Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Internal Seminar

A microglia-targeted covalent imaging probe reveals region-specific P2RY12 receptor turnover in the brain

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Microglia are resident innate immune cells of the central nervous system (CNS). Under physiological conditions, homeostatic microglia dynamically surveil the CNS parenchyma using their motile processes, thereby maintaining tissue homeostasis via interactions with neurons, astrocytes, oligodendrocytes, and the cerebrovascular network. Beyond their immunological functions, microglia are critically involved in synaptic pruning, neurogenesis, and neural circuit maturation during development. Increasing evidence further implicates dysregulated microglial activation in the pathogenesis of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. Therefore, there is an unmet need for novel imaging technologies and therapeutic agents for microglia. Microglia is mostly refractory to genetic modifications, which limits our understanding of these cells in live human tissues and in animals. Currently, we lack molecular tools for targeted in vivo imaging of microglia that are readily deployable across laboratory model systems. To address this, we describe here a small-molecule-based covalent fluorescent imaging technology for multicolour imaging of microglia in live organisms (e.g., in zebrafish and mice) without inducing immune activation. Using this technology, we have successfully visualised microglia-pathogen interactions in the brains of larval zebrafish. Furthermore, by performing microglial labelling in the mouse brain, we revealed different morphological states of microglia present across brain regions. In addition, two-photon imaging of probe-labelled cortical microglia allowed us to observe their dynamics during laser-induced brain injury. Building on this, we further demonstrated the utility of the microglia-labelling approach in creating a brain-wide, lifetime map of the ADP-sensing purinergic receptors (P2RY12). Notably, we identified both short (~2 days) and long-lived (~8 days) P2RY12-receptor populations in distinct, region-specific microglia by developing an in vivo pulse-chase labelling paradigm.

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14:30 Hrs

Seminar Hall, TIFRH