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Protein misfolding in disease - Toxic aggregation-prone proteins in aging and age-related diseases: from structure to pathology and spreading

Mépliement des protéines – Vers une agrégation toxique des protéines au cours du vieillissement et des maladies liées à l'âge : de la structure à la pathologie et sa propagation

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Rapport sur la Conférence
Conference Report

Final report from the Jacques-Monod Conference entitled: Protein misfolding in disease: TOXIC AGGREGATION-PRONE PROTEINS IN AGING AND AGE-RELATED DISEASES: FROM STRUCTURE TO PATHOLOGY AND SPREADING. (Chairs: Luc Buée et Ellen Nollen) September 12-16, 2016

The conference was focused on protein misfolding diseases, mostly brain disorders, such as Alzheimer's, Parkinson's, Huntington's and prion diseases. This meeting followed on from the series of previous three meetings (2007 (Tuite M & Melki R), 2010 (Melki R & Serpell L) and 2013 (L Serpell & L Buée)) on protein misfolding and aggregation and this time, centered around transmission, spreading and potential for therapies. This field has evolved and expanded and this meeting was generally agreed to be particularly timely and exciting. As in the previous meetings, the talks were multidisciplinary and spanned between "structure and cell biology" and "experimental models of proteinopathies". The program included talks in which the research utilized model organisms and also those focused on *in vitro* research. The presentations generated very lively discussions regarding the nature of the toxic species, the definition of "prion-like" transmission and potential targets for novel therapies. Proteinopathies were a central focus of discussion, in particular investigation of how organisms maintain their protein synthesis degradation balance via the proteasome and chaperone machinery, and how proteins aggregate, spread, seed and are toxic.

We invited 25 internationally world-renowned speakers from diverse countries including Belgium, Canada, France, Germany, Israel, Switzerland, the Netherlands, UK and the USA. All the speakers we invited accepted enthusiastically. We also selected 15 talks from the submitted abstracts and accepted a total of 104 participants. We were delighted to accept participants from Croatia, Denmark, Italy, Japan, Lithuania, Poland, Portugal, Russia, as well as those from countries described above and we had also an excellent representation from North America.

Our panel of invited speakers was very attractive and allowed us to be sponsored by different pharmaceutical companies: Servier, Sanofi, UCB Pharma and Lundbeck. Those supports were managed by CNRS, delegation Bretagne et Pays de Loire.

The meeting was composed of five titled sessions and two poster sessions with all participants either presenting a talk or poster.

The sessions were entitled

I. **Protein misfolding and chaperones**
II. **From experimental models to brain imaging**
III. **Brain imaging and diagnosis**
IV. **Protein aggregates and prion-like propagation**
    a. **Aß and Prion**
    b. **α-synuclein and Huntingtin**
    c. **Tau**
V. **Cell biology: aggregation and ways of propagation**

Summary of Lectures and associated discussion

The following provides a brief overview of the science discussed in the oral presentations.

The conference was opened by a plenary lecture from Professor Don Cleveland (La Jolla, USA) who gave an excellent introduction to proteinopathies and the therapeutic strategy of gene silencing with a specific focus on amyotrophic lateral sclerosis.

I Protein folding and chaperones

This session was separated into two sessions, 1 and 2. In session 1, Richard Morimoto (Evanston, USA) made a nice introduction talk on the role of protein homeostasis and heat-shock elements in reproduction and aging. Ellen Nollen (Groningen, NL) described her work on modifyers of proteotoxicity, previously identified in *C. elegans*, MOAG-4/SERF. She is interested in their role in development, physiology and pathology. Simon Alberti (Dresden, Germany) suggested that stress granules and other RNA-granules may co-aggregate with misfolded proteins. He focussed his talk on two genes involved in amyotrophic materal sclerosis (FUS and SOD1). Bernd Bukau was sick and not able to join. Mathias Jucker (Tübingen, Germany) gave a talk on disease biomarkers in mouse models of neurodegenerative disorders. He showed that neurofilament light chain is a good marker of neuronal death in plasma. He also focussed on Aß peptide and its variations in concentration in APP/PS1 mice under different pharmacological treatments. From selected abstracts, Joost Schymkowitz showed that some structural hot spots in globular proteins are essential for solubility/aggregation. Such regions can be predicted by computing.
In session 2, Daniel Kaganovich (Jerusalem, Israel) explained how cells respond to stress and how proteins diffuse and interact with different compartments (lipid droplets, protein granules). He also raised interesting new hypotheses on the role of protein granules as temporary physiological structures. Giovanna Mallucci (Cambridge, UK) proposed to modulate protein synthesis/translation by genetic and pharmacological approaches for therapeutic strategies in proteinopathies. Four talks were then selected from abstracts: Céline Martineau (Belgium/NL) on pathological aging and functional decline in C. elegans; Frédéric Rousseau (Belgium) on the use of protein aggregates as antibiotic agents; Rosie Staniforth (UK) on the role of Cystatin C for inhibiting Aß fibrillization and Clement Danis (France) on the molecular characterization of innovative tools against tau protein (VHH/nanobodies) for future diagnostic and therapeutic strategies.

