Computationally Elucidating Rotational Coupling of the transmembrane Domain in VEGF Receptor 2 Activation

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Vascular endothelial growth factor receptor-2 (VEGFR-2), which plays a major role in regulating angiogenesis, requires dimerization with specific positioning of monomeric receptor to control signal transduction pathways to be activated. For this, vascular endothelial growth factor-A (VEGF-A) is bound to change the extra cellular domain (ECD) conformation and reorient the intracellular kinase domain followed by TMD orientation. Because it is impossible to experimentally produce a sufficient amount of full-length VEGFR-2 functional recombinant protein, ECD and TMD have been studied separately. Thus, mutant TMD has been used so far to explain the conformational change of TMD helices such as rotation. However, the use of computational method overcomes the experimental limitation. Here, we show a possibility to explain the exact structural change of TMD helices in full length VEGFR-2 using coarse-grained molecular dynamics (CG MD). We could confirm that rotation occurs in TMD helices connected to the activated ECD structure. Although the initial experimental setting was expected to have a clear difference in the rotational change of TMD helices depending on the binding of VEGF-A to activated ECD, the two structures showed similar TMD helices conformational change. It can be seen that the ECD change according to the presence or absence of VEGF-A binding was not properly made within the simulation time. Therefore, in future research, the simulation will be conducted so that the effective time scale is more than ms. We also will apply enhanced sampling such as umbrella sampling to CG MD to rule out the possibility that the ECD structure is stabilized to prevent proper sampling.