Séminaire ibs

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Conférencier invité

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A 11h - Salle des séminaires de l'IBS

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Mass spectrometry: a diverse tool applied to human aging and disease

Current work in our group includes looking at changes to the human eye lens with age, and the aetiology of amyotrophic lateral sclerosis (ALS). This talk will describe how we use various mass spectrometry (MS) approaches to identify post-translational changes which, in both cases, may contribute to irreversible changes in proteostasis.

1. Human eye lens contains endogenous low molecular weight (LMW) peptides (< 4 kDa) derived from crystallin proteins. We identified a total of 316 different LMW peptides in extracts of human lenses using nanoLC-ESI-MS/MS. We showed that one of the most abundant LMW peptides detected, αA-crystallin57-65, not only increased steadily with age, but was also present in three isobaric forms as a result of Asp58 racemization and isomerization. We had αA57-65 synthesized to include Asp variants D-Asp, L-Asp, D-isoAsp and L-isoAsp. Similar to the lens derived peptides, clear and reproducible differences in the product ion spectra were observed between Asp and isoAsp. An analysis of the terminal residues of all LMW peptides indicated that trypsin-like proteolysis may take place in the lens, along with chemical cleavages at Ser, Gly, Thr and Asp residues. The large number of peptides discovered suggests that crystallin proteolysis may impact upon proteostasis within the aging lens.

2. Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by loss of motor neurons resulting in progressive paralysis. To date, more than 140 different mutations in the gene encoding Cu-Zn-superoxide dismutase (SOD1) have been associated with ALS. Defects in SOD1 are the cause of a familial form of the disorder resulting in fatal paralysis and death within 2 to 5 years. We have used tandem and ion-mobility MS to compare the stability of six SOD1 mutants with the wild-type form and demonstrate a correlation between mutant-associated disease severity and the dissociation behaviour of the SOD1 dimers.

Hôte : E. Boeri Erba (IBS/VIC)