of the menin-MLL1 and menin-JunD interactions in MEN1 gene-associated pathogenic conditions.

Presentation: No date and time listed

Abstract citation ID: bvac150.1788

Tumor Biology

LBODP106

Multi-omics Analyses Of MEN1 Missense Mutations Identify Disruption Of Menin-MLL And Menin-JunD Interactions As Critical Requirements For Molecular Pathogenicity

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Loss-of-function mutations of the multiple endocrine neoplasia type 1 (MEN1) gene are causal to the MEN1 endocrine tumor syndrome, but they are also commonly found in sporadic pancreatic neuroendocrine tumors and other types of cancers. The MEN1 gene product, menin, is involved in transcriptional and chromatin regulation, most prominently as an integral component of KMT2A/MLL1 and KMT2B/MLL2 containing COMPASS-like histone H3K4 methyltransferase complexes. In a mutually exclusive fashion, menin also interacts with the JunD subunit of the AP-1 and ATF/CREB transcription factors. After in silico screening of 253 disease-related MEN1 missense mutations, we selected a set of nine menin mutations in surface-exposed residues. The protein interactomes of these mutants were assessed by quantitative mass spectrometry, which indicated that seven of the nine mutants disrupt interactions with both MLL1/2 and JunD complexes. Interestingly, we identified three missense mutations, R52G, E255K and E359K, which predominantly reduce the interaction with MLL1 compared to JunD. This observation was supported by a pronounced loss of binding of the R52G, E255K and E359K mutant proteins at unique MLL1 genomic binding sites with less effect on unique JunD sites. These findings support the general importance