

Synucleins: What do they do in the Nucleus?

Andrei Surguchov

Professor, Retinal Biology Research Laboratory, VA Medical Center and Kansas University Medical Center

***Corresponding author:** Andrei Surguchov, Professor, Retinal Biology Research Laboratory, VA Medical Center, 4801 East Linwood Boulevard, Kansas City, MO, 64128, and Kansas University Medical Center. Tel: 816-861-4700 x 57078; Fax : 816-861-1110; E-mail: asurguchova@kumc.edu

Keywords: Synucleins; Transcription; Gene regulation; Neurodegenerative diseases; Cancer

Received Date: 03 May 2014

Accepted Date: 06 May 2014

Published Date: 10 May 2014

Synucleins are small (113-143 amino acids) proteins expressed primarily in neural tissue. The family consists of three proteins: α -synuclein, β -synuclein, and γ -synuclein with high amino acid sequence similarity at the N-termini and variable C-termini. All synucleins have in common a highly conserved alpha-helical lipid-binding motif [1].

For almost 26 years since the discovery of the first synuclein by Maroteaux et al. [2] a main question and a main direction of their studies were directed to understanding synuclein's normal function(s). The role of these proteins in human diseases was established much earlier: α -synuclein was implicated in Parkinson's disease and several other neurodegenerative disorders [3], whereas γ -synuclein was associated with several types of cancer [4] and some neurodegenerative disorders [1].

Several studies pointed to a role of α -synuclein in synaptic transmission. α -Synuclein may act as a chaperone, assisting in the folding and refolding of synaptic proteins called SNAREs. These proteins are crucial for release of neurotransmitters at the neuronal synapse, vesicle recycling, and synaptic integrity [4]. These results may explain at least partially what synuclein's functions in synapsis are. However, in addition to synaptic localization, synucleins have been detected in the nucleus. In spite of the absence of nuclear targeting sequences nuclear localization has been described for all three forms of synucleins: α -synuclein [5-7], β -synuclein [8] and γ -synuclein [9].

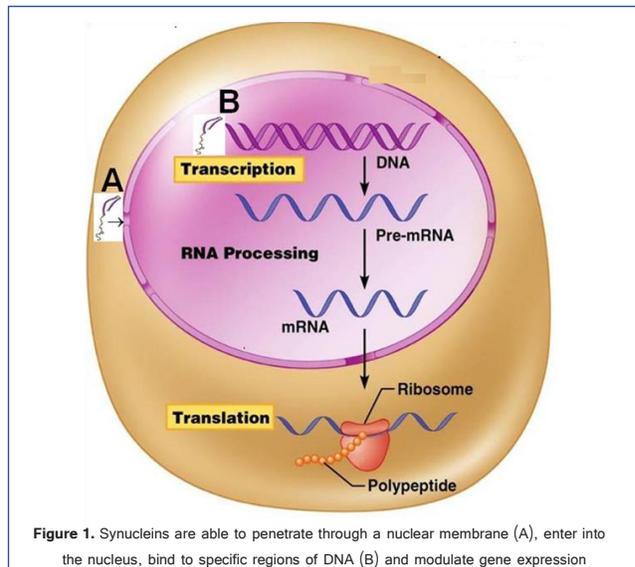
Nuclear localization of α -synuclein have been described in a variety of experimental systems, including transgenic *Drosophila* [10], mice [11, 12], and cultured cells [13,14]. β -Synuclein is revealed in nuclei of human astrocytes

Citation: Giroh L, Tong Y, Sun W (2014) Chinese Cancer Status - Challenge and Opportunity. Enliven: Challenges Cancer 1(1): e001.

Copyright: © 2014 Dr. Wenjie Sun. This is an Open Access article published and distributed under the terms of the Creative Commons Attribution License that permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

in culture [8], while γ -synuclein in nuclei of several types of cultured cells [15]. The question arises when and why synuclein are translocated to the nucleus?

Increasing evidence indicates that synucleins participate in the regulation of gene expression (Figure 1) in response to changing conditions. For example, α -synuclein downregulates c-Jun N-terminal kinase protecting cells against oxidative stress, upregulates caveolin-1 expression and downregulates ERK expression which may play a role in the pathogenesis of Parkinson disease [16,17].



In another publication α -synuclein effect in reducing Bcl-xL expression and increasing bax expression was described [18]. Importantly α -synuclein is able to directly bind to promoter region of specific genes and affect the transcription of selected genes. For example Siddiqui et al. [19] described α -synuclein binding to a promoter of the transcriptional co-activator PGC-1 α which reduces its expression in response to oxidative stress.

γ -Synuclein is also a modulator of specific genes expression. For example, it significantly upregulates matrix metalloproteinases-9 (MMP 9) expression and activity. This effect is mediated via γ -synuclein binding to AP-1 binding sites in the promoter region of the MMP-9 gene [20].

Under stress conditions a translocation of γ -synuclein to the nucleus reduces neurite outgrowth in a greater extent than α -synuclein overexpression [20]. Furthermore, γ -synuclein is able to bind to transcription factors and has a dynamic intracellular localization [21, 22]. These data support the view that γ -synuclein may change its intracellular localization in response to stress and make appropriate alterations in the gene expression pattern.

