Greet De Baets

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BSc Biochemistry-BiotechnologyUniversity of Antwerp, 2007
MSc Biochemistry-Biotechnology, University of Ghent, 2009
PhD Biomedical Sciences, K.U. Leuven, 2013
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Current Position

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Protein aggregation – protein stability - cancer – p53 – disease mutations

Science

Evidence for an active role of protein aggregation in cancer is now present. Different groups, including ours, have identified aggregated p53 in human and murine tumors from different tissues. Second, my lab demonstrated that aggregation of misfolded mutant p53 results in the inactivation of p63 and p73 but also in the upregulation of an Hsf-1 regulated stress response, two phenomena known to enhance tumor malignancy. Hsf-1 is a master transcription factor regulating the expression of molecular chaperones under cellular stress in response to protein misfolding. This suggests that the role of protein aggregation in disease could be much more widespread than the field of neurodegeneration, and, therefore, we tried to identify protein-intrinsic parameters that discriminate novel aggregation prone mutants, which would aid in the estimation of the impact of protein aggregation on disease.
Analysis of an unbiased and representative dataset of variants, taught us that 34% of disease mutations could result in protein aggregation by being destabilizing (calculated by FoldX; ddG > 2) and occurring in a domain with a strong aggregating stretch (TANGO > 75). Applying this basic rule (ddG > 2 & TANGO > 75) suggests that protein aggregation could be a major disease modifier, not only in neurodegeneration and cancer, but also in metabolic diseases and infection sensitizing genes. The results described above already substantiated our computational analysis.
In a next step, RNA sequencing at sufficiently high coverage of several cancer cell lines will be performed. High coverage will enable both mutation calling and expression analysis, whereby the obtained data would be directly processed by our bioinformatics pipeline, ultimately resulting in a set of candidate aggregation prone mutants, that would be further investigated by a) immunofluorescence co-staining of a protein-specific antibody and an aggregation marker, and b) analyzing the effect on the expression of Hsf-1 targets.

Recent Research Projects

2014-present: Post-doctoral fellow, SWITH Laboratory, Leuven, Belgium.

PDM post-doctoral project: *Identifying novel aggregation-associated disease mutants*

2009-2013: Pre-doctoral fellow, SWITCH (VIB), Brussel/Leuven, Belgium.

IWT Ph.D. project: *Development of a position-specific recognition profile for molecular chaperones.*

Selected Publications

Vandersteen A, Hubin E, Sarroukh R, **De Baets G**, Schymkowitz J, Rousseau F, Subramaniam V, Raussens V, Wenschuh H, Wildemann D, Broersen K. (2012) A comparative analysis of the aggregation behavior of amyloid-β peptide variants. *FEBS Lett*

Vandersteen A, Masman MF, **De Baets G**, Jonckheere W, van der Werf K, Marrink SJ, Rozenski J, Benilova I, De Strooper B, Subramaniam V, Schymkowitz J, Rousseau F, Broersen K. (2012) Molecular plasticity regulates oligomerization and cytotoxicity of the multi-peptide length Ab pool. *J. Biol. Chem*

Siekierska A, **De Baets G**, Reumers J, Gallardo R, Rudyak S, Broersen K, Couceiro J, Van Durme J, Schymkowitz J, Rousseau F. (2012) α-Galactosidase aggregation is a determinant of pharmacological chaperone efficacy on Fabry disease mutants. *J. Biol. Chem*

De Baets G, Van Durme J, Reumers J, Maurer-Stroh S, Vanhee P, Schymkowitz J, Rousseau F. (2012) SNPeffect 4.0: on-line prediction of molecular and structural effects of protein-coding variants. *Nucleic Acids Research*, D935-0 (http://snpeffect.switchlab.org/)

De Baets G, Reumers J, Delgado Blanco J, Dopazo J, Schymkowitz J, Rousseau F. (2011) An evolutionary trade-off between protein turnover rate and protein aggregation favors a higher aggregation propensity in fast degrading protein. *PLOS Computation Biology,* e1002090