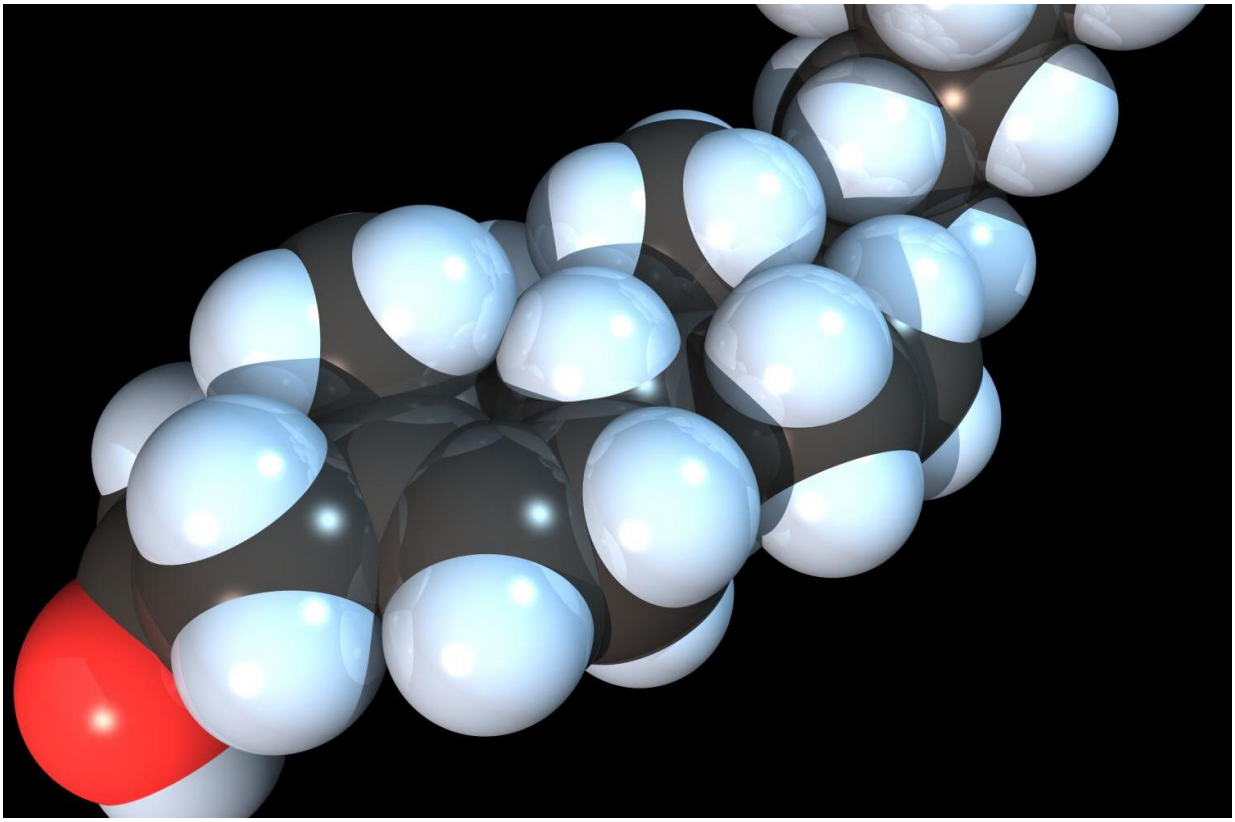
Targeting cholesterol metabolism in macrophages to eliminate viral infection

December 27 2019, by Liu Jia



Space-filling model of the Cholesterol molecule. Credit: RedAndr/Wikipedia

Recent evidence suggests a link between cholesterol metabolism and innate immunity. Upon viral infection, macrophages show reduced cholesterol synthesis accompanied by enhanced expression of antiviral

genes, including type I interferon (IFN-I).

IFN-I can induce 25-hydroxycholesterol (25-HC) accumulation, which blocks viral entry. However, it has been unclear whether other cholesterol-associated metabolic products or enzymes regulate innate immunity.

A new study published in *Immunity* now provides important new information. Wang Hongyan's team from the Center for Excellence in Molecular and Cellular Science, Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences (CAS), in collaboration with Prof. Wei Bin at Shanghai University (the former PI of the Wuhan Institute of Virology of CAS), screened expression levels of multiple enzymes that regulate cholesterol metabolism to better understand how cholesterol metabolites combats infection.

In order to find the enzymes or corresponding natural cholesterol metabolites involved in antiviral infection, the researchers screened differentially expressed genes in liver tissue from patients infected with hepatitis B virus and from mice infected with vesicular stomatitis virus (VSV).

DHCR7 (7-dehydrocholesterol reductase) is an enzyme that converts 7-dehydrocholesterol (7-DHC) into cholesterol. Patients carrying Dhcr7 mutations have mental retardation. However, the role of DHCR7 in innate immunity has been unclear. This study shows that DHCR7 knock-out (KO) or DHCR7 inhibitor treatment can promote IRF3 activation and type I interferon (IFNβ) production to clear multiple viruses in vitro or in vivo.

Interestingly, Tamoxifen, a chemotherapy drug used to treat breast cancer, was approved by the U.S. Food and Drug Administration to inhibit DHCR7's enzyme activity.

This study also reveals that Tamoxifen treatment inhibits infection by VSV and the Zika virus at the cellular level, suggesting a possible application for Tamoxifen as an anti-infective. Mice treated with the DHCR7 inhibitor AY9944 showed a significant increase in serum 7-DHC concentration, which promotes IRF3 phosphorylation and enhances IFNβ production in macrophages, thus protecting mice against lethal doses of VSV or the H1N1 influenza virus.

In addition, the research shows that viral infection enhanced AKT3 expression and 7-DHC treatment further activated AKT3. AKT3 directly bound and phosphorylated IRF3 at Ser385, together with TBK1-induced phosphorylation of IRF3 Ser386, to achieve IRF3 dimerization and full activation.

In conclusion, this study reveals that both the intermediate cholesterol metabolite 7-DHC and DHCR7 inhibitors promote IFN-I production and an antiviral response by activating AKT3 and IRF3. These findings may aid in the development of new drugs to treat viral infections. The research also provides new insights on how cholesterol metabolism regulates innate immunity.

More information: Jun Xiao et al, Targeting 7-Dehydrocholesterol Reductase Integrates Cholesterol Metabolism and IRF3 Activation to Eliminate Infection, *Immunity* (2019). DOI: 10.1016/j.immuni.2019.11.015

Provided by Chinese Academy of Sciences