Targeting mitochondrial pyruvate carrier in nonalcoholic steatohepatitis: Growing evidence and future challenges.

UNIVERSITÀ DEGLI STUDI DI TORINO

Targeting mitochondrial pyruvate carrier (MPC) in NASH: growing evidence and future challenges

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To the Editor

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we read with interest the article by McCommis et al, reporting on the anti-fibrotic properties of the Mitochondrial Pyruvate Carrier(MPC) inhibitor MSDC-0602 in a mouse model of NASH(1). MSDC-0602 belongs to a class of next-generation thiazolidinedione(TZD) insulin sensitizers, that potently bind and inhibit the MPC protein but have negligible Peroxisome Proliferator-Activated Receptor(PPAR)-γ binding activity, the latter retained responsible for the undesired TZD-related effects of weight gain, oedema and bone fractures. Growing human evidence indirectly supports the effectiveness of this approach in NASH: when we compared the effect between pioglitazone and rosiglitazone on liver histology in patients with NASH, we found pioglitazone, which possesses both PPAR-γ agonist activity and MPC inhibiting activity, reversed NASH and advanced fibrosis also in nondiabetic patients, while rosiglitazone, a more potent PPAR-γ agonist devoid of MPC-binding activity, did not(2). Furthermore, in nondiabetic insulin resistant patients with prior acute cerebrovascular disease enrolled in the Insulin Resistance Intervention after Stroke(IRIS) trial, pioglitazone reduced the risk of new-onset diabetes and new cardiovascular events(3). Although the presence of NAFLD was not reported in this trial, the benefits were largely driven by the effect of pioglitazone in patients with metabolic syndrome, which is commonly encountered in NAFLD. Although collectively encouraging, some questions remain: compared with PPAR-γ agonists, MPC-modulators are weaker stimulators of the secretion of adiponectin, a key anti-inflammatory antifibrotic adipokine(1,4). Although in strictly controlled experimental conditions the weight loss associated with adipocyte browning may partially make up for the lack of PPAR-γ-stimulated adiponectin secretion, the difficulty in mantaining a durable weight loss in the real life may blunt the benefits of this approach. Furthermore, recent metabolomics analysis identified compensatory changes in hepatic amino acid and lipid metabolism that may offset long term effects of MPC inhibition(5). These factors need to be taken into account in the design and monitoring of the effects of MPC-modulators in human trials.

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Giovanni Musso: conducted research, analyzed data, wrote paper, has primary responsibility for final content;

Roberto Gambino: conducted research, analyzed and discussed data, approved final version of the paper

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(1)McCommis KS, Hodges WT, Brunt EM. Targeting the Mitochondrial Pyruvate Carrier Attenuates Fibrosis in a Mouse Model of Nonalcoholic Steatohepatitis. Hepatology. 2016 Dec 27. doi: 10.1002/hep.29025

(2)Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and Advanced Liver Fibrosis in NASH: A Meta-analysis. JAMA Intern Med. 2017 Feb 27. doi: 10.1001/jamainternmed.2016.9607

(3)Kernan WN, Viscoli CM, Furie Kl.. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016;374: 1321-31

(4)Colca JR, VanderLugt JT, Adams WJ. Clinical proof-of-concept study with MSDC-0160, a prototype mTOT-modulating insulin sensitizer. Clin Pharmacol Ther. 2013;93:352-9

(5)Bowman CE, Zhao L, Hartung T, Wolfgang MJ. Requirement for the Mitochondrial Pyruvate Carrier in Mammalian Development Revealed by a Hypomorphic Allelic Series. Mol Cell Biol. 2016;36:2089-104