Modifying the entry of pyruvate into mitochondria may provide a unique approach to treat metabolic disease. The pharmacology of a new class of insulin sensitizers directed against a newly identified mitochondrial target may treat many aspects of nonalcoholic steatohepatitis, including fibrosis. This commentary suggests treating nonalcoholic steatohepatitis through a newly identified mechanism consistent with pathophysiology. (Hepatology Communications 2017;1:193-197)

Classical drug discovery programs have sought to design compounds for defined cellular targets in a single disease state. A new mitochondrial drug target has been identified that provides an opportunity to treat metabolic diseases by changing the way pyruvate is metabolized, and this may have implications for treating diseases as diverse as Parkinson’s disease and liver disease. Mitochondrial target of thiazolidinediones (mTOT)\(^1\)\(^-\)\(^3\) modulators have been selected for their ability to bind to and modulate the activity of the mTOT, which was subsequently identified as the mitochondrial pyruvate carrier (MPC). The MPC is a heterologous complex composed of two proteins, MPC1 and MPC2, in the inner mitochondrial membrane.\(^4\)\(^,\)\(^5\) This complex is required for pyruvate to enter the mitochondrial matrix, where it is metabolized, from its site of synthesis in the cytosol. Recent work has suggested the utility of targeting the MPC for treatment of a variety of metabolic and inflammatory diseases, including diabetes,\(^1\)\(^,\)\(^6\)\(^,\)\(^7\) Parkinson’s and other neurodegenerative diseases,\(^8\)\(^,\)\(^9\) and now nonalcoholic fatty liver disease (NAFLD).\(^10\)

Most researchers agree with the definition of NAFLD as the ectopic deposition of lipid in the liver parenchyma in the absence of excessive alcohol use. It is also clear that in some patients NAFLD progresses to nonalcoholic steatohepatitis (NASH), which increases the risk of cirrhosis, liver failure, and hepatocellular carcinoma. At the current time, NASH is diagnosed based on liver biopsies showing characteristic histologic changes, including fat deposition, inflammation, hepatocyte ballooning, and importantly in terms of prognosis, fibrotic scarring.\(^11\)\(^,\)\(^12\) While there are many treatments in development that specifically address individual aspects of liver disease, epidemiologic studies have defined a strong linkage between overnutrition and incidence of NAFLD, and this linkage is driving the prevalence of this disease of the liver to pandemic proportions.\(^13\) Despite considerable efforts, there are currently no approved treatments for NAFLD or NASH.

In evaluating potential approaches that might be effective to treat NASH, it is important to consider the pathophysiology. At its core, NAFLD is caused by fat...

Abbreviations: MPC, mitochondrial pyruvate carrier; mTOT, thiazolidinediones; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPAR\(_\gamma\), peroxisome proliferator-activated receptor gamma; TZD, thiazolidinedione.
accumulation that is likely driven by nutrient excess. At the same time, the progression to NASH in mice and humans has been tightly linked to a number of factors, including insulin resistance\(^{14,15}\), abnormal mitochondrial function\(^{16-19}\), oxidative damage, and hepatic inflammation, that promote a state conducive to necroptosis and replacement of dead hepatocytes with a collagen matrix secreted by hepatic stellate cells in response to these stimuli.\(^{20,21}\) It is interesting to note that the entire spectrum of this pathophysiology from insulin resistance to fibrotic scarring may involve dysfunctional metabolism driven by overnutrition. Moreover, the pathology might be regulated by the delivery of pyruvate by the MPC.

We have recently shown that genetic or pharmacologic targeting of the MPC, either by selective knock-out of the MPC in hepatic parenchymal cells or by using a new-generation insulin sensitizer MSDC-0602K, was able to reduce the NASH pathology in a mouse model fed a diet high in transfat, cholesterol, and fructose.\(^{10}\) Indeed, MSDC-0602K treatment both prevented and reversed the development of NASH symptoms in this mouse model, including attenuation of fibrosis in the continued presence of the aggressive diet treatment producing the pathology. The antifibrotic effects seen in these mice involve both direct effects on parenchymal and mesenchymal (stellate) cells of the liver. The overall pharmacology was also suggested to include changes in the composition of circulating exosomes secreted by hepatocytes to influence hepatic stellate cell activation. MSDC-0602 also potently stimulates secretion of adiponectin, which has been suggested to have beneficial effects on NASH endpoints, by adipocytes. Thus, there seem to be both direct and indirect effects of MSDC-0602K to impact the development of fibrosis (Fig. 1).

MSDC-0602K is a member of a new class of insulin sensitizers called mTOT modulators\(^{1}\) from a structural class of compounds known as thiazolidinediones (TZDs). The first-generation insulin sensitizers, such as pioglitazone and rosiglitazone (currently marketed as a second-line treatment for type 2 diabetes), are agonists with varying potencies for the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR\(_\gamma\)).\(^{22}\) Although there are beneficial effects attributed to PPAR\(_\gamma\) agonism, a series of PPAR\(_\gamma\)-knockout studies have clearly shown that the side effects that limit the use of pioglitazone and rosiglitazone are driven by PPAR\(_\gamma\).\(^{23,24}\) Until recently, it has been less well appreciated that all active TZDs also attenuate mitochondrial pyruvate uptake through the MPC\(^2\) in a manner that is separable from their PPAR\(_\gamma\) agonist activity.\(^{25}\) It is our opinion that the focus on the PPAR\(_\gamma\) agonist activity has reduced the chances of finding TZDs or other compounds that mainly affect the mitochondrial target but avoid direct activation of PPAR\(_\gamma\) which limits doses that can be taken to the clinic.\(^{25}\) We and others have hypothesized that there may be a beneficial TZD pharmacology that is separable from PPAR\(_\gamma\) agonism and that this realization could change the drug discovery approach for the treatment of metabolic diseases.\(^{23,24}\) Recent data point to the modification of pyruvate metabolism as a site of this pharmacology.

