The dynamic mechanism of presenilin-function: Sensitive gate dynamics and loop unplugging control protein access - DTU Orbit (08/11/2017)

The dynamic mechanism of presenilin-function: Sensitive gate dynamics and loop unplugging control protein access

There is no molecular explanation for the many presenilin 1 (PSEN1) mutations causing Alzheimer's disease, but both gain of function relating to amyloid production and loss of isolated PSEN1 function have been implied. We report here the first detailed dynamic all-atom model of mature PSEN1 from molecular dynamics in an explicit membrane with particular account of the as yet unexplored loop dynamics. We find that mature PSEN1 contains multiple distinct conformational states whereas non-mature PSEN1 is a typical one-state protein. We confirm a previously suggested gating mechanism, and find that the 106-131 loop acts as a "hinge" for the TM2 and TM6 "doors". More importantly, we identify an unplugging mechanism of the Exon 9 loop associated only with mature PSEN1. Proper opening of both the "gate" and "plug" in the membrane produces channel-like morphologies and access to the catalytic aspartates. Dynamically, these features seem linked. The long-range sensitivity of this gate-plug system to subtle conformational changes can explain why so many PSEN1 mutants cause disease. Reduced access and imprecise substrate cleavage associated with impaired gate-plug dynamics is directly illustrated by the effect of maturation in our work and could explain the overall reduction in Aβ levels upon PSEN1 mutation and the increase in the Aβ 42/40 ratio. Yet, our PSEN1-only dynamics are particularly insightful in revealing PSEN1-only dynamics relating to e.g. its role as membrane channel. Thus, our identified gate-plug mechanism is relevant for designing PSEN1 modulating therapies for treatment of Alzheimer's disease within both the amyloid/γ-secretase hypothesis and within the PSEN1 loss of function paradigm.

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