Poster Presentation

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Structural studies of a novel phosphatase-transpoter interaction

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The Phosphatase of Regenerating Liver (PRL) family, a subgroup of the protein tyrosine phosphatases, comprises three highly oncogenic members, PRL-1, -2 and -3, implicated in the progression of numerous cancer types. PRL-2 is overexpressed in breast cancer and was shown to promote mammary tumour growth in mice, but its full role in these oncogenic effects remains elusive. Recently, PRL-2 was found to interact with cyclin M3 (CNNM3), a magnesium transporter. To characterize this novel interaction, I crystallized PRL-2 in complex with the cytosolic cystathionine-β-synthase (CBS) domain of CNNM3. The binding surface consists of an elongated loop from CBS that makes contact close to the catalytic site of PRL-2. Site-directed CBS mutants confirmed the loop residues important for binding. PRL-2 and CBS bind particularly tightly, as determined by isothermal titration calorimetry, and PRL-2 enzyme assays revealed that CBS binding reduces the phosphatase's catalytic activity in vitro. The novel role of oncogenic PRL-2 as modulator of intracellular magnesium levels may represent the link between its overexpression and its effects on tumour growth. Small-molecule inhibitors of the PRL-2/CNNM3 complex formation are a potentially valuable tool for exploring the physiological function of this new interaction and may be used as future drug leads for the treatment of breast cancer.

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