Exploring the potential of a rab inhibition to treat MASLDs

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Abstract Text :

Small GTPases of the Rab protein family are pivotal regulators of intracellular membrane trafficking and signaling pathways[1]. Increasing evidence highlights their involvement in numerous human diseases, including cancer[2], neurodegenerative disorders[3], and metabolic diseases. As such, Rab proteins represent attractive therapeutic targets, although the development of specific inhibitors remains limited.

Recently, our laboratory identified a Rab protein whose inactivation reduces hepatic steatosis by enhancing the expression of genes involved in lipid catabolism. However, no specific inhibitors targeting this Rab protein are currently available.

In this study, we used structural biology approaches combining sequence conservation analysis and residue network analysis to identify amino acids that are both essential and specific to our Rab protein of interest. Using molecular and cellular biology approaches, we performed site-directed mutagenesis of these residues and expressed the resulting mutants in hepatocytes. We found that several mutations alter the subcellular localization of the Rab protein.

Importantly, overexpression of these mutants was sufficient to reduce intracellular lipid droplet accumulation, confirming that loss of Rab function decreases steatosis. Strikingly, we also identified a mutant that strongly reduces lipid droplets without affecting subcellular localization, suggesting that this mutation disrupts interaction with an effector involved in the repression of lipid catabolism.

Together, these results reveal an allosteric regulatory architecture specific to this Rab protein and identify critical residues required for the repression of lipid catabolism. This work provides a framework for the development of selective allosteric inhibitors targeting this Rab protein as a potential strategy to reduce hepatic steatosis.

Bibliography :

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