In-silico Modeling of the HAMLET (Human Alpha-lactalbumin Made LEthal to Tumor cells) Alpha-1 Complex

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HAMLET (Human Alpha-lactalbumin Made LEthal to Tumor cells) is a tumoricidal complex of partially unfolded Alpha-lactalbumin and Oleic Acid [1]. The smallest subunit of Human Alpha-lactalbumin capable of forming tumoricidal complexes with oleic acid are it's alpha helical domains [2]. No high resolution structural model detailing atomistic interactions is available, despite experimental evidence characterizing the tumoricidal activity of the complexes. We used Hamiltonian Replica Exchange Molecular Dynamics simulations to sample the conformational landscape and model the interactions between the Alpha1 peptide derived from the Human Alpha-lactalbumin Alpha1 domain, and oleic acid. By comparison with a parallel simulation of the Alpha1 peptide alone, we show key differences in the free energy landscape of the Alpha1 peptide in the presence and absence of oleic acid. We show that oleic acid is required to stabilize the partially unfolded Alpha1 peptide in a dominant conformation. The dominant conformational model of the Alpha1 peptide-oleic acid complex is described as containing alpha-helical mortifs binding with the oleic acid in a hydrophobic core. This study provides atomistic insights into the interactions between the Alpha1 peptide and oleic acid, and proposes a structural basis for the tumoricidal activity of the complex.

References

1. J.C.S. Ho, A. Nadeem, and C. Svanborg, *Biochemical and Biophysical Research Communications*. **482**(2017), 454-458.

2. C.S. Ho, et al., *PLoS One*. **7**(2012), e53051.