Relevant to this discussion is the comparison of the two antidiabetic TZDs that are currently in use to treat type 2 diabetes and that have also been evaluated in subjects with NASH. Clinical studies of the approved doses of pioglitazone in patients with NASH have shown significant resolution of NASH pathology, including fibrosis.\(^{26,27}\) On the other hand, rosiglitazone, which is a 5-fold to 10-fold more potent PPAR\(_\gamma\) agonist compared to pioglitazone,\(^{22}\) improved some NASH endpoints but failed to significantly affect fibrosis.\(^{27-31}\) The dissociation between the affinity for PPAR\(_\gamma\) and the effectiveness in treating NASH, and particularly hepatic fibrosis, could be explained by the failure of rosiglitazone to achieve adequate effects on the mitochondrial target.

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MPC. The attenuation of the activity of the pyruvate carrier seems essential to this effect; in the studies conducted in rodents, either MSDC-0602K or genetic MPC deletion consistently attenuated stellate cell activation and histologic evidence of fibrosis. These data and this rationale suggest that the PPARγ-sparing MSDC-0602K should have a preserved pharmacology for treating NASH with a diminished risk of PPARγ-driven side effects in human patients with NASH.

Based on this rationale and efficacy in rodent models,(6,10) a phase 2 clinical trial has been initiated to evaluate the efficacy of MSDC-0602K. This study is a 12-month, double-blind, placebo-controlled evaluation of three exposures of MSDC-0602K to determine the potential of this PPARγ-sparing mTOT modulator to resolve NASH (EMMINENCE; NCT02784444; https://clinicaltrials.gov/ct2/show/NCT02784444).

Multiple noninvasive measures are included to determine whether these provide a correlation with the histologic improvement of the liver produced by this pharmacology. Noninvasive measures include insulin sensitivity (e.g., homeostasis model assessment of insulin resistance) together with a variety of standard and novel biomarkers. This clinical study together with ongoing studies in preclinical models will provide a better understanding of how mTOT modulator pharmacology impacts NASH and should enable both the development and the practical use of such agents going forward. The preclinical approaches being used to further elucidate these mechanisms include newly available animal models with tissue-specific knockout of the MPC.(7–10)

There are many potential treatments in development for NASH. Current drug development is trained on...
several specific targets directed at specific symptoms along the natural history of the disease, including lipid synthesis, inflammation, and fibrosis. The new data suggest that modification of the usage of pyruvate could be useful at several steps along the progression of the disease from insulin resistance to reduction of ballooning and fibrosis. Such a treatment modality could be useful on its own or as a component of combination therapy.

It should be noted that knockout or knockdown of the MPC results in significant compensatory changes in metabolism, and thus compensatory metabolic pathways (increased amino acid and/or fatty acid metabolism) could reduce the efficacy of these compounds for treating NASH. However, knockout of the MPC proteins is likely to have different effects than attenuation of function by TZDs. Clearly, metabolomics studies should be performed after chronic MPC inhibition with TZDs. Another possible limitation of inhibiting MPC activity is that the MPC proteins are significantly down-regulated in cancer cell lines, and regulation of pyruvate use is likely important in stem cells and solid tumor expansion. In this respect, it is reassuring to know that in over 20 years of clinical use of pioglitazone, which also works through attenuation of the MPC, hepatocellular cancer incidence appears to be reduced.

At the present time, there are numerous questions that remain to be answered regarding this newly understood pharmacology. For example, how does the attenuation of pyruvate metabolism result in the downstream events resulting in increased insulin sensitivity, improved lipid metabolism, and reduction of hepatic fibrosis? Can the pharmacology be tied to biomarkers measurable in the clinic? Are there changes in the epigenomic regulation that can be related to the pathophysiology? What are the factors in the exosomes that transmit signals to the stellate cells, thus regulating fibrosis?

In summary, the study of the pleotropic pharmacology of the first generation TZDs first identified empirically over 35 years ago has led to the discovery of a novel mitochondrial target and a new class of drugs called mTOT modulators. The mechanism of action for these compounds involves alterations in mitochondrial pyruvate metabolism, which leads not only to increased insulin sensitivity but also to a modification of a wide variety of cellular processes, such as differentiation, autophagy, and suppression of inflammation, all as a result of the coordinated responses involving nutrient signals. Although MSDC-0602K is currently in clinical development for the treatment of NASH, one could imagine that this pharmacology would be applicable to pathologic conditions that typically occur along the natural pathology of NAFLD, as shown in Fig. 2. Most importantly, the translational preclinical and clinical studies now in progress should provide the noninvasive biomarkers needed to facilitate the rational and effective use of these compounds in clinical practice. Ongoing studies should show whether modification of pyruvate metabolism might be used to effectively treat NASH and, perhaps eventually, NAFLD in general.

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