Dopaminergic neuron

Dopaminergic neurons of the midbrain are the main source of dopamine (DA) in the mammalian central nervous system. Their loss is associated with one of the most prominent human neurological disorders, Parkinson's disease (PD).

Diagnosis largely depends on clinical observation, but motor dysfunctions do not emerge until 70%-80% of the nigrostriatal nerve terminals have been destroyed. Therefore, a biomarker that indicates the degeneration dopaminergic neurons is urgently needed.

Dopaminergic neurons are found in a 'harsh' region of the brain, the substantia nigra pars compacta, which is DA-rich and contains both redox available neuromelanin and a high iron content. Although their numbers are few, these dopaminergic neurons play an important role in the control of multiple brain functions including voluntary movement and a broad array of behavioral processes such as mood, reward, addiction, and stress. Studies into the developmental pathways which are involved in the generation of dopaminergic neurons in the brain have led to the identification of several specific transcription factors including Nurr1, Lmx1b and Pitx3, all shown to be important in the development of the mesencephalic dopaminergic system. The selective degeneration of these dopaminergic neurons in the substantia nigra pars compacta leads to PD but the exact cause for this nigral cell loss is still unknown [1].

The subthalamic nucleus (STN) has been divided into three distinct subdivisions, motor, limbic, and associative parts in line with the concept of parallel information processing. The extent to which the parallel information processing coming from distinct cortical areas overlaps in the different territories of the STN is still a matter of debate and the proposed role of dopaminergic neurons in maintaining the coherence of responses to cortical inputs in each territory is not documented.

Generation of midbrain dopaminergic (mDA) neurons from human pluripotent stem cells provides a platform for inquiry into basic and translational studies of Parkinson's disease (PD). However, heterogeneity in differentiation in vitro makes it difficult to identify mDA neurons in culture or in vivo following transplantation. Here, we report the generation of a human embryonic stem cell (hESC) line with a tyrosine hydroxylase (TH)-RFP (red fluorescent protein) reporter. We validated that RFP faithfully mimicked TH expression during differentiation. Use of this TH-RFP reporter cell line enabled purification of mDA-like neurons from heterogeneous cultures with subsequent characterization of neuron transcriptional and epigenetic programs (global binding profiles of H3K27ac, H3K4me1, and 5-hydroxymethylcytosine [5hmC]) at four different stages of development. We anticipate that the tools and data described here will contribute to the development of mDA neurons for applications in disease modeling and/or drug screening and cell replacement therapies for PD [2].

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2)
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