Recognition of LD motifs by the Focal Adhesion Targeting Domains of FAK and PYK2: Insights from Molecular Dynamics Simulations

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Abstract

The focal adhesion kinase (FAK) and the proline-rich tyrosine kinase 2-beta (PYK2) are implicated in cancer progression and metastasis and represent promising biomarkers and targets for cancer therapy. FAK and PYK2 are recruited to Focal Adhesions (Fas) via interactions between their Focal Adhesion Targeting (FAT) domains and conserved segments (LD motifs) on the proteins Paxillin, Leupaxin and Hic-5. A promising new approach for the inhibition of FAK and PYK2 targets interactions of the FAK domains with proteins that promote localization at Focal Adhesions. Advances toward this goal include the development of surface plasmon resonance, HSQC-NMR and fluorescence polarization assays for the identification of fragments or compounds interfering with the FAK-Paxillin interaction. We have recently validated this strategy, showing that Paxillin mimicking polypeptides with 2-3 LD motifs displace FAK from FAs and block kinase-dependent and independent functions of FAK, including downstream integrin signalling and FA localization of the protein p130Cas. In the present work we study by all-atom molecular dynamics simulations the recognition of peptides with the Paxillin and Leupaxin LD motifs by the FAK-FAT and PYK2-FAT domains. Our simulations and free-energy analysis interpret experimental data on binding of Paxillin and Leupaxin LD motifs at FAK-FAT and PYK2-FAT binding sites, and assess the roles of consensus LD regions and flanking residues. Our results can assist in the design of effective inhibitory peptides of the FAK-FAT:Paxillin and PYK2-FAT:Leupaxin complexes and the construction of pharmacophore models for the discovery of potential small-molecule inhibitors of the FAK-FAT and PYK2-FAT focal adhesion based functions.

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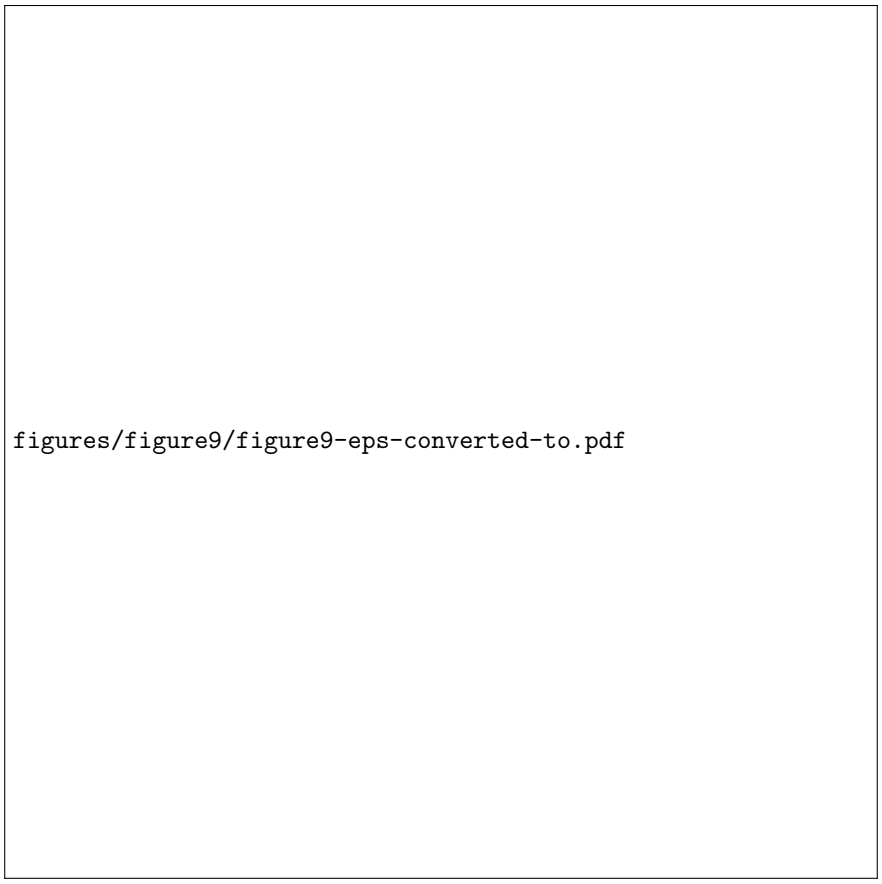

