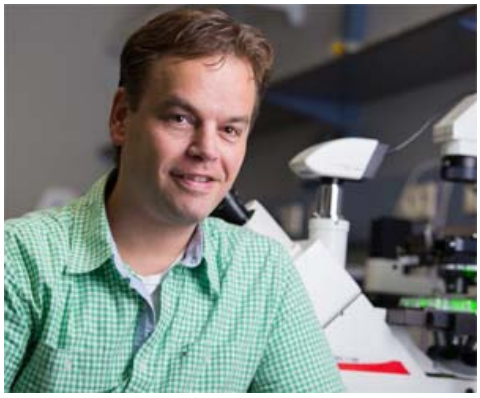

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Improving polyQ huntingtin degradation by the ubiquitin-proteasome system

Huntington's disease is hallmarked by intracellular protein aggregates. A reigning dogma is that the ubiquitin-proteasome system (UPS), the main intracellular protein degradation machinery, is impaired by these aggregates, with fatal consequences for the cell. We recently showed that the proteasome is not sequestered but only reversibly recruited into aggregates, remains catalytically active, and is able to degrade the expanded polyQ-repeat of the mutant huntingtin (mHtt) protein[2,3]. Our preliminary data also shows that if ubiquitinated, mHtt is very efficiently and entirely degraded by the proteasome.

Our central hypothesis is that mHtt is poorly recognized by the UPS and that this leads to inefficient degradation that results in accumulation, aggregation and neurodegeneration. Importantly, the efficiency of these processes seems to differ in a cell-type specific manner suggesting the existence of yet unrecognized cell-type-specific factors. These processes may underlie the difference in the clinical presentation of patients carrying the same disease-causing mutation and the age-of-disease onset. Importantly, as most involved UPS components are ubiquitously expressed, their activities can be manipulated in order to improve their functioning, which is my goal: define novel therapeutic approaches to treat HD and related polyQ diseases.

Expertise

- Ubiquitine-proteasome system
- polyQ proteins
- Huntington
- Protein degradation
- Advanced fluorescence microscopy

Techniques

- Fluorescence and electron microscopy
- Fluorescent substrates for proteasome and peptidases
- Proteomics and protein ubiquitination

Selection of 10 most relevant publications

1. Detection of ubiquitinated huntingtin species in intracellular aggregates. Juenemann K, Wiemhoefer A, **Reits EA**. Front Mol Neurosci. 2015 Jan 28;8:
2. Dynamic recruitment of active proteasomes into polyglutamine initiated inclusion bodies. Schipper-Krom S, Juenemann K, Jansen AH, Wiemhoefer A, van den Nieuwendijk R, Smith DL, Hink MA, Bates GP, Overkleeft H, Ovaa H, **Reits E**. FEBS Lett. 2013 Nov 26
3. Expanded polyglutamine-containing N-terminal huntingtin fragments are entirely degraded by mammalian proteasomes. Juenemann K, Schipper-Krom S, Wiemhoefer A, Kloss A, Sanz Sanz A and **Reits EA**. J Biol Chem, 2013 Sep 20;288(38):27068-84.
4. The DNAJB6 and DNAJB8 Protein Chaperones Prevent Intracellular Aggregation of Polyglutamine Peptides. Gillis J, Schipper-Krom S, Juenemann K, Gruber A, Coolen S, van den Nieuwendijk R, van Veen H, Overkleeft H, Goedhart J, Kampinga HH, **Reits EA**. J Biol Chem. 2013 14;288(24):17225-37.
5. The Ubiquitin-Proteasome System in Huntington's Disease: Are Proteasomes Impaired, Initiators of Disease, or Coming to the Rescue? Schipper-Krom S, Juenemann K, **Reits EA**. Biochem Res Int. 2012:837015
6. Mimicking proteasomal release of polyglutamine peptides initiates aggregation and toxicity. Raspe MA, Gillis JM, Krol HA, Krom S, Bosch KS, Van Veen HA and **Reits EA**. J Cell Sci 2009 Aug 18
7. A major role for TPPII in trimming proteasomal degradation products for MHC class I antigen presentation. **Reits E,** Neijssen J, Herberts C, Benckhuijsen W, Janssen L, Drijfhout JW, Neefjes J Immunity 2004. 20: 495-506.
8. Peptide diffusion, protection, and degradation in nuclear and cytoplasmic compartments before antigen presentation by MHC class I. **Reits E**, Griekspoor A, Neijssen J, Groothuis T, Jalink K, van Veelen P, Janssen H, Calafat J, Drijfhout JW, Neefjes J (2003). Immunity 18(1):97-108.
9. From fixed to FRAP: measuring protein mobility and activity in living cells. **Reits EA** and Neefjes J (2001). Nature Cell Biology 5: 145-147.
10. The major substrates for TAP in vivo are derived from newly synthesized proteins. **Reits EA**, Vos JC, Gromme M, Neefjes J (2000). Nature 404: 774-778.
11. Dynamics of proteasome distribution in living cells**. Reits EA**, Benham AM, Plougastel B, Neefjes J, Trowsdale J (1997). EMBO J. 16: 6087-6094.