II From experimental models to brain imaging

Day 2 was opened by Luc Buée (Lille, France) on the prion-like propagation of tau isoforms among Tauopathies such as Alzheimer's disease, progressive supranuclear palsy and Pick's disease. He showed variations in spreading and seeding among tau isoforms in experimental models (mice and rats) of Tauopathies. Benoit Delatour (Paris, France)

showed the interest of PET brain imaging. They developed VHH against Aß peptide which may be useful tools in such imaging approach. Philippe Hantraye (Fontenay-aux-Roses, France) described a new model of Tauopathy in macaques using AAV2/9 viral vector. Behaviour, imaging and neuropathological analyses indicated that it is a promising model for investigating Tau PET ligands. Marc Dhenain (Fontenay-aux-Roses, France) gave a selected abstract talk describing the brain innoculation of Alzheimer brain homogenates in mouse lemur primates. Animals show functional and morphological alterations without seeding and protein aggregation.

III Brain imaging and diagnosis

Gael Chetelat (Caen, France) showed how resting-state functional MRI may be useful to dissect brain connectivity and spreading of neurodegeneration in Alzheimer's patients. Denis Guilloteau was ill and did not join the meeting. A selected abstract talk by Fabien Chauveau (Lyon, France) described new radioligands for alpha-synuclein PET imaging. Another selected abstract talk was given by John Viles (London, UK) described their work on Aβ interactions with copper II and how zinc^{2+} impacts on fibre assembly.

IV Protein aggregates and prion-like propagation

a) Aß and prion
   Frédéric Checler explored the role of Aß oligomers in neuronal degeneration. His group showed that kalirin-7/XBP-1 pathway is essential to this amyloid toxicity. Louise Serpell (Brighton UK) described how Aß self-assembles into toxic species (oligomers, fibrils…). Her group also identified a dityrosine cross-linked Aß which is directly related to neurodegeneration. She also gave some new preliminary insights about the binding of tau to nucleic acids.

b) Alpha-synuclein and huntingtin
   On day 3, Francesca Cicchetti showed evidence of prion-like propagation in Huntington's disease patients who received fetal neural allografts. Her team is also developing a mouse model to mimic this prion-like propagation. Abstracts were also selected with talks of Alexander Buntru (Wanker's lab, Berlin, Germany) on a FRET-assay of Huntingtin aggregates and Janine Kirstein (Berlin, Germany) on distinct chaperone complexes that can suppress or huntingtin fibril formation. Alexis Brice (ICM, Paris) gave an overview on the genetics of synucleinopathies. Ronald Melki (Gif sur Yvette, France) presented an overview on alpha-synuclein aggregates among synucleionopathies. He also showed mechanisms of toxicity related to the binding of recombinant alpha-synuclein fibers to the alpha3 Na^+/K^+-ATPase. From the same laboratory, the abstract of Luc Bousset was selected for oral presentation. They showed that synuclein fibers differ among tauopathies suggesting that different strains exist among synucleinopathies with different seeding and toxic properties. Veerle Baekelandt

(KUL, Belgium) further confirmed distinct neurotoxic and prion-like propagation effects of recombinant alpha-synuclein strains in a mouse model of synucleinopathy. Finally, Erwan Bezard (Bordeaux, France) used preparations of synuclein aggregations from brain extracts from patients presenting with synucleinopathies for testing toxicity and prion-like propagation in animal models. His team also found comparable data to Baeckelandt and Melki's labs.

c) Tau

Susanne Wegmann (from Brad Hyman lab, Boston, USA) described a AAV eGFP-2a-tau which allows for the expression of both eGFP and tau in transduced neurons. Propagation across neuronal populations can be observed showing that age appears to have settle effects on tau propagation and aggregation. Marc Diamond (Dallas, USA) demonstrated the existence of tau prions and characterized different strains, among Tauopathies, which have been injected in rodent tau models. Such materials were able to recapitulate neuropathological presentations, similar to those that define human tauopathies. Gabi Kaminski (Cambridge, UK) showed an analysis in live neuronal cells by two-color super resolution imaging of amyloid growth dynamics. Her team also showed that tau endocytosis may participate to conformational changes. As selected abstract, Daniel Segal (Ramat Gan, Israel) gave an oral presentation of the role of glycosylated tau peptide able to interfere with tau aggregation.