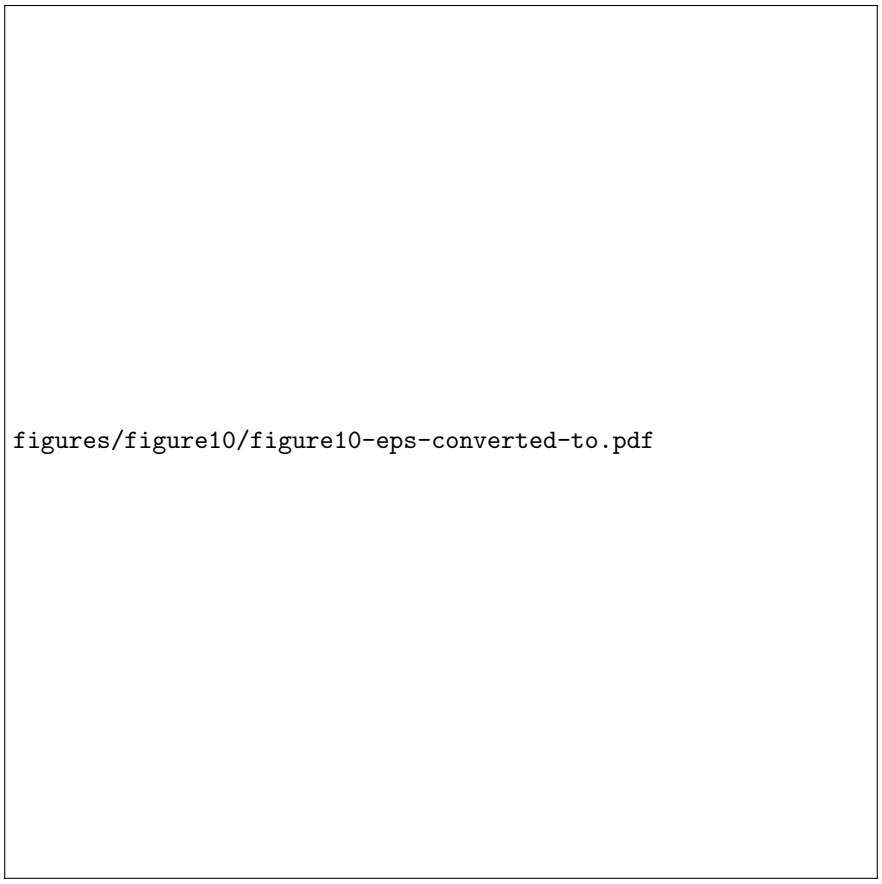

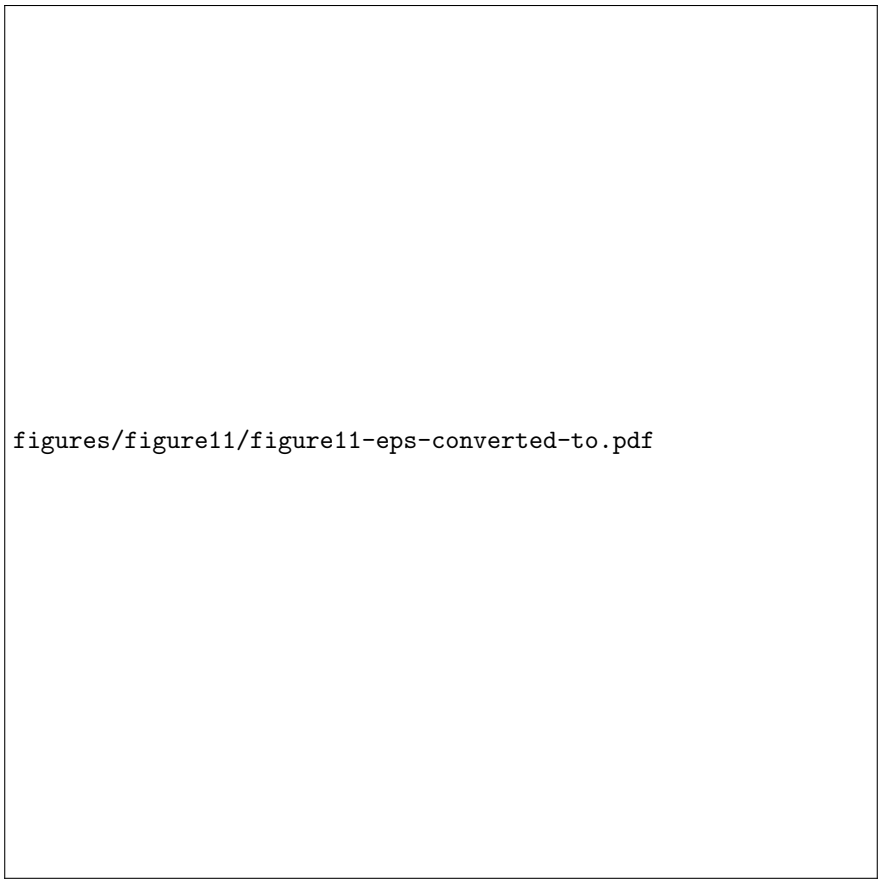

