sex-biased incidence, severity, progression of specific neurodegenerative diseases. Therefore, to mimic the microglia brain environment we setup a primary co-culture of pups-derived neurons with microglia isolated from adult mice; then, we applied a systematic high-content screening approach based on time-lapse fluorescence microscopy to assess the dynamics of microglia phenotype in control and diseased conditions. This approach allowed us generating cell shape-index (CSI) maps useful for the quantification of changes in cell morphology, which are potentially related to deviations in microglia function induced by the treatments. CSI analyses confirmed the differences in microglia phenotype related to the sex of origin and evidenced more frequent contacts of microglia with neuronal dendrites. Treatment with the prototypical stimuli used to modulate the inflammatory state of immune cells (e.g. LPS) induced differential CSI changes in male and female cells, suggesting the existence of a sex-bias in the microglial response. Moreover, preliminary experiments evidenced that exposure to neurodegenerative stimuli led to the acquisition of different morphological phenotypes depending on the sex of origin of microglia. Taken together, these results suggest a direct involvement of microglia in the sex differences in the incidence and progression of specific neurological disorders