Characterization of IKK–substrate interaction mechanisms

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Résumé

NF-B signaling (Nuclear Factor kappa-light-chain-enhancer of activated B cells) controls fundamental biological processes, including inflammation, immune responses, cell survival, and tissue repair (Mulero et al., 2019). There are two main NF-B signaling pathways: the canonical and the alternative pathways, both converge on the IKK (IB kinase) complexes. Those IKK complexes share a commun catalytic core composed of homo- or heterodimers of the homologous subunits IKKα and IKKβ. These proteins display a similar architecture consisting of a kinase domain, a ubiquitin-like domain, and a dimerization domain.
In both the canonical and alternative pathways, IKK complexes phosphorylate their substrates (IBα and p100), leading to their partial or complete degradation by the proteasome and the release of NF-B dimers, which then translocate into the nucleus to regulate gene expression. Dysregulation of these pathways results in severe outcomes, including complex and chronic diseases. Therefore, a comprehensive understanding of the molecular mechanisms, particularly the specific interactions of IKK complexes with their substrates, is essential to identify new therapeutic targets.
The recent identification of a conserved docking motif (YDDΦxΦ consensus with Φ : hydrophobic amino acid) located at the C-terminus of IBα has represented a significant breakthrough, providing the first insights into this interaction mechanism (Li C, Moro S et al., *Nat. Commun.*, 2024. Based on this discovery, an initial model of the interaction between an IKKβ homodimer and a peptide containing the docking motif has been established, paving the way for more comprehensive structural studies. Hence, this project aims to determine the structure of the IKK/IBα/NF-B complex by cryo-electron microscopy, in order to elucidate the mechanisms of substrate recognition and interaction.

Mots-Clés: IKK complex, protein–protein interactions, NF, B signaling

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