V Cell biology: aggregation and ways of propagation

On the next day, another selected presentation was given by Morvane Colin (Lille, France) on how tau is transferred from cell to cell: free tau assemblies, extracellular vesicles or tunneling nanotubes (TNTs). Guy Lippens (Toulouse, France) analysed by NMR spectroscopy post-translational modifications of recombinant tau after in vitro incubation with enzymes and brain extracts. His team defined a phosphorylation code allowing for aggregation. Chiara Zurzolo (Paris, France) gave a talk on the role of TNTs in prion-like disorders. Finally, another abstract by Mehdi Kabani was presented on the transfer of yeast prions by extracellular vesicles

Conclusions and recommendations

This was the fourth meeting in a series of CJM meetings on protein misfolding and it was extremely successful. The content included the central theme of protein misfolding and the field has evolved towards issues regarding proteinopathies, prion-like transmission and emerging diagnostic and therapeutic strategies since the meeting in 2013. Major issues were discussed regarding cell to cell transmission, templated aggregation and the nature of the toxic species. The conference again attracted diverse participants from structural biologists and protein chemistry to cellular neuroscientists, physiologists and clinicians.

It was generally considered that this was a highly successful, enjoyable and fruitful meeting resulting in excellent discussions regarding key issues in protein misfolding and yielding potential new collaborations. The participants were unanimous in their support for a fifth meeting and were excited about the prospect of this being held within 3-4 years. Dr Ellen Nollen (Groningen, the Netherlands) will become Chair and he will be joined by Dr Ronald Melki (Gif sur Yvette, France) as co-chair and they will submit an application to CJM for a follow up meeting in this series.

We were lucky enough to receive many highly complementary comments, some of which are quoted anonymously below:
"Thank you very much for the great conference, the wonderful company, and of course the delicious food!"

« Je pensais justement à vous remercier de l'expérience scientifique et humaine de ma 1er Conf JM, c'était super, un grand grand merci à vous et à bientôt »

"just a short thank-you note for organising the wonderful meeting. I had a great time! Thanks for putting all this effort into this."

Recommendations were made for increasing the number of poster sessions or to have additional posters within Gulf-stream hotel to allow a display of posters around meals time and to generate discussion throughout the meeting.

Summary in French

La conférence était axée sur les maladies liées au mépliement des protéines, principalement les troubles dégénératifs, tels que les maladies d'Alzheimer, de Parkinson, de Huntington et de prion. Cette réunion fait suite à la série des trois réunions précédentes (2007 (Tuite M & Melki R), 2010 (Melki R & Serpell L) et 2013 (L Serpell & L Buée)) sur le mépliement et l'agrégation des protéines. Cette fois-ci, elle était centrée autour de la transmission, la propagation et les potentielles thérapies. Ce domaine a évolué et s'est élargi. La réunion a été généralement reconnue comme particulièrement opportune et excitante. Comme lors des conférences précédentes, les discussions ont été multidisciplinaires et ont porté sur la «structure et la biologie cellulaire» et les «modèles expérimentaux de protéinopathies». Le programme comprenait des exposés dans lesquels la recherche utilisait des organismes modèles ou in vitro. Les présentations ont suscité des discussions très animées sur la nature des espèces toxiques, la définition de la transmission «prion-like» et les cibles potentielles pour de nouvelles thérapies. Les protéinopathies ont été au cœur des discussions, en particulier sur la façon dont les organismes maintiennent leur équilibre de dégradation de la synthèse protéique par le protéasome et les chaperonnes, et comment les protéines s'agrègent, se propagent, se multiplient et sont toxiques.

Nous avons invité 25 conférenciers de renommée internationale provenant de divers pays dont la Belgique, le Canada, la France, l'Allemagne, Israël, la Suisse, les Pays-Bas, le Royaume-Uni et les États-Unis. Tous les conférenciers que nous avons invités ont accepté avec enthousiasme. Nous avons également sélectionné 15 présentations parmi les résumés soumis et avons accepté un total de 104 participants. Nous avons été ravis d'accueillir des participants venus de Croatie, du Danemark, d'Italie, du Japon, de Lituanie, de Pologne, du Portugal, de Russie, ainsi que des pays décrits ci-dessus et d'Amérique du Nord.

Notre panel de conférenciers invités a été très attractif et nous a permis d'être sponsorisé par différentes sociétés pharmaceutiques: Servier, Sanofi, UCB Pharma et Lundbeck. Ces supports ont été gérés par le CNRS, délégation Bretagne et Pays de Loire. La réunion était composée de cinq sessions intitulées et de deux sessions d'affiches avec tous les participants présentant une conférence ou une affiche.

Les sessions étaient intitulées :

I. Mauvais repliement des protéines et chaperonnes
II. Des modèles expérimentaux à l'imagerie cérébrale
III. Imagerie cérébrale et diagnostic
IV. Agrégats de protéines et propagation de type prion
    a. Aß et Prion
    b. α-synucléine et Huntingtine
    c. Tau
V. Biologie cellulaire: agrégation et voies de propagation


Île de Batz
Enez-Vaz

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