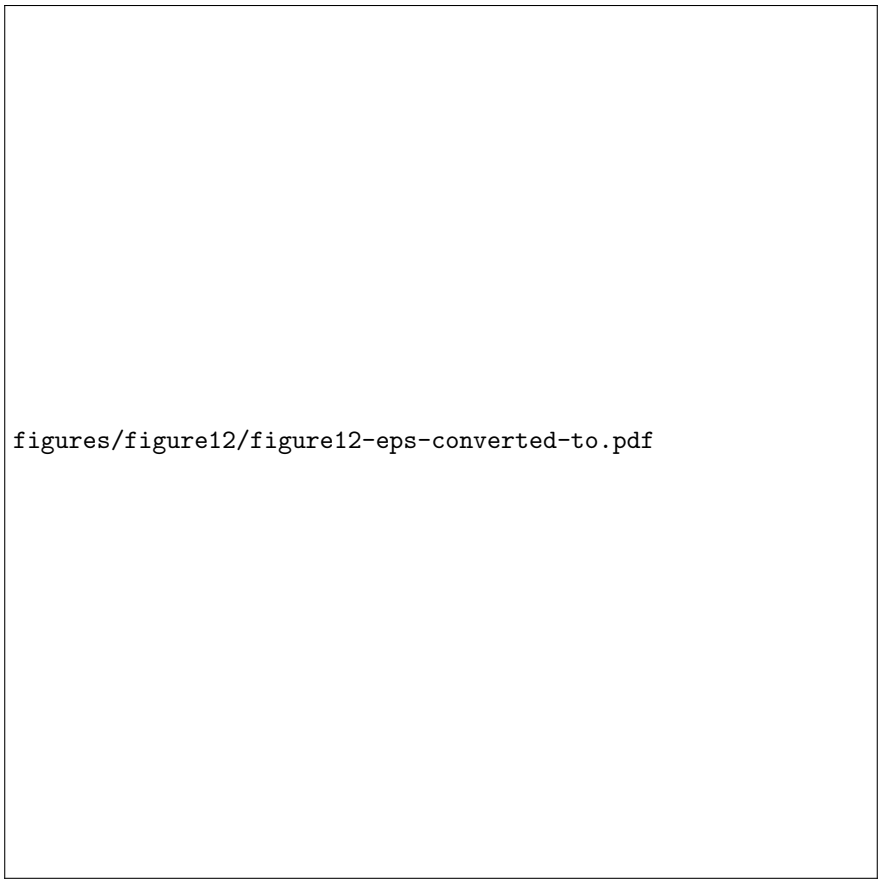

