Chapter

Introductory Chapter: Little Pigeons Can Carry Great Messages

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1. Introduction

Synucleins are a family of proteins involved in neurodegenerative diseases and cancer. The family contains three structurally similar and evolutionary conserved proteins: α-, β-, and γ-synuclein. Synucleins are small proteins containing 140, 134, and 127 amino acids, respectively. In spite of their minor size, these proteins are implicated in numerous functions, including regulation of synaptic transmission, signal transduction, gene expression, and membrane permeability. They are localized in the cytoplasm, nucleus, and mitochondria [1]. After the discovery of the three synucleins, their investigations were primarily focused on α-synuclein for its involvement in several human neurodegenerative diseases known as synucleinopathies, including Parkinson's disease (PD), Parkinson's disease dementia (PDD), dementia with Lewy bodies, multiple system atrophy, and a number of less well-characterized neuroaxonal dystrophies [2]. Structurally α-synuclein can be subdivided into three regions: residues 1–60 belong to an amphipathic N-terminal region, containing four 11-residue repeats including the consensus motif KTKEGV. This part of the molecule has a structural alpha helix propensity similar to apolipoprotein-binding domains. The middle part of the molecule (residues 61–95) is a hydrophobic region which includes the non-amyloid-β component (NAC) region, involved in protein aggregation. Finally, C-terminus (residues 96–140) is a highly acidic, proline-rich region which is the most variable among the three members of the family.

Molecular and cellular studies of synucleins brought many exciting discoveries, such as their prion-like properties, ability to bind to DNA and change its functional state [3], and spreading and propagating between cells transducing certain signals from one cell type to another [4].

Interestingly, recent findings suggest that not only are synucleins located inside the cell but also extracellular synucleins present in the plasma, serum, cerebrospinal fluid, as well as in conditioned media and play important regulatory functions. Synucleins are secreted from cells by unconventional secretion and exocytosis or by exosomes and can spread readily between cells. Transfer can occur not only between neurons but also from neurons to glial cells, as well as between glial cells [5]. Binding of extracellular α-synuclein to CD11b integrin (the α-chain of integrin $\alpha_M\beta_2$) switches on an intracellular signaling cascade leading to the activation of microglia [6]. The results of another recent study further support the relevance of integrin CD11b to synuclein-mediated signaling. CD11b regulate intracellular signaling induced by the aggregated α-synuclein through a RhoA-dependent pathway [7]. Thus, these small proteins carry great messages inside and outside the cell.

In this book, the results of synuclein investigation by methods of biochemistry, genetics, and cell and molecular biology are presented.

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