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S E M I N A R

Friday, 20 Mar 2015 | 11am | S1A-0217

Hosted by A/P Christoph Winkler

Using in vitro and in vivo approaches for the study of pathogenic mechanisms in SCA3

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Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease (MJD) is an autosomal-dominantly inherited, neurodegenerative disorder caused by the expansion of a CAG repeat in the MJD1 gene resulting in an expanded polyglutamine repeat in the encoded ataxin-3 protein. SCA3/MJD, therefore, belongs to the group of polyglutamine diseases comprised of nine neurodegenerative diseases including five other types of Spinocerebellar ataxias as well as Huntington's disease. In the recent years, we studied several different aspects of the pathogenesis of SCA3 on the molecular genetic, protein biochemical and cell biological level as well as generated multiple mouse models for the disease. Interestingly, it turned out that specific isoforms of ataxin-3 (due to the presence of single nucleotide polymorphisms which lead to amino acid changes or even a premature stop) modify important pathogenic mechanisms of SCA3. In addition, we observed that the intracellular localization of ataxin-3 is of critical relevance for the pathogenesis: In transgenic mice, targeting Ataxin-3 to the nucleus gave rise to a strong phenotype with a high number of protein aggregates. Purely cytoplasmic Ataxin-3, however, even with a highly expanded polyglutamine repeat (148 glutamines), was not able to induce a phenotype and even did not aggregate. We further identified and characterized intracellular transport signals within the coding sequence of Ataxin-3 and characterized highly relevant proteins of the nucleocytoplasmic transport machinery impacting the intracellular localization of ataxin-3. Based on these findings, we identified and validated in vivo FDA-approved compounds impacting this transport pathway. We believe that our results will improve the understanding of pathological mechanisms influencing the progression of the disease and are an important contribution towards a treatment of SCA3/MJD.

Artwork by Ann Nee, DBS, NUS