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The Role of Parkin in Parkinson's Disease: a stem cell perspective

Parkinson's disease (PD) is a movement disorder characterized by the degeneration of nigral dopaminergic (DA) neurons. The defining locomotor symptoms (rest tremor, rigidity, bradykinesia and postural instability) are caused by a relatively selective loss of nigral DA neurons [1]. Current pharmacological treatments focus on augmenting dopamine levels in the brain (e.g. levodopa, MAO-B inhibitors, COMT inhibitors) or mimicking the actions of dopamine (e.g. dopamine agonists). These drugs mostly provide symptomatic relief; the unabated degeneration of nigral DA neurons and other cells invariably kills the patients. Surgical interventions such as deep brain stimulation are similar in that they only alleviate locomotor symptoms and have no impact on the neurodegeneration process. Thus, the central problems for PD research are to understand the cause for the degeneration of nigral DA neurons and to identify a strategy to intervene, preferably as early as possible.

Mechanistic studies on PD-linked monogenic mutations have revealed significant insights into the unique vulnerabilities of nigral DA neurons and how mutations of a single gene, such as parkin, expose these vulnerabilities. A variety of mouse genetic models of Parkinson's disease have revealed surprisingly little information on the human disease [2]. For example, parkin knockout mice do not exhibit any robust phenotype [3], in sharp contrast to PD patients with parkin mutations [4]. It suggests that human nigral DA neurons are quite different from the murine counterpart. The landmark discovery of induced pluripotent stem cells (iPSC) [5, 6] has made it possible for us to generate patient-specific midbrain DA neurons from PD patients with parkin mutations and normal controls [7]. Our study shows that parkin mutations significantly disrupt the precision of dopaminergic transmission by increasing spontaneous dopamine release and decreasing dopamine reuptake. In addition, parkin mutations greatly elevate dopamine-induced oxidative stress by increasing the transcription of monoamine oxidases (MAO), which catalyze the oxidative deamination of dopamine - a reaction that produce large amount of reactive oxygen species. Overexpression of wild-type parkin, but not its PD-linked mutant, significantly rescues all these phenotypes. Thus, mimicking the beneficial actions of parkin, for example, with small-molecule drugs, may provide a novel strategy to protect midbrain DA neurons. It is particularly encouraging to note that parkin suppresses the transcription of monoamine oxidases, while MAO-B inhibitors are the only known PD drugs that significantly slow down the progression of the disease, albeit at a modest rate [8]. Our study shows that parkin increases the ubiquitination and degradation of estrogen related receptors to suppress the transcription of MAO [9]. Small-molecule inhibitors of estrogen related receptors may thus be able to substitute the function of parkin in limiting the level of MAO transcripts. This would be a very intriguing alternative to develop an MAO-based disease-modifying drug for PD.

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Because these phenotypes are seen in iPSC-derived midbrain DA neurons, but not in parkin knockout mice, it becomes a necessity to consider the use of human DA neurons to screen for novel PD drugs. Humans are unique in our strictly bipedal movement vis-à-vis the quadrupedal movements of almost all other mammalian species. While it is not possible with the current technology to estimate the computational requirement needed to support the highly unstable bipedal movement of a human adult, a reasonable guess is that the dopamine-driven motor control for the bipedal human would be much more complicated than that for quadrupedal species, perhaps requiring more dopamine. Fundamentally, the function of dopamine in the control of voluntary movement is to regulate the computational network of basal ganglia. The fact that diminished level of dopamine leads to dysfunction of the basal ganglia network and abnormal movement suggests that the more complex the movement, the more dopamine it needs to calculate the movement.

Another unique feature of human as we consider movement is the large size of our brain. Nigral DA neurons have massive axon arborization; the total length of axon arbors of a single rat nigral DA neuron averages **45 cm** [10]. If we use the cube root of brain weights (1350g for human vs. 2 g for rat) to estimate linear dimension, a single human nigral DA neuron would have axon arbors with a total length of **400 cm**. Striking as the estimate is, the only assumption is that the wiring plan connecting different brain regions is largely conserved between rodents and human. Anatomical evidence strongly supports this idea, although the data for human nigral DA neurons is impossible to acquire with the current technology, given its invasive nature.

