Repurposing drugs to target NASH: Auranofin- a gold-organic molecule complex for the treatment of a complex trait

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Abbreviations
NAFLD, nonalcoholic fatty liver disease
NASH, nonalcoholic steatohepatitis

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Drug discovery in nonalcoholic steatohepatitis (NASH) is moving fast. Drugs under development aim to target two primary endpoints: NASH resolution and fibrosis reduction. Disease mechanisms and pathogenic-related pathways are the main focus of novel compounds, which are still in early phase studies.

Drug repurposing consists in identifying and developing new uses for existing drugs. This approach can offer an alternative for overcoming the obstacles of novel drug discovery, including time-consuming assessment of pharmacokinetics, pharmacodynamics, and toxicity profiling evaluation.

In addition, drugs are also already approved by major regulatory agencies, including the United States Food and Drug Administration and or the European Medicines Agency.

In this issue, Lee and coworkers aimed to evaluate the effects of auranofin on hepatic steatosis, inflammation, and fibrosis using \textit{in vivo} and \textit{in vitro} models of the disease. The authors’ experimental observations showed that auranofin reduces the expression of inflammation-related targets, such as NF-κB (Nuclear Factor Kappa B Subunit 1) and IκBα (NFKB Inhibitor Alpha), and fibrogenesis-related pathways in LX-2 cells. Likewise, auranofin reduced palmitic acid-induced inflammation and adipogenesis in HepG2 cells. Furthermore, using two different animal models, the authors found that auranofin attenuated liver fibrosis in the bile duct-ligation mouse model and reduced hepatic steatosis and fibrosis in the western diet-induced NASH model of nonalcoholic fatty liver disease (NAFLD).

These exciting results prompt several reflections.

First, auranofin, a small molecule used as a second-line drug to treat rheumatoid arthritis, targets key metabolic-related pathways. Previous experimental evidence showed that auranofin improved lipid accumulation and hepatic inflammation in \textit{in intro} models by inhibiting NLRP3-related inflammasome. In addition, auranofin decreased body weight, epididymal fat weight, serum aspartate aminotransferase, and several metabolic parameters, including serum glucose, triglycerides, cholesterol, and low-density lipoprotein cholesterol levels in an animal model of NAFLD.

Second, auranofin has anti-inflammatory properties. The primary mechanism of action of auranofin is through the inhibition of reduction/oxidation enzymes such as thioredoxin reductase (TrxR). Indeed, auranofin has helped prevent immune cell infiltration to the site of inflammation in

\textbf{Figure 1}.
patients with rheumatoid arthritis because the drug indirectly inhibits the secretion of pro-inflammatory cytokines, such as IL-8 and IL-6 from macrophages and monocytes, by inhibiting the NF-κB-STAT3 signaling pathway. For that reason, auranofin has been tested for treating several chronic conditions, including cancer, neurodegenerative diseases such as Alzheimer’s or Parkinson’s, viral infections such as AIDS, and even parasitic and bacterial infections. More recently, auranofin has been tested for the treatment of COVID-19 due to its antiviral, anti-inflammatory, and anti-reactive oxygen species (ROS) properties, which might stop the cytokine storm associated with the severe form of the disease. Conversely, auranofin may induce cell death by enhancing free radical production.

Third, the above-mentioned experimental results show that auranofin could reduce inflammation and fibrogenesis in human NASH by targeting key molecular disease pathways. Figure 1 depicts the interaction network of compounds, genes, and proteins associated with auranofin. The most significant chemical-protein interaction shown in green lines denotes an attractive connection with ALOX5 (arachidonate 5-lipoxygenase) and arachidonic acid, two relevant actors in NAFLD biology. Another meaningful chemical-protein interaction is with E1A binding protein p300, which functions as histone acetyltransferase regulating gene transcription via chromatin remodeling. This pathway might partly explain the epigenetic mechanisms associated with the pathogenesis of NAFLD. Some other known transcription factors and proteins, including STAT1 and STAT3, BIRC3 and BIRC2, TRAF3, caspases, MTOR, some of which are critical mediators of inflammation and fibrogenesis in NAFLD among others, are highlighted in Figure 1.

Finally, as altogether, there is plausible evidence of the potential role of auranofin in ameliorating molecular drivers of NASH and NASH fibrosis, this gold salt might be repurposed for the treatment of NAFLD/NASH.

The United States Food and Drug Administration (FDA) approved an auranofin-gold (I)-containing oral pill in 1985 as a primary treatment against active, progressive, or destructive forms of inflammatory arthritis. However, this drug was replaced by modern compounds, which, in part, was clinically justified by the large number of adverse effects associated with the long-term use of the drug. Some of the most problematic adverse events were thrombocytopenia and bone marrow
suppression, which is why this drug has a black box warning from the FDA. Despite that, auranofin, which chemical name is (1-Thio-beta-D-glucopyranosato) (triethylphosphine) gold 2,3,4,6-tetraacetate, is being tested in many Phase-I clinical trials for diverse conditions, including HIV infection, glioblastoma multiforme, lung adenocarcinoma, amebiasis, small cell, non-small cell, and squamous cell lung carcinoma, as well as in Phase II for the treatment of pain, chronic lymphocytic leukemia, ovarian carcinoma, and chronic lymphocytic leukemia (ClinicalTrials.gov).

As a result, the potential effect/s and safety profile of auranofin in human NAFLD need to be proven.
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Figure 1. Auranofin chemical-protein interaction network

The prediction was performed by the web resource STITCH version 5.0, available at http://stitch.embl.de, a database of known and predicted interactions between chemicals and proteins. The interactions include direct (physical) and indirect (functional) associations; they stem from computational prediction, knowledge transfer between organisms, and interactions aggregated from other (primary) databases. The prediction was restricted to human evidence.

Thicker lines represent stronger associations. For example, protein-protein interactions are shown in grey, chemical-protein interactions in green, and interactions between chemicals in red.