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Ph.D., Biology 1995
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M.Sc., Biology 1990
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Current Position

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Keywords
proteostasis, protein aggregation, human embryonic stem cells, neuronal differentiation, p53

Science

The concept of the proteostasis network (PN) represent a systems biology approach to protein deposition diseases (e.g. neurodegenerative diseases, amyloidoses, type II diabetes). The PN includes all the cellular components involved in the synthesis, folding, and degradation of proteins, as well as the regulatory mechanisms required for maintaining a functioning proteome despite cellular stress, mutations, or protein misfolding.

When the misfolded protein load exceeds the capacity of the PN to maintain, protein aggregation can occur. Protein misfolding and subsequent aggregation is already thought to be the main cause of neuronal death in neurodegenerative diseases. Our lab's report that the aggregation of p53 can lead directly to increased cell proliferation of the same cell in which the aggregation occurs by a gain of function mechanism provides a unexpected link between neurodegenerative diseases and cancer.

p53 is a potent tumor suppressor, and it is the most frequently mutated gene in human cancer (approximately half of the cases). We observed that mutant p53 not only strongly aggregated in tumor cells, - thereby already eliminating one copy of p53 – but that it also co-aggregated in a dominant negative way with wild type p53 and its paralogs, p63 and p73, sequestering these tumor suppressors that are pivotal to prevent tumorigenesis.

The ability of the PN to cope with mutant or damaged biological material varies with the differentiation stage of cells, as well as deteriorates with cellular senescence, probably explaining the strong correlation of neurodegenerative diseases with aging. According to our hypothesis, the decline of the PN, particularly its decreasing ability to control aggregation-prone mutant p53 proteins, is one of the contributing factors to the steadily increasing incidence of cancer with age. We are currently investigating the aggregation of mutant p53 proteins in undifferentiated human embryonic stem cells (hESCs), as well as in hESCs differentiated to neuronal cells to test our hypothesis and gain information on the key factors keeping p53 aggregation, and tumorigenesis, at bay. Since aggregation of p53 can also occur in Alzheimer's disease, that the underlying proteostatic changes leading to neurodegenerative disease and those leading to cancer are similar, putting our project in the crossroads of the two disease groups.

Recent Fellowships

Seventh Framework Program of the European Union
Marie Curie International Incoming Fellowship
VIB (Flemish Institute of Biotechnology)
KU Leuven
Switch laboratory
08/08/2012 to 07/08/2014

Senior Fellow
KU Leuven
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01/08/2011 to 07/31/2012

Selected Publications

Ahner A, Gong X, **Schmidt BZ**, Peters KW, Rabeh WM, Thibodeau PH, Lukacs GL, Frizzell RA. Small heat shock proteins target mutant CFTR for degradation via a SUMO-dependent pathway. Mol. Biol. Cell. 24(2):74-84, 2013. (PMID: 23155000)

Schmidt BZ, Watts RJ, Aridor M, and Raymond Frizzell RA. Cysteine string protein promotes proteasomal degradation of the cystic fibrosis transmembrane conductance regulator (CFTR) by increasing its interaction with the C-terminus of HSP70-interacting protein (CHIP) and promoting CFTR ubiquitylation. J. Biol. Chem. 284(7):4168-78, 2009. (PMID: 19098309)

Scott CM, Kruse KB, **Schmidt BZ**, Perlmutter DH, McCracken AA, and Brodsky JL. ADD66, a Gene Involved in the Endoplasmic Reticulum Associated Degradation (ERAD) of Alpha-1-Antitrypsin-Z in Yeast, Facilitates Proteasome Activity and Assembly Mol. Biol. Cell. 18: 3776-3787, 2007. (PMID: 17634286)

Hidvegi T, **Schmidt BZ**, Hale P, Perlmutter DH. Accumulation of mutant alpha 1 antitrypsin Z in the ER activates caspases-4 and -12, NFkappa B and BAP31 but not the unfolded protein response. J. Biol. Chem. 280(47):39002-15. 2005. (PMID: 16183649)

Schmidt BZ, Perlmutter DH. Grp78, Grp94 and Grp170 Interact With Alpha-1-Antitrypsin Mutants That Are Retained in the Endoplasmic Reticulum. Am. J. Physiol. Gastrointest. Liver Physiol. 289(3):G444-55, 2005. (PMID: 15845869)