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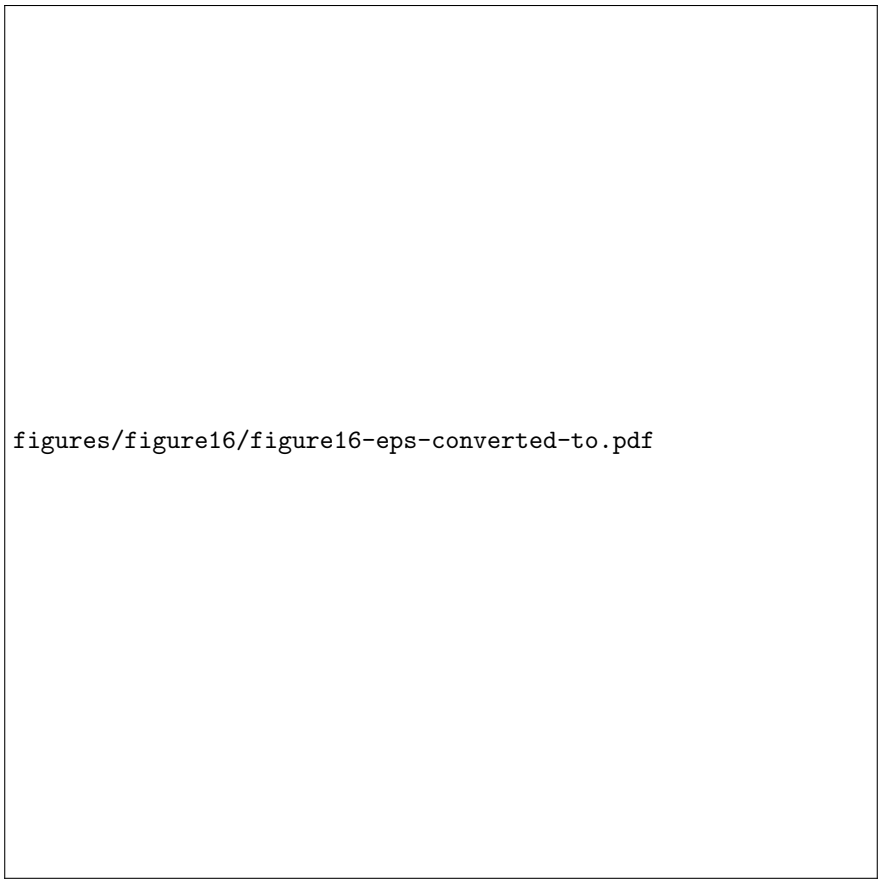

