Allosteric signal transduction in neuronal protein reelin

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Introduction

Reelin is a an extracellular matrix glycoprotein which governs cell migration through activation of multiple intracellular signaling events by interactions with receptors: ApoE receptor 2 (ApoER2, complex is partially known: 5b4x) and very low density lipoprotein receptor (VLDLR), as well as with intracellular protein Disabled-1 (Dab1) [1].

In order to characterize crucial elements of reelin which may play an important role in singal transduction, perturbation scanning response (PRS) analysis of molecular dynamics (MD) simulations results was performed. PRS method has been used succesfully for other systems to predict the signal transduction pathways and potential receivers of allosteric signals [2,3]. We show that this approach helps to elucidate residues critical for reelin signal transduction through ApoER2, VLDLR and its other parthers.

[1] E. Khialeeva et al., Develop. Dynamics 246, 4 (2017).
[2] C. Atilgan et al., Biophys. J. 99, 3 (2010).
[3] K. Mikulska-Ruminska et al., J. Chem. Inform. Model. 59 (2019).
[4] C. Quattrocchi et al., J. Biol. Chem. 277, 1 (2002).

Conclusions

Effectors (propagators of allosteric signal) are buried inside the BNR domains whereas residues denoted as a potential receivers of allosteric signals (sensors) were identified in following regions: (i) the binding interface of ApoER2, (ii) ion binding sites (Zn^{2+} or Ca^{2+}) and (iii) a fragment of EGF domain.

The results clearly imply on the presence of a signal transduction pathway between the catalytic site (Zn^{2+}) and the ApoER2/Ca^{2+} binding site in both modules, BEB5 and BEB6. Experimental findnings corroborate our results.

Sensors in BEB3 are localized in BNR5 module (the left side of BEB containing S1283) which has been reported as a crucial element of reelin protease activity.

Methods

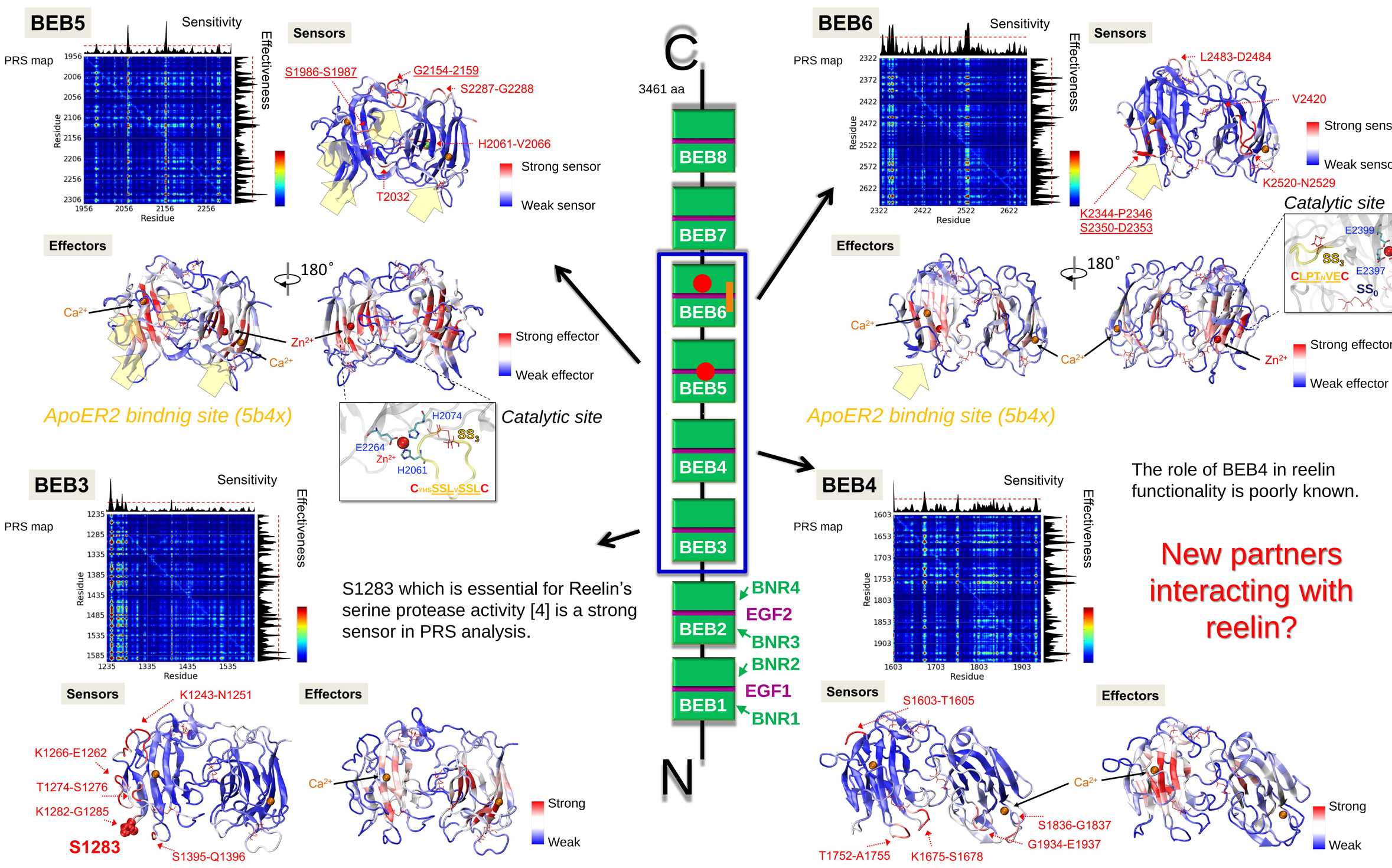
MD (Molecular Dynamics)

- NAMD code, CHARMM 27 force field, TIP3P waters
- Systems include: Zn^{2+} and Ca^{2+} ions, sugars: NAGs, BMA
- Water equilibration: 0.2 ns, minimization: 10 000 steps
- Heating from 0 K up to 300 K: 0.5 ns
- MD runs time: over 800 ns (200 ns for each BEB structure)

PRS (Perturbation Response Scanning)

- ProDy API (I. Bahar) was used to perform PRS analysis of MD trajectories.
- PRS provide the magnitude and directionality of the residue displacements in response to external force (PRS maps); successfully used for revealing allosteric signal transduction elements in proteins – effectors and sensors.
  - **Effector** - ability of residue to affect the dynamics changes in all other residues (propagation of allosteric signals to protein partner).
  - **Sensor** - receiver of allosteric signals (involved in the execution of allosteric structural changes).

Results



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