

A Computational Study of the Role of Asparagine 79 in Ubc13

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Ubiquitin (Ub) is a regulatory protein with the ability to flag proteins to be degraded. Ub is covalently attached to a lysine on the target protein by a series of reactions catalyzed by three types of enzymes: ubiquitin activating enzymes, E1; ubiquitin conjugating enzymes, E2; and ubiquitin ligases, E3. If ubiquitin is not attached properly, it can lead to various diseases, like Alzheimer's, Parkinson's and anemia. Our lab has recently published data on the mechanism of the E2 enzyme (Ubc13) and contrary to a popular hypothesis, our data shows that it is unlikely that the amino acid asparagine 79 in Ubc13 stabilizes a reaction intermediate. Instead, our results suggest that asparagine 79 plays an important role in maintaining the structure of Ubc13; however, this hypothesis was based on molecular dynamics simulations of a simplified model of the Ubc13~Ub system. The model system consisted of a Ubc13 bonded to a Ub and with a zwitterionic lysine residue as a substrate. This model is incomplete because it is missing the full substrate ubiquitin, an E3 ligase, and a ubiquitin conjugating enzyme variant (UeV). Therefore, we are currently using molecular dynamics to explore the effects of these additional proteins by generating trajectories of Ubc13~Ub complexed with different combinations of E3, UeV, and full substrate Ub. Finally, it has been suggested that amino acid histidine 77 in Ubc13 may also play an important structural role and we are currently conducting simulations to probe its function.