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FKBP12 and calcineurin matter: Repurposing FK506 to ameliorate synucleinopathies

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Calcineurin is a highly conserved Ca^{2+} calmodulin-dependent phosphatase that plays a key role in sensing Ca^{2+} concentrations and transducing that information into cellular responses. α-Synuclein (α-syn) is a small lipid binding protein whose misfolding and accumulation in Lewy Bodies is a pathological hallmark of several neurodegenerative diseases collectively known as synucleinopathies for which Parkinson's Disease (PD) is the most prevalent. We previously showed that α-syn overexpression leads to high rises in cytosolic Ca^{2+} leading to an over-activation of calcineurin which dephosphorylates a subset of substrates that result in toxicity. Decreasing, but not eliminating calcineurin activity with compounds such as FK506 shifts the spectrum of substrates and results in protection. FK506 impairs calcineurin function by locking it into a complex with the immunophilin FKBP12. Through an integrated genetic and unbiased whole shotgun proteomic approach we now establish the importance of FKBP12 in modulating α-syn toxicity in both calcineurin-dependent an independent manner. Moreover, we demonstrate the efficacy of FK506 *in vivo* using a rat model for PD. FK506 has the ability to cross the blood brain barrier and is an FDA approved drug typically used as an immunosupressant in the clinic. Since our findings establish the importance of modulating FKBP12 activities at sub-immunosupressive doses to achieve neuroprotection, FK506 could immediately translate into the clinic to treat patients with synucelinopathies such as PD.

Biography

Gabriela Caraveo is a Postdoctoral Associate in the laboratory of Susan Lindquist at the Whitehead Institute for Biomedical Research. She completed her undergraduate studies at the department of Biology, School of Sciences at the National Autonomous University of Mexico (UNAM) in Mexico City. She then went to Johns Hopkins University as a Fulbright Scholar in 1999, where she obtained her PhD in Immunology in 2007. Her research seeks to understand the role of calcium signaling pathways in neurodegenerative diseases such as Parkinson Disease using diverse model systems, from yeast to mammalian neuronal models.

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