Identification of targets and markers of Parkinson's disease-associated neuroinflammation

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Résumé

While effective symptomatic treatments exist, major unmet needs for PD include disease-modifying treatments as well as biomarkers predicting disease progression among others. Undoubtedly, the improved characterization of molecular and cellular pathways underlying pathological mechanisms will facilitate the identification of new potential targets for therapeutic intervention as well as the discovery of disease-relevant markers. In PD, mounting evidence suggests that neuron-released α-Syn assemblies could be central to microglial cell activation and pathological inflammatory responses. Yet, the models used so far paid little attention as to whether 1/ patient-derived protein assemblies display similar or different immunomodulatory properties compared to synthetic assemblies, 2/ microglial cell response to α-Syn assemblies is modulated by chronic-type inflammatory factors such as Tumor-necrosis factor-a (TNFa) and prostaglandin E2 (PGE2) known to be elevated in the brain of PD patients. These questions are of most importance since the phenotypes and functions that activated microglia can adopt are diverse and strongly depend on the nature, intensity and complexity of stimulation to various cues. It is crucial to define and understand the mechanisms that shape microglial cell polarization to design tools to therapeutically modulate this response in a beneficial orientation. To tackle these issues, we developed, characterized and studied new cellular models of PD-relevant inflammatory paradigms that should lead to the discovery of disease-relevant mechanisms and markers. We show that human aSyn fibrils obtained by protein misfolding cyclic amplification (PMCA) of PD-derived aSyn brain aggregates dose-dependently induce a pro-inflammatory response in mouse primary microglial cells (morphological changes, cytokine release, glutamate release). Microglial cells exposed simultaneously with PD aSyn fibrils, TNFa and PGE2 (the so-called TPF stimulation) display similar but less intensive cytokine and glutamate release than aSyn fibril alone. Yet, when compared to classical LPS-induce M1 polarization, TPF-exposed microglial cells release more glutamate while producing equal amount of ROS. Unbiased molecular characterization of TPF-stimulated cells through metabolomic and transcriptomic analysis revealed both common and specific features compared to LPS stimulation. In particular, TPF-treated microglia display similar glycolytic switch and TCA cycle break as reported for LPS-induce M1 macrophages as well as increased glutamate and GSSG levels. Pathway analysis derived

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from transcriptomic data revealed that TPF-stimulated cells engage into molecular programs dedicated to iron uptake, glutathione synthesis, cholesterol and steroid/terpenoid biosynthesis, and phagocytosis, among others. Interestingly, TPF-treated cells become highly efficient in phagocytosing large targets as compared to LPS-exposed microglia. Finally, data integration analysis reveals that 4 metabolites and 4 genes discriminate TPF-stimulated cells from LPS- and non-treated microglia. The validation of the identified targets and markers in human monocyte-derived microglial-like cells and PD brains is in progress.

Mots-Clés: Parkinson's disease, alpha synuclein, chronic neuroinflammation, primary microglial cells