Advancing Stem Cell Models of Alpha-Synuclein Gene Regulation in Neurodegenerative Disease.

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Public Summary:

Alpha-synuclein plays a central role in the pathogenesis of Parkinson's disease (PD) and related Lewy body disorders such as Parkinson's disease dementia, Lewy body dementia, and multiple system atrophy. Since its discovery as a disease-causing gene in 1997, alpha-synuclein has been a central point of scientific interest both at the protein and gene level. Mutations, including copy number variants, missense mutations, short structural variants, and single nucleotide changes, can be causative for PD and affect conformational changes of the protein, can contribute to changes in expression of alpha-synuclein and its different forms, and can influence regulation of alpha-synuclein in different tissues and cell types. A lot of progress has been made to understand both the physiological transcriptional and epigenetic regulation of the alpha-synuclein gene and whether changes in transcriptional regulation could lead to disease and neurodegeneration in PD and related alpha-synucleinopathies. In this review, we describe different genetic alterations that contribute to PD and neurodegenerative conditions and review aspects of transcriptional regulation of the alpha-synuclein gene in the context of the development of PD. New technologies, advanced gene engineering and stem cell modeling, are on the horizon to shed further light on a better understanding of gene regulatory processes and exploit them for therapeutic developments.

Scientific Abstract:

Alpha-synuclein (non A4 component of amyloid precursor, SNCA, NM_000345.3) plays a central role in the pathogenesis of Parkinson's disease (PD) and related Lewy body disorders such as Parkinson's disease dementia, Lewy body dementia, and multiple system atrophy. Since its discovery as a disease-causing gene in 1997, alpha-synuclein has been a central point of scientific interest both at the protein and gene level. Mutations, including copy number variants, missense mutations, short structural variants, and single nucleotide polymorphisms, can be causative for PD and affect conformational changes of the protein, can contribute to changes in expression of alpha-synuclein and its isoforms, and can influence regulation of temporal as well as spatial levels of alpha-synuclein in different tissues and cell types. A lot of progress has been made to understand both the physiological transcriptional and epigenetic regulation of the alpha-synuclein gene and whether changes in transcriptional regulation could lead to disease and neurodegeneration in PD and related alpha-synucleinopathies. Although the histopathological changes in these neurodegenerative disorders are similar, the temporal and spatial presentation and progression distinguishes them which could be in part due to changes or disruption of transcriptional regulation of alpha-synuclein. In this review, we describe different genetic alterations that contribute to PD and neurodegenerative conditions and review aspects of transcriptional regulation of the alpha-synuclein gene in the context of the development of PD. New technologies, advanced gene engineering and stem cell modeling, are on the horizon to shed further light on a better understanding of gene regulatory processes and exploit them for therapeutic developments.