Title of the thesis: Evolutionary selection on toll-like receptor genes.
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Abstract

Infectious diseases have posed the greatest threat to survival and wellbeing during human evolution. Natural selection is thus expected to exert a major influence on host defence genes, specifically on the genes involve in innate immunity, whose products intervene direct interactions between the host and the pathogen. Toll-like receptors (TLRs) are well-known for their roles in innate immunity, where they recognise pathogens and initiate a signalling response. These receptors can recognize a different types of pathogen-associated molecular patterns (PAMPs) as their ligands and are implicated in immunological response, signalling process development, and cell adhesion. Mammalian TLRs recognise molecular signatures linked with infections and trigger an innate immune response. This study emphasised the significance of evolutionary selection on the diverse mutation of TLR genes from mammals.

In my study I have noted difference in amino acid usage between primate and non-primate mammalian TLR genes. The GC content of TLR genes and the hydrophobicity of encoded proteins are the important factors in determining the distinct pattern of amino acid usage. The GC-content was found to be consistent evolutionary force throughout the course of evolution of TLR genes between primate and non-primate mammalian species. I have observed TLR genes are generally under purifying selection, however several positively selected sites have been found in the ligand binding domain. My study also presented that the amino acid usage pattern of TLRs are influenced by their subcellular location. Different branching patterns of primate and non-primate mammalian TLRs have also been demonstrated through phylogenetic tree. These findings clearly indicate that natural selection influenced the evolution of primate and non-primate mammalian TLR genes.

Following these findings, an amino acid usage analysis of all mammalian TLRs was done to investigate the evolutionary diversity of mammalian TLRs and differences in immunological response. A detailed examination of mammalian TLRs found that TLR9 evolved in a completely different way compared to other mammalian TLRs. Different sequence-based features, including amino acid usage, hydrophobicity, GC content, and evolutionary parameters, have been identified to impact the divergence of TLR9 from other TLRs. Reconstructing ancestral sequences is an important component of molecular evolution of TLR because it allows to follow changes across genes. Ancestral sequence reconstruction study also demonstrated that TLR genes evolved gradually across numerous ancestral lineages, resulting in the distinct TLR9 pattern. It exhibits evolutionary divergence, with the gradual accumulation of mutations resulting in the specific pattern of TLR9.

The evolutionary genetics approach to determine the magnitude of natural selection operating on TLR genes and the progressive changes that lead to divergence will help us better understand the mechanism of host defence mediated by TLRs.

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