COMPUTATIONAL ANALYSIS OF THE MECHANISM OF THE UBIQUITIN CONJUGATING ENZYME UBC13

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Ubc13 is an E2 enzyme that catalyzes a post translational modification of proteins called lysine ubiquitination, i.e. the addition of ubiquitin to the lysine of a target protein via a thioester aminolysis reaction. Lysine ubiquitination is important because, one of its functions is to signal for the degradation of damaged proteins, and defects in ubc13 are linked to different disorders. The accepted mechanism for Ubc13-catalyzed ubiquitination is a stepwise mechanism that creates an oxyanion intermediate. This intermediate is hypothesized to be stabilized by a nearby asparagine residue, which is known as the "oxyanion hole." However, the validity of the accepted mechanism has come into question because, there has never been a comprehensive study of the ubiquitination mechanism, the accepted mechanism was inferred from the reverse reaction, and recent studies suggest a different role for the oxyanion hole. In our study, we use molecular dynamics to examine the hydrogen bond environment of the active site in two structures of Ubc13 and determine the likelihood for the formation of the oxyanion hole. Furthermore, we present initial data wherein we calculate the energies of the different possible steps of the reaction coordinate with the ONIOM quantum mechanics/molecular mechanics (QM/MM) extrapolation procedure.

Acknowledgements

Research for this project was funded by the National Science Foundation, grant numbers CHE-1062629 in 2013 and CHE-1461175 in 2015, The Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1053575, and The Thomas F. and Kate Miller Jeffress Memorial Trust, Bank of America, N.A., Trustee.