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Structural and Functional Studies of FOXM1 Regulation by ?-catenin

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Background/Aims Forkhead box protein M1 (FOXM1) is a proliferation-related transcription factor (TF) exhibiting increased levels of expression in a variety of human cancers. A link between FOXM1 and Wnt signalling has been reported recently. Aberrant oncogenic activation of the Wnt pathway is characterized by increased concentration of nuclear ?-catenin. FOXM1 and ?-catenin seem to mutually depend on each other for recruitment to Wnt target-gene promoters. Given that parts of FOXM1 share similar structural features with TFs for which we recently revealed the ?-catenin binding sites, I hypothesize that ?-catenin regulates transcriptional activity of FOXM1 by binding a mixed acidic/hydrophobic transactivation domain (TAD). I aim to explore the interaction of FOXM1 with ?-catenin in vitro, its regulation by post-translational modifications, solve the structure of the FOXM1/?-catenin complex, and corroborate my findings with cell-based assays in a defined pathophysiological context Method/Results I will present first results characterizing the FOXM1 TAD/?-catenin interaction by using biophysical techniques such as NMR spectroscopy. I discovered that the C-terminal part of FOXM1 TAD adopts a transient ?-helical structure in the absence of binding partners and that this region directly binds the Armadillo repeat region of ?-catenin. This part of FOXM1 TAD sequence overlaps with the binding site for the FOXM1 negative regulatory domain (NRD) and is involved in interactions with DNA-binding domains of other TFs Conclusion I found that FOXM1 TAD is recognized by ?-catenin, and that the binding site for ?-catenin overlaps with the one for NRD. Assuming that this leads to FOXM1 activation, our data could provide a first molecular explanation for the pro-oncogenic role of the ?-catenin/FOXM1 axis. In the next steps, we aim to proceed with the in vitro characterization, cellular validation, and development of molecules interfering with the ?-catenin-dependent FOXM1 activation