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ABSTRACT

Prevalence in ageing population, difficulties in early diagnosis, and lack of efficient therapies make Alzheimer's disease (AD) one of the most devastating neurodegenerative disorders of our time. AD is associated with misfolding and formation of toxic aggregates of amyloid β (Aβ) peptide, subsequently producing β-rich amyloid deposits [1]. Evidence has emerged that amyloid fibrils may catalyse the process of corruptive misfolding through a positive-feedback reaction loop [2]. However, detailed molecular mechanisms of this process remain elusive. In an effort to better understand molecular mechanisms of Aβ misfolding and fibrillization, we performed all-atom molecular dynamics (MD) simulations of interaction of $A\beta_{1-42}$ chains with fragments of β-rich amyloid fibrils in water. As the fibril models, we employed the solution NMR model 2NAO [3] and the cryo-EM model 5OQV [4]. Four disordered $A\beta_{1-42}$ chains were placed in random positions at a distance from the fibrils, and evolution of the entire systems was investigated. Multiple independent simulations were done for each system. For each fibril model, we observed attachment of $A\beta_{1-42}$ chains to the fibril. Importantly, both threading of $A\beta_{1-42}$ chains around the edge of the fibril (precursor of fibril elongation) and attachment of the chains to fibril's side surface (precursor of secondary nucleation) were detected with each of two fibril models. For the 5OQV model, threading around both the 'ridge' and 'groove' ends of the fibril were observed. Surprisingly, attachment of $A\beta_{1-42}$ chains to side surface of 5OQV fibrils occurred with the Aβ chains' preferential orientation along the fibril axis, rather than along cross-β strands. In one of simulations with the 2NAO fibril model, we observed detachment of an Aβ chain caused by its interaction with a different Aβ chain in solution (precursor of fibril dissociation). In contrast, the 5OQV fibrils have exhibited a remarkable structural stability in our simulations. In conclusion, the MD simulations have shed light into early stages of two major molecular mechanisms of misfolding and aggregation of $A\beta_{1-42}$, fibril elongation and secondary misfolding, as well as captured a fibril dissociation event, revealing important molecular-level details behind these processes.

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154. TSEs in European goats discriminated by Western blotting into five types based on five robust molecular parameters

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ABSTRACT

Contrasting the knowledge about prion diseases or TSEs in sheep, only a very limited number of strain typing studies are available in goats. Two cases deriving from the zoonotic bovine BSE epidemic were however detected in goats. During 2004–2012, over 70 TSE goat brain samples were collected from seven European countries and evaluated for TSE type/strain variation. A selection of these materials was chosen for in-depth analysis based on various criteria: tissue quality, genotype, broad geographical distribution, potential type variation. Of these, 37 cases were biochemically analysed (present study) and a subset of these subjected to bioassays in seven rodent models (see parallel study of Nonno et al.). Analyses of these isolates showed that in goats different PrP^{Sc} types exist, comparable to those found in sheep such as classical scrapie, CH1641-like scrapie and Nor98/atypical scrapie. However, classical scrapie isolates could be further differentiated in two molecular subtypes based on the PK susceptibility of the N-terminus and

on the molecular weight of PrP^{res}.

on the molecular weight of PrP^{res}. Importantly, the two subtypes of classical scrapie showed different geographical distribution, as one subtype was only detected in goats deriving from Italy and France. These analyses also show, that none of the field samples exhibited BSE-like features and offer a comprehensive set of robust molecular PrP^{res} properties to exclude suspicion for the presence of BSE. These are: molecular mass of the triplet bands, presence of N-terminus epitope, glycoprofile markers, a dual population marker and the structural stability of PrP-core.

155. Expert opinions on the potential role of Indigenous peoples in wildlife management in Alberta

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ABSTRACT

Background: Natural resource management in many parts of the world are increasingly based around the recognition of Indigenous knowledge and the rights of resource users [1]. In Alberta, there has been a historical lack of consideration of the knowledge of First Nations and Métis peoples and decisions about the development, use, management and monitoring of natural resources [2–5]. As a result of these histories, Indigenous peoples and their knowledge have little influence within provincial wildlife management regimes in contemporary Alberta [6]. Wildlife diseases such as Chronic Wasting Disease (CWD) have added further challenges for wildlife managers in Alberta. CWD is a fatal form of transmissible spongiform encephalopathy (TSE) primarily found in cervids (e.g. deer, moose, elk, and caribou). CWD in Alberta as of the 2017/2018 hunting season, has continued to spread westward along the Red Deer/South Saskatchewan/Bow watershed, the Battle watershed, and north along the Alberta/Saskatchewan border. Incidence of deer that have tested positive for CWD has increased markedly since the 2016/2017 hunting seasons, and several new Wildlife Management Units (WMU) will be added to the mandatory surveillance list for the 2018/19 hunting season [7]. First Nations and Métis communities in the Treaty 6 area – including Saddle Lake First Nation, Frog Lake First Nation, Kehewin First Nation, Fishing Lake Métis settlement, and the Elizabeth Métis settlement – are within the mandatory surveillance zone yet it remains unclear whether these communities are being actively engaged in the process of management.

Methods: This research sought to explore diverse expert perspectives on the role of Indigenous Knowledge in wildlife monitoring and management in relation to the issue of CWD; and better understand the key challenges and opportunities regarding wildlife management in Alberta. The methods used in this thesis include a modified qualitative expert elicitation, probabilistic sampling, and thematic analysis.

Results: The major thematic results experts discussed include: the lack of Indigenous compliance in cervid monitoring with varying reasons provided; the necessity of both scientists and Indigenous communities to engage in intercultural and technical capacity development; and the need for both scientists and Indigenous communities to form a functional and mutually beneficial working relationship. This research is a preliminary investigation into the social, cultural, and economic aspects of CWD management, and is intended to provide further insights towards this end with a focus on future areas of research.

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156. Screening and characterization of unusual sCJD cases in a CWD endemic state in the USA

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