

Brief Summary

Title: Sequence analysis of Toll/interleukin-1 receptor (TIR) involved in Toll-like Receptor (TLR) signaling pathway and targeting one of the TLR adaptors (TRAM) in case of autoimmune disorders and sepsis-like conditions.

Summary:

The essential proteins of innate immune-related pathways have TIR domains. Not only do they constitute a primary domain in all Toll-like receptor (TLR) proteins, but they are also found in the adaptor proteins required for TLR communication. The TLR4 protein, which identifies both endogenous (associated with danger) and exogenous (related to pathogens) ligands, is one of the most significant of these. When autoimmune diseases arise, a multitude of interleukins and cytokines are produced by TLR4 signalling, which can be detrimental to the human body [1]. The TRAM adaptor protein-mediated TLR4 signalling complex is the focus of our investigation.

By searching a database for naturally occurring small compounds, we have discovered potential ligands that bind to TRAM and inhibit downstream signalling. These ligands were obtained from *Punica granatum* & *Mangifera indica* (compound 4) and *Cornus Officinalis* (compound 2), and our experimental results showed that they outperformed the well-known VIPER peptide [2]. We also looked at the important residues that are involved in the interaction between these protein partners and carefully examined the implications of mutations that happen at the interface. This work shed additional light on the impact of mutations that cause structural alterations that are allosterically caused to abrogate downstream signals [3]. We also examined these adaptor proteins' ancestry from their ancestral lineages. We looked at how they diverged to become homologs. The discovery that both adaptors (TRAM and TRIF) are conserved in vertebrates was intriguing [4]. Additionally, we modelled these complexes from representative organisms to comprehend the immunological route in different taxa through an understanding of signaling mechanisms [5]. Collectively, these proteins are essential components of the innate immune system and play a major role in immunity maintenance by regulating the balance of pro- to anti-inflammatory mediators.



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References:

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