Solving the pathogenecity of TMEM16 variants using structural modeling based on AlphaFold 2 predictions

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POSTERS

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Abstracts submitted to the 47th FEBS Congress from 8th to 12th July 2023 and accepted by the Congress Management Board are published in this Supplement of *FEBS Open Bio*. Late-breaking abstracts are not included in this supplement. The abstracts are available as two PDF files: Talks (Plenary Lectures, Symposia and Speed Talks) and Posters.

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P-08.5-18
Solving the pathogenecity of TMEM165 variants using structural modeling based on AlphaFold 2 predictions

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TMEM165 is a protein playing a crucial role in Mn^{2+} transport in the Golgi, and whose mutations in patients are known to cause congenital disorders of glycosylation (CDG). Whereas some of those mutations affect either the expression or the localization of TMEM165, others clearly impair the Mn^{2+} transport which is essential for the function of many Golgi glycosylation enzymes. The identified mutations either affect the highly-conserved consensus motifs E-φ-G-D-[KR]-[TS] characterizing the UPF00016/CaCA2 family, hence presumably important for the protein function, or, like the $G>R^{304}$ mutation, are far away from these motifs in the sequence. Until recently, the classical membrane protein topology prediction methods were unable to provide a clear picture of the organization of TMEM165 inside the cell membrane, or to explain in a convincing manner the impact of patient and experimentally-generated mutations on the transporter function of TMEM165. In this study, the abilities of AlphaFold 2 have been used to build a TMEM165 model that was then subjected to molecular dynamics (MD) simulation including membrane lipids and water. This model provides a credible picture of the 3D protein scaffold formed from a two-fold repeat of three transmembrane helices/domains (TMD) where the consensus motifs face each other to form a putative acidic cation-binding site at the cytosolic side of the protein. It sheds new light on the impact of mutations on the transporter function of TMEM165, found in patients and studied experimentally *in vivo*, formerly and within this study. More particularly and very interestingly, this model explains the impact of the $G>R^{304}$ mutation on TMEM165's function. These findings give great confidence in the predicted TMEM165 model whose structural features are discussed in the study and compared with other structural and functional homologues of TMEM165.

P-08.5-19
Comparative analysis of both the cerebrospinal fluid beta-amyloid and tau in idiopathic normal pressure hydrocephalus and neurodegenerative dementia

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Idiopathic normal pressure hydrocephalus (iNPH) is the leading reversible cause of cognitive impairment and gait disturbance possessing similar clinical manifestations and accompanies to major neurodegenerative disorders in older adults. We aimed to investigate whether cerebrospinal fluid (CSF) biomarker for Alzheimer's disease (AD) may be useful in the differential diagnosis of iNPH. Amyloid-beta (Aβ) 42 and 40, total tau (t-tau), phosphorylated tau (p-tau) were measured via ELISA in 192 consecutive CSF samples of patients with iNPH (n = 80), AD (n = 48), frontotemporal dementia (FTD) (n = 34), Lewy body diseases (LBDs) (n = 30) consisting of Parkinson's disease dementia and dementia with Lewy bodies. The mean age of the study population was 75.6 ± 7.7 years, and 54.2% were female. CSF Aβ42 levels were significantly higher, and p-tau and t-tau levels were lower in iNPH patients than in AD and LBDs patients. Also, iNPH patients had significantly higher levels of t-tau than those with FTD. Age and sex-adjusted multi-nominal regression analysis revealed that the odds of having AD relative to iNPH decreased by 37% when the Aβ 42 level increased by one standard deviation (SD), and the odds of having LBDs relative to iNPH decreased by 47%. The odds of having LBDs relative to iNPH increased 76% when the p-tau level increased 1SD. It is 2.5 times more likely for a patient to have LBD relative to NPH and 2.1 times more likely to have AD relative to iNPH when the t-tau value increased 1SD. Levels of CSF Aβ42, p-tau, and t-tau, in particularly decreased t-tau, are of potential value in differentiating iNPH from LBDs and also confirm previous studies reporting t-tau level is lower and Aβ42 level is higher in iNPH than in AD.

P-08.5-20
The PAR-2 and its downstream MAPKs signaling mediate thrombin-induced COX-2 upregulation and thromboxane production/ secretion in human primary cultured ovarian follicular granulosa cells

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While angiogenesis is known to be essential for folliculogenesis that contributes to oocyte growth, the prostaglandins (PGs) have been implicated in modulating angiogenesis. Since some previous studies have indicated the presence of coagulation factors such as factor X and prothrombin (a latent form of thrombin) in ovarian follicular fluid, this study sought to explore the mechanism of action of thrombin in regulating PG induction and secretion in ovarian follicular granulosa cells (GCs). The level of thromboxane B2 (TXB2), a stable metabolite of TXA2, in human GC culture medium was analyzed by ELISA and the cyclooxygenase (COX) induction and cellular signaling were determined by western blotting and RT-PCR. We found that thrombin induced COX-2 mRNA and protein expression and TXB2 secretion in human GCs. Intriguingly, thrombin also induced COX-1 protein upregulation but did not affect COX-1 mRNA expression. In parallel, the proteinase-activated receptor 2 and 3 (PAR 2 and 3)-activating agonist induced similar effects to thrombin on GCs. However, only the PAR2 antagonist and p38 MAPK, ERK 1/2, and JNK1/2 inhibitors could attenuate thrombin-induced COX expression and TXB2 release. Our results demonstrated that