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Loss of nuclear Menin alters lipid homeostasis in pancreatic neuroendocrine tumor cells

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BACKGROUND

Background: Reduced expression of nuclear Menin encoded by the *MEN1* gene is a common feature in *MEN1*-mutated and *MEN1*-unaffected pancreatic neuroendocrine tumors (PanNETs). Prior studies have largely relied on genetic knockdown approaches to modulate Menin expression levels, however the impact of recent Menin inhibitors (MIs) on subcellular Menin expression and its tumor suppressor function are less understood. Here, we launch an original investigation to define the downstream consequence of MI-mediated Menin regulation in the pathogenesis of PanNETs.

METHODS

Methods: We evaluated the impact of three MIs, MI-503, MI-3454, and Ziftomenib, on Menin protein expression in an established human PanNET cell line (BON-1). Nuclear-to-cytoplasmic shuttling of Menin in response to small molecule inhibition was evaluated by western blot and immunofluorescent staining. Bulk RNA sequencing (RNA-seq) was performed to identify differentially expressed pathways resulting from loss of nuclear Menin. The functional consequence of Menin loss was evaluated using an MTT assay, crystal violet staining, and BrdU incorporation in the presence and absence of statin-mediated cholesterol inhibition. Lastly, surgically resected PanNETs were evaluated for dysregulated lipid homeostasis using quantitative PCR, western blot, and immunohistochemical staining.

RESULTS

Results: Menin inhibition using MI-503, MI-3454, and ziftomenib led to a decrease in Menin total protein expression in BON-1 cells. At the subcellular level, MIs induced nuclear export of Menin in a dose-dependent manner. Low-dose treatment with MI-3454 and ziftomenib increased cell proliferation, whereas treatment with MI-503 elicited the opposite effect. Menin inhibition strongly upregulated the expression of genes mapped to cholesterol biosynthesis, including *HMGCS1, HMGCR, ACAT2, SQLE, IDI1, LSS,* and *FDFT1* and this was consistent with decreased expression of the lipid efflux transporter *ABCG1*. Treatment of BON-1 cells with atorvastin led to a dose-dependent reduction in cell proliferation, suggesting a potential role for dysregulated lipid homeostasis in driving tumor cell growth.

CONCLUSIONS

Conclusions: These studies raise a potential role for altered lipid homeostasis downstream of nuclear Menin loss. Future work will focus on dissecting the mechanism and clinical relevance of targeting this pathway in expanded PanNET models.

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