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Vaccination with heat-shock protein-'chaperoned' α-synuclein as a novel immunotherapeutic strategy against parkinson's disease

Cintia Roodveldt
University of Seville, Spain

α-synuclein (α-Syn) is an amyloid-forming protein whose aggregation is linked to Parkinson's disease (PD), a 'misfolding' neurodegenerative disorder. α- Syn α has also been found to play a critical role in the immune imbalance accompanying disease progression, a feature that has prompted research on the immunological role of α-Syn in PD as well as the search for an effective α-Syn-based immunotherapy. In this work, we investigated a novel approach that simultaneously exploits two important features of certain heat-shock proteins (HSPs): Their classical 'chaperone' activities and their recently discovered and diverse 'immunoactive' properties. In particular, we have characterized the immune response elicited by immunization of naïve C57BL/6 mice with α-Syn/HSP protein combination. Our results show specific differences in mice immunized with the α-Syn/HSP complex when compared to controls, including their Treg ($CD4^+CD25^+Foxp3^+$) and Teff ($CD4^+Foxp3^-$) cell contents, altered antigen specific response of isolated splenocytes, and different anti-α Syn antibody levels in blood. Moreover, the measured serum levels of IFN-α and IL-10 cytokines indicated a unique shift towards aTh2 immunomodulatory/immunoprotective phenotype in mice immunized with α Syn/HSP. Finally, we have tested the therapeutic potential of the α-Syn/HSP vaccine in a 1.methyl-4.phenyl-1,2,3,6-tetrahydropyridine (MPTP) PD mouse model, showing improvements of PD symptoms in treated mice, according to standard behavioral tests (e.g. limb stride variation, rearing). Overall, we propose the use of functional 'HSP-chaperoned amyloid/ aggregating proteins' generated with appropriate HSP-client protein combinations, such as the α-Syn/HSP complex used in this study, as a novel strategy for immune-based intervention against synucleinopathies and other amyloid or 'misfolding' neurodegenerative disorders.

Biography

Cintia Roodveldt completed her PhD in 2005 at the Weizmann Institute of Science (Rehovot, Israel) and performed a Postdoc in amyloid protein studies in 2006-2009 at the University of Cambridge, UK (Prof. ChrisM. Dobson). She was a FEBS Long-Term Research Fellow, and was honored with the Clare Hall Research Fellowship (Cambridge, UK) in 2007 and with the FEBS Distinguished Young Investigator Award 2010. Since 2011 she has been leading a research group focusing on 'immunothearapeutic approaches for neurodegenerative diseases' at CABIMER Center (Seville, Spain). She has published her work in reputed journals as high-impact articles (holding >65 citations/article av.).

Cintia.Roodveldt@cabimer.es

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