Structural insights into the role of deleterious mutations at the dimeric interface of TRAM protein

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Abstract

Toll-like receptors (TLRs) are major players of the innate immune system – recognizing pathogens and differentiating self/non-self components of immunity. These proteins are present either on the plasma membrane or endosome and recognise pathogens at their extracellular domains. They are also characterised by a single transmembrane helix and an intracellular TIR domain. Few TIRs directly invoke downstream signalling, while others require other TIR domains of adaptors like TRAM and TRIF. On recognizing pathogenic lipopolysaccharides (LPS), TLR4 dimerises and interacts with the intracellular TRAM dimer through the TIR domain to further recruit TRIF molecules. We have performed an in-depth study of the effect of two mutations, P116H and C117H, at the dimeric region of the adaptor TRAM, which are known to abrogate downstream signalling. We modelled the structure and performed molecular dynamics studies to infer the structural changes occurring across the trajectory due to the point mutations in order to decipher the structural basis of this dramatic effect. We observed that these mutations led to increased RoG (Radius of Gyration) of the complex and resulted in several changes to the interaction energy values when compared against the wild type and few positive control mutants. We identified highly interacting residues as hubs and few such hubs that were lost in the mutant dimers. Further, changes in the protein residue path, hampering the information flow between the crucial AEDD and TS sites, happen for the mutants. Overall, we show that such residue changes can have subtle but long-distance effects, impacting the signaling path allosterically.

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