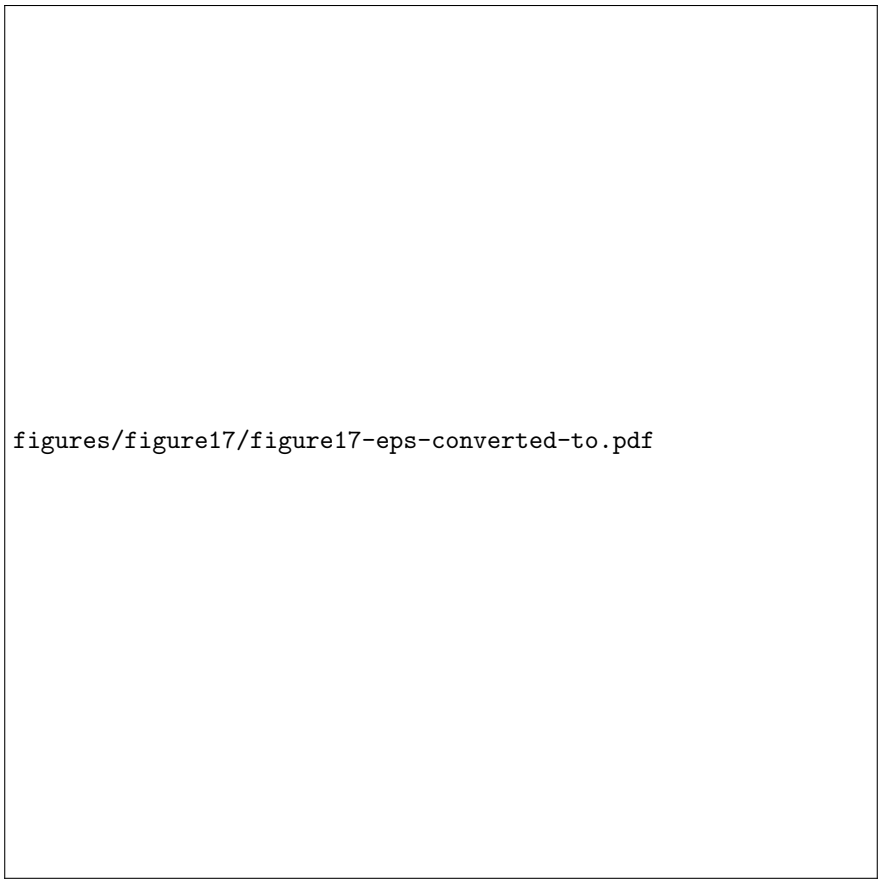

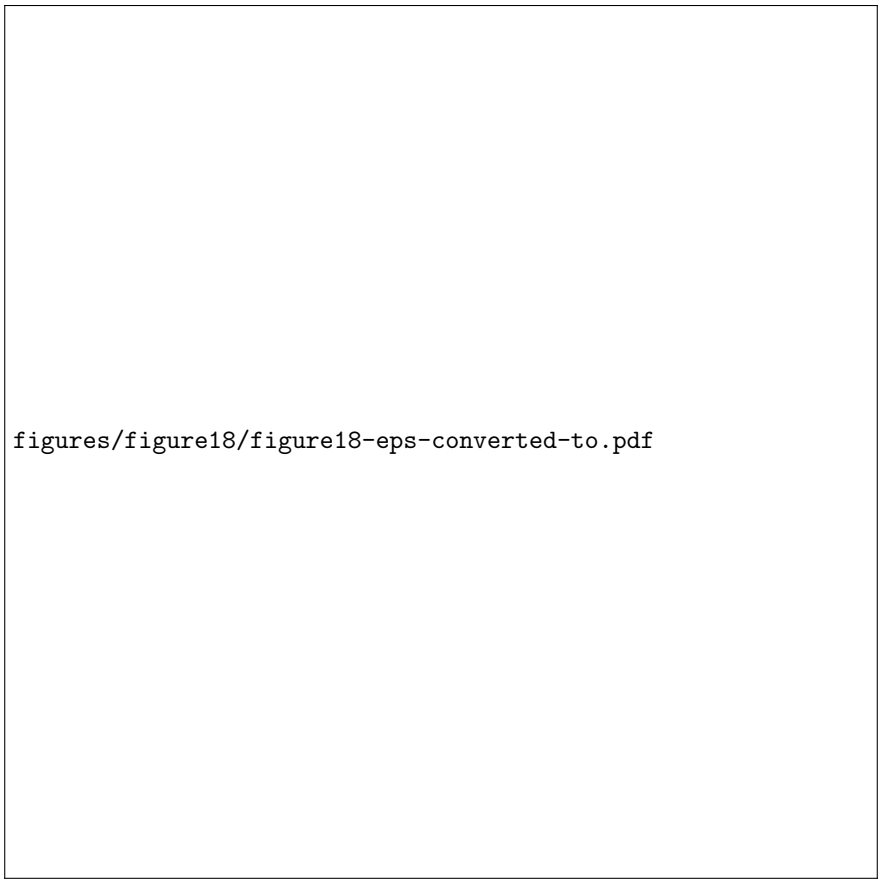

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