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**Structural and Functional Insights into the Role of Themis2 and Themis2-protein Complexes**

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Themis2 is an adapter protein belonging to the CABIT domain protein family and is primarily expressed in B cells, macrophages, NK cells, and epithelial cancer cells. Themis2 contains two copies of a novel structural domain termed the Cysteine-containing All-Beta in Themis (CABIT) domain and a C-terminal proline-rich sequence (PRS), both of which are indispensable for its activity. The CABIT domain is conserved across multiple metazoan species and is suggested to serve a significant and conserved function in multiple signalling pathways. However, despite being first described over ten years ago, the structural and mechanistic basis of the pleiotropic functions of Themis2 remain poorly understood. This research proposal aims to provide insights into the structure and function of Themis2 in complex with its binding partners SHP-1 and Grb2, as well as to investigate its unexplored potential trimolecular complex. Characterization of how Themis2 structural domains, particularly the CABIT domain, interact with and regulate these binding partners will provide timely insights into the function of CABIT domain-containing proteins in signalling pathways. This research is expected to enhance our understanding of Themis2 and related proteins as well as contribute to the development of novel therapeutic strategies to target these protein complexes in inflammation and cancer.