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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

NRF2 Induction for NASH Treatment: A New Hope Rises

Nonalcoholic fatty liver disease (NAFLD) is a complex disease characterized by excessive fat storage in the liver. NAFLD ranges from simple steatosis (fat accumulation) to nonalcoholic steatohepatitis (NASH), which in addition to steatosis involves liver inflammation (hepatitis) and fibrosis, and can progress into cirrhosis or liver cancer. Coupled with a worldwide increase in obesity, type 2 diabetes, metabolic syndrome, and hypertension, the incidence of NAFLD/NASH is also steadily increasing.[1] Currently there are no treatments for NASH other than lifestyle changes (diet and exercise) or liver transplantation[2] despite the great advances that have been made in understanding the pathophysiology of this condition. Thus, the study presented by Sharma et al[3] in this issue of *Cellular and Molecular Gastroenterology and Hepatology* offers hope to patients with NASH because they identified pharmacologic activation of NRF2 reverses NASH in mouse models.

NAFLD/NASH is characterized by insulin resistance, increased lipogenesis (coupled to increased adipocyte fat mobilization) and gluconeogenesis, inflammation, and oxidative stress. These symptoms can be mechanistically linked to endoplasmic reticulum stress and dysfunction of the antioxidant response controlled by the transcription factor nuclear factor E2-related factor 2 (NRF2). Sharma et al[3] focused on targeting NRF2 for NASH treatment considering previous evidence that pharmacologic activation of NRF2 ameliorates hepatitis and diabetes in diverse mouse models.[4,5] Moreover, NRF2 activation is known to increase insulin sensitivity, improve glucose and lipid blood profiles, reduce inflammation, and prevent fibrosis. Molecularly, NRF2 activates the expression of a battery of genes involved in the antioxidant response, glucose metabolism, and fatty acid oxidation, while it also downregulates the expression of *de novo* lipogenesis and inflammatory genes.

The grand contribution of the present study by Sharma et al[3] is to demonstrate that the acetylenic tricyclic bis (cyano enone) compound TBE-31 reverses high-fat diet and fructose-induced NASH in an NRF2-dependent manner. TBE-31 was able to increase whole-body insulin sensitivity and improve glucose homeostasis, and to lower steatosis, inflammation, and fibrosis. Additionally, TBE-31 reduced oxidative stress and endoplasmic reticulum stress. There seemed to be other Nrf2-independent effects of TBE-31, as can be expected of electrophilic compounds, but most of its beneficial effects were exerted through NRF2 induction. These are certainly encouraging results that suggest great advancement could be achieved in the clinical treatment of NASH through NRF2 pharmacologic modulation.

Several questions still need to be addressed to obtain a full understanding of TBE-31-mediated NRF2 activation for NASH treatment. First, it is unclear how TBE-31 restores a full NRF2 antioxidant gene expression signature when the high-fat and fructose diet used to induce NASH already increased NRF2 protein levels and a subset of NRF2 target genes. There is much discrepancy among diabetes and NASH studies regarding whether NRF2 expression is upregulated or downregulated, a fact that might stem from methodological (how is diabetes or NASH induced, what NRF2 activators are used) and endpoint differences. Furthermore, off-target effects of TBE-31 should be fully explored and correlated to the NRF2-independent effects.

Second, future studies could investigate other systemic effects associated to TBE-31 treatment and NRF2 induction in other tissues involved in a metabolic disease like NASH, such as fat tissue, the cardiovascular system, and the immune system. Patients with NASH have higher incidence of cardiovascular mortality, so a reduction of this risk by TBE-31 should be explored. Third, it would be interesting to determine if NRF2 induction by TBE-31 is effective in diet and genetically induced NASH in both low- and high-risk human populations. Inclusive clinical trials enrolling patients from different demographics and ethnicities that also analyze genetic risk determinants are essential.

Finally, extreme caution is advised when developing long-term therapeutic interventions with an NRF2 inducer. Long-term NRF2 activation has been associated to liver fibrosis,[6] reductive stress,[7] and promotion of pre-existing malignancies.[8] Therefore, scientists and clinicians must perform a risk assessment and test different treatment schedules that do not further compromise the health of their patients with NASH.

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Conflicts of interest
The authors disclose no conflicts.

Funding
This work was funded by the National Institutes of Health (R01 ES026845, R01 DK109555, and R01 ES023758 to D.D.Z.).

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2352-345X
https://doi.org/10.1016/j.jcmgh.2017.12.009