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:

TIR domains are present in the key proteins of innate immune-related pathways. Apart from being a principal domain of all Toll-like receptor (TLR) proteins, they are also present in the adaptor proteins necessary for TLR signaling. One of the most important among these is the TLR4 protein, which recognizes both exogenous (pathogen-associated) and endogenous (danger-associated) ligands. In the case of autoimmune disorders, this TLR4 signaling produces a plethora of interleukins and cytokines, that become harmful to us [1]. Our study aims to target the TRAM adaptor protein-mediated TLR4 signaling complex. Through our work, we have screened a database for naturally occurring small molecules and found putative ligands that bind to TRAM and suppress the downstream signaling. We found these ligands were isolated from *Cornus Officinalis* (compound 2) and *Punica granatum* & *Mangifera indica* (compound 4) and these performed experimentally better than the known VIPER peptide [2].

Further, we investigated the key residues involved in the interaction between these protein partners and studied the implication of mutations occurring at the interface in detail. This study provided more insights into the effect of mutations leading to structural changes allosterically and resulting in downstream signaling abrogation.

Additionally, we investigated the origin of these adaptor proteins from their ancestral lineages. We observed the pattern of their divergence into homologs. It was exciting to find the conservation pattern of both adaptors (TRAM and TRIF) across vertebrates [3]. Altogether, these proteins are crucial players of the innate immune system and are significantly involved in maintaining our immunity by balancing the amounts of pro and anti-inflammatory mediators.

References:

[1] M. K. Vidya, V. G. Kumar, V. Sejian, M. Bagath, G. Krishnan, and R. Bhatta, "Toll-like receptors: Significance, ligands, signaling pathways, and functions in mammals," *International Reviews of Immunology*. 2018, doi: 10.1080/08830185.2017.1380200.

[2] **S. Verma**, P. Reddy, and R. Sowdhamini, "Integrated approaches for the recognition of small molecule inhibitors for Toll-like receptor 4," *Comput. Struct. Biotechnol. J.*, vol. 21, no. July, pp. 3680–3689, 2023, doi: 10.1016/j.csbj.2023.07.026.

[3] **S. Verma** and R. Sowdhamini, "A genome-wide search of Toll/Interleukin-1 receptor (TIR) domain-containing adapter molecule (TICAM) and their evolutionary divergence from other TIR domain containing proteins," *Biol. Direct*, vol. 17, no. 1, pp. 1–14, 2022, doi: 10.1186/s13062-022-00335-9.

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