Aberrant mTOR signaling impairs whole body physiology

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Activated mTORC1 signaling (top) correlates with increased FGF21 expression (below) in human liver tumor. Credit: University of Basel, Biozentrum

The protein mTOR is a central controller of growth and metabolism. Deregulation of mTOR signaling increases the risk of developing metabolic diseases such as diabetes, obesity and cancer. In the current issue of the journal *Proceedings of the National Academy of Sciences*, researchers from the Biozentrum of the University of Basel describe how aberrant mTOR signaling in the liver not only affects hepatic metabolism but also whole body physiology.

The protein mTOR regulates cell growth and metabolism and thus plays a key role in the development of human disorders. In the cell, this regulatory protein is found in two structurally and functionally distinct protein complexes called mTORC1 and mTORC2. In a recent study, the research group of Prof. Michael Hall from the Biozentrum of the University of Basel has shed light on the role of hepatic mTORC1 in whole body physiology and the relevance for human liver cancers.

Hepatic mTORC1 controls whole body physiology

In mammals, the liver is a key organ that controls whole body physiology in response to nutrients. Hall's team investigated the role of the nutrient sensor mTORC1 in this process. The researchers were able to show that activation of mTORC1 in the liver of mice reduces not only hepatic lipid metabolism but also locomotor activity and body temperature. Upon investigating the underlying molecular mechanism, they observed that mTORC1 hyperactivation enhances the level of the stress hormone FGF21 by depletion of the amino acid glutamine. Treatment of animals with glutamine reduced the level of FGF21 and thus prevented the physiological impairments.

Cancer treatment with mTORC1 inhibitors

Human cancers often exhibit aberrant mTORC1 signaling and glutamine addiction. "We were excited to see that in human liver tumors mTORC1 signaling correlates with FGF21 expression", comments cell biologist Dr. Marion Cornu and first author of the study. Moreover, mTORC1 inhibitors such as rapamycin are currently used as immunosuppressive agents and anti-cancer drugs. Thus, the novel findings of Hall's team provide evidence that treatment of glutamine addicted human cancers with rapamycin might have beneficial effects by blocking tumor growth and by preventing deregulation of whole body physiology.

More information: Marion Cornu, Wolfgang Oppliger, Verena Albert, Aaron M. Robitaille, Francesca Trapani, Luca Quagliata, Tobias Fuhrer, Uwe Sauer, Luigi Terracciano, Michael N. Hall , Hepatic mTORC1 controls locomotor activity, body temperature, and lipid metabolism through FGF21 , *PNAS*; published online 31 July 2014 DOI: 10.1073/pnas.1412047111