Therefore, synucleins can be targeted to the nucleus in response to stress and reprogram the pattern of gene expression. Thus, nuclear translocation of synuclein can be considered as a target for therapeutic intervention.

References

1. Surguchov A (2008) Molecular and cellular biology of synucleins. *Int Rev Cell Mol Biol* 270: 225-317.
2. Maroteaux L, Campanelli JT, Scheller RH (1998) Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal. *J Neurosci* 8: 2804-2815.
3. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, et al. (1997) Alpha-synuclein in Lewy bodies. *Nature* 388: 839-840.
4. Ahmad M, Attoub S, Singh MN, Martin FL, El-Agnaf OM (2007) Gamma-synuclein and the progression of cancer. *FASEB J* 21: 3419-3430.
5. Chandra S, Gallardo G, Fernández-Chacón R, Schlüter OM, Südhof TC (2005) Alpha-synuclein cooperates with CSP α in preventing neurodegeneration. *Cell* 123: 383-396.
6. Kontopoulos E, Parvin JD, Feany MB (2006) Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity. *Hum Mol Genet* 15: 3012-3023.
7. Boyer F, Dreyer JL (2007) Alpha-synuclein in the nucleus accumbens induces changes in cocaine behaviour in rats. *Eur J Neurosci* 26: 2764-2776.
8. Tanji K, Mori F, Nakajo S, Imaizumi T, Yoshida H, et al. (2001) Expression of beta-synuclein in normal human astrocytes. *Neuroreport* 12: 2845-2848.
9. Surgucheva I, McMahon B, Surguchov A (2006) gamma-Synuclein has a dynamic intracellular localization. *Cell Motil Cytoskeleton* 63: 447-458.
10. Takahashi M, Kanuka H, Fujiwara H, Koyama A, Hasegawa M, et al. (2003) Phosphorylation of alpha-synuclein characteristic of synucleinopathy lesions is recapitulated in alpha-synuclein transgenic *Drosophila*. *Neurosci Lett* 336: 155-158.
11. Masliah E, Rockenstein E, Veinbergs I, Mallory M, Hashimoto M, et al. (2000) Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. *Science* 287: 1265-1269.
12. Goers J, Manning-Bog AB, McCormack AL, Millett IS, Doniach S, et al. (2003) Nuclear localization of alpha-synuclein and its interaction with histones. *Biochemistry* 42: 8465-8471.
13. Seo JH, Rah JC, Choi SH, Shin JK, Min K, et al. (2002) Alpha-synuclein regulates neuronal survival via Bcl-2 family expression and PI3/Akt kinase pathway. *FASEB J* 16: 1826-1828.
14. McLean PJ, Ribich S, Hyman BT (2000) Subcellular localization of alpha-synuclein in primary neuronal cultures: effect of missense mutations. *J Neural Transm Suppl* 58: 53-63.
15. Specht CG, Tigret CM, Rast GF, Thalhammer A, Rudhard Y, et al. (2005) Subcellular localisation of recombinant alpha- and gamma-synuclein. *Mol Cell Neurosci* 28: 326-334.
16. Surgucheva I, Ninkina N, Buchman VL, Grasing K, Surguchov A (2005) Protein aggregation in retinal cells and approaches to cell protection. *Cell Mol Neurobiol* 25: 1051-1066.
17. Hashimoto M, Hsu LJ, Rockenstein E, Takenouchi T, Mallory M, et al. (2002) alpha-Synuclein protects against oxidative stress via inactivation of the c-Jun N-terminal kinase stress-signaling pathway in neuronal cells. *J Biol Chem* 277: 11465-11472.
18. Hashimoto M, Takenouchi T, Rockenstein E, Masliah E (2003) Alpha-synuclein up-regulates expression of caveolin-1 and down-regulates extracellular signal-regulated kinase activity in B103 neuroblastoma cells: role in the pathogenesis of Parkinson's disease. *J Neurochem* 85: 1468-1479.
19. Siddiqui A, Chinta SJ, Mallajosyula JK, Rajagopalan S, Hanson I, et al. (2012) Selective binding of nuclear alpha-synuclein to the PGC1 α promoter under conditions of oxidative stress may contribute to losses in mitochondrial function: implications for Parkinson's disease. *Free Radic Biol Med* 53 :993-1003.
20. Surgucheva IG, Sivak JM, Fini ME, Palazzo RE, Surguchov AP (2003) Effect of gamma-synuclein overexpression on matrix metalloproteinases in retinoblastoma Y79 cells. *Arch Biochem Biophys*. 410: 167-176.
21. Surgucheva I, Surguchov A (2008) γ -Synuclein: cell-type-specific promoter activity and binding to transcription factors. *J Mol Neurosci*. 35: 267-71
22. Surgucheva I, McMahon B, Surguchov A (2006). γ -Synuclein has a dynamic intracellular localization. *Cell Motil Cytoskeleton*. 2006; 63:447-58

Submit your manuscript at

<http://enlivenarchive.org/submit-manuscript.php>

New initiative of Enliven Archive

Apart from providing HTML, PDF versions; we also provide [video version](#) and deposit the videos in about 15 freely accessible social network sites that promote videos which in turn will aid in rapid circulation of articles published with us.