The uniquely human features of our locomotion, including the two analyzed above, may explain why animal models such as parkin knockout mice, are inadequate for studying Parkinson's disease. By the same logic, the analysis suggests that it is necessary to use human midbrain DA neurons to study Parkinson's disease. The iPSC-derived midbrain DA neurons have many advantages. First, they capture all the genetic information of a PD patient and are thus critical for the evaluation of gene-environment relationship in Parkinson's disease. One can now test all sorts of hypotheses that are too invasive, too expansive, too long to test on human subjects, all under controlled conditions to evaluate the impact of genetics and/or environmental factors on the function and survival of human midbrain DA neurons. This would be most powerful for idiopathic Parkinson's disease, for which we have very little mechanistic insights on why nigral DA neurons die in the patients. Second, the iPSC-derived midbrain DA neurons would be highly valuable for the discovery of biomarkers, as we can now directly analyze the differences in these cells between normal subjects and PD patients. This is much more advantageous than analyzing blood, urine, cerebrospinal fluid, etc., as none of those materials provides direct information on the dopaminergic neurons. Third, the iPSC-derived midbrain DA neurons offer the most promising platform to discover disease-modifying drugs for PD. Instead of doing drug discovery research on animal models that do not accurately reflect PD, human cell lines that are not even neurons, or rodent midbrain neuronal cultures that do not show the same vulnerability as the human counterparts, we now can directly screen compounds and perform assays on iPSC-derived midbrain DA neurons from PD patients and normal subjects. It will generate definitive information on what compounds work on human DA neurons and whether the compounds make the PD neurons behave more like normal neurons. Such a drug discovery platform will be more likely to produce a drug that can significantly alter the function and survival of nigral DA neurons and modify the progression of Parkinson's disease. Combined with the identification of biomarkers, the stage is set for the discovery of objective criteria that can be used to predict and diagnose Parkinson's disease, track its progression and evaluate the efficacy of disease-modifying therapies.

Obviously, iPSC-derived midbrain DA neurons have their limitations. The most significant issue is the lack of *in vivo* developmental cues that endow the cells with all the properties and synaptic connections of the nigral DA neurons in an adult human brain. This goal, although perhaps unattainable, can be partially achieved by transplanting the neural precursor cells differentiated from patient-specific iPSCs to an animal brain. Non-human primates such as rhesus monkeys offer the closest host brains that are ethically acceptable. At 95 grams on average, a rhesus monkey brain resembles a human brain in many more significant ways than a rodent brain does. The possibility of studying patient-specific nigral DA neurons (e.g. labeled with GFP) in a monkey brain will generate unique insights into how human nigral DA neurons work *in vivo* and how this goes awry in PD. The other limitation is the different genetic backgrounds between different lines of iPSC cells, which may confound the analysis of the phenotypes. Fortunately, there is already solution for this by generating isogenic pairs of iPSCs that differ only in the absence or presence of the mutation of interest [11]. The isogenic iPSCs offer more stringent conditions for the discovery of phenotypes and drugs that can rescue the phenotypes.

In conclusion, the discovery of iPSC cells opens a brave new world where Parkinson's disease will be predicted, prevented and cured. The study of parkin using patient-specific iPSC cells offers a glimpse of what is possible in the near future.

Bibliography

- Lang AE, Lozano AM. Parkinson's disease. First of two parts. N Engl J Med. 1998; 339(15):1044–1053. [PubMed: 9761807]
- Dawson TM, Ko HS, Dawson VL. Genetic animal models of Parkinson's disease. Neuron. 2010; 66(5):646–661. [PubMed: 20547124]
- Perez FA, Palmiter RD. Parkin-deficient mice are not a robust model of parkinsonism. Proc. Natl. Acad Sci U. S. A. 2005; 102(6):2174–2179. [PubMed: 15684050]
- Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998; 392(6676):605–608. [PubMed: 9560156]
- Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007; 131(5):861–872. [PubMed: 18035408]
- Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin II, Thomson JA. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007; 318(5858):1917–1920. [PubMed: 18029452]
- Jiang H, Ren Y, Yuen EY, Zhong P, Ghaedi M, Hu Z, Azabdaftari G, Nakaso K, Yan Z, Feng J. Parkin controls dopamine utilization in human midbrain dopaminergic neurons derived from induced pluripotent stem cells. Nat. Commun. 2012; 3:668. [PubMed: 22314364]
- Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N. Engl. J. Med. 2009; 361(13):1268–1278. [PubMed: 19776408]
- Ren Y, Jiang H, Ma D, Nakaso K, Feng J. Parkin degrades estrogen-related receptors to limit the expression of monoamine oxidases. Hum. Mol. Genet. 2011; 20(6):1074–1083. [PubMed: 21177257]
- Matsuda W, Furuta T, Nakamura KC, Hioki H, Fujiyama F, Arai R, Kaneko T. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. J. Neurosci. 2009; 29(2):444–453. [PubMed: 19144844]
- Soldner F, Laganieri J, Cheng AW, Hockemeyer D, Gao Q, Alagappan R, Khurana V, Golbe LI, Myers RH, Lindquist S, Zhang L, Guschin D, Fong LK, Vu BJ, Meng X, Urnov FD, Rebar EJ, Gregory PD, Zhang HS, Jaenisch R. Generation of isogenic pluripotent stem cells differing exclusively at two early onset Parkinson point mutations. Cell. 2011; 146(2):318–331. [PubMed: 21757228]