Pluripotent stem cells and 3D midbrain organoids as models for Dopaminergic Neurons and the study of environmental toxins associated to Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by the progressive loss of Dopaminergic neurons (DAn) in the midbrain. The loss of DAn leads to motor symptoms, autonomic dysfunction and psychological alterations. Although some genetic factors have been associated with the development of PD, this only makes up a small percentage of cases, while the majority have unknown causes. Recently, studies have found increased risk of PD associated with the exposure to environmental toxins, especially pesticides, solvents and some metals. However, since most cases of PD are sporadic, it has been difficult to create appropriate animal models for the study of the development of this disease. In this work, we suggest an alternative approach by reprogramming mouse embryonic fibroblasts (Mefs) to create a stable cell line of mouse induced pluripotent stem cells (miPSC) as an in vitro model for the development of DAn. We reprogrammed Mefs using the CoMIP minicircle plasmid and characterized the cells to demonstrate their pluripotency and ability to self-renew. This was then followed by the directed differentiation of miPSCs to DAn. We also used these miPSCs to create mini-midbrain organoids, whose 3D structure allows us to emulate the development of DAn in vivo. Once established, these same techniques could be implemented and adapted to human cell systems, which could substitute the use of animal models to study the development of PD. Both miPSCs and midbrain organoids could then be used to study the effects of environmental toxins, either individually or in combinations usually present together in the environment. This could then give us insight to how these toxins impact DAn and the development of PD.