Structure and dynamics of the intracellular domain of toll-like receptor 1: the basis for Zn2+ modulating the receptor signaling

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The family of Toll-Like Receptor (TLR) refers to the first type of membrane proteins. TLRs play a critical role in innate immunity as the first line of host defense. The medical and biological significance of the TLR signaling is obvious, since the dysregulation of the TLR system causes various autoimmune diseases and septic shock, and some therapeutic strategies targeting TLRs have already emerged. Despite the fact that the general scheme of the operation of TLR receptors is known and even there are structures of individual fragments for some proteins of this family, the detailed mechanism of receptor functioning remains unclear.
The research presents the results of the structure and dynamics of the TLR1 toll-interleukin-like (TIR) cytoplasmic domain in crystal and in solution. The work demonstrates data on specific binding of the TLR1 TIR with the zinc ions with nanomolar affinity. Cysteine residues 667 and 686 are mediated interactions between TLR1 TIR and Zn, and C667 is required for Zn binding. Using functional assays for the heterodimeric TLR1 /2 receptor, the effect of Zn addition and Zn depletion on TLR1 activity was shown, and also was shown the key role of 667 cysteine: the C667A mutation disrupts the activity of the receptor. Analysis of the data presented in the work suggests that the ability of the TIR domain of TLR1 to bind zinc is critical for receptor activation.
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