Statin side effects linked to off-target reaction in muscle mitochondria

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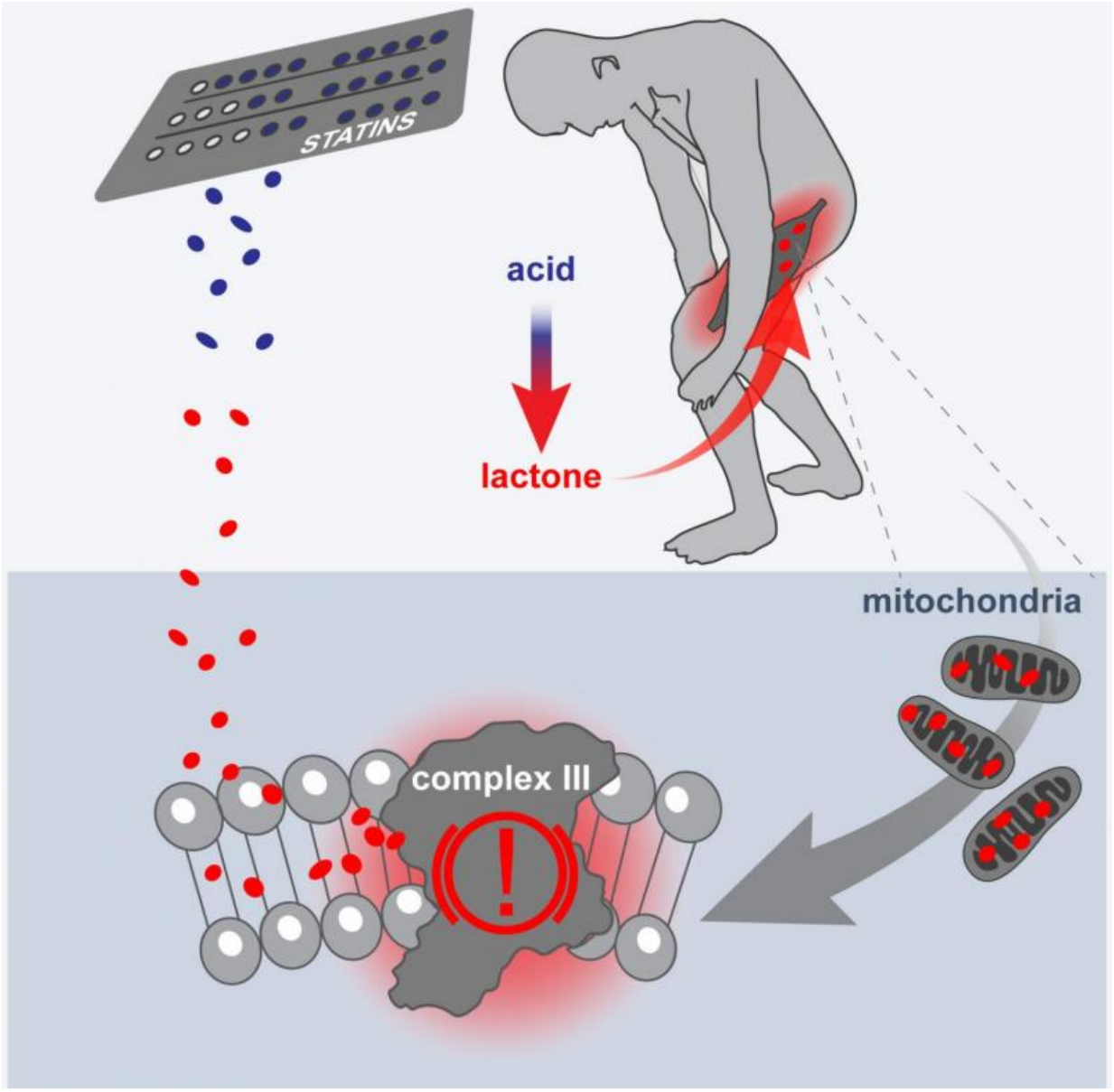

Statin-induced myopathies are the mostcommon side effects of these widely usedcholesterol-lowering drugs, affectingmillions of patients. Schirris et al.identified the Qo site of mitochondrialcomplex III as off-target of statin lactonesand show possible mechanisms for theattenuation of their inhibitory effect. Credit: Schirris et al./*Cell Metabolism* 2015

Statins are a popular and easy-to-swallow option for people looking to lower their cholesterol. But for a quarter of patients, statins come with muscle pain, stiffness, cramps, or weakness without any clear signs of muscle damage. These symptoms may affect daily activities so much that people stop using the drugs. In *Cell Metabolism* on September 1, Dutch researchers show, in mice and humans, that statins yield an off-target reaction that disrupts muscle mitochondria function, possibly causing the side effects.

"Adverse drug effects, like those of statins and many other drugs, have been linked to mitochondria—the cell's powerhouses—though the exact mechanisms are often unknown," says co-senior study author Frans Russel of the Nijmegen Center for Mitochondrial Disorders at the Radboud University Medical Center in the Netherlands. "This research leads to several opportunities to synthesize new classes of cholesterol-lowering drugs without the unwanted muscle effects, as well as the development of new avenues to counteract these effects, both of which we are currently investigating."

Statins exist in the body in two chemical forms, acid and lactone. Most statins are administered (as a tablet) in their acid form, which slows down the production of cholesterol in the liver. The acid form can turn into the lactone form within the body, but the lactone form has no therapeutic effect.

Russel, along with co-senior author Jan Smeitink, postdoctoral researcher Tom Schirris, and colleagues, found that lactones can, however, unintentionally interfere with a mitochondrial pathway that produces the cell's energy currency, ATP. In mouse muscle cells, lactones were about three times more potent at disturbing mitochondrial function than their acid forms. These findings could be confirmed in muscle biopsies of patients suffering from statin-induced side effects, in which ATP production (via lactone inhibition of the Qo site of complex III of the mitochondrial oxidative phosphorylation system) was reduced, as compared to healthy control subjects.

"Further independent studies are needed on the effects of the different statins on mitochondrial function and to indicate the usefulness of complex III activity as a predictive marker for statin-induced myopathies," Russel says. "Interindividual differences in the enzymatic conversion of the acid into the lactone form could be an explanation for the differences between patients in susceptibility for statin-induced muscle pain."

The researchers are also excited to explore whether current statins can be improved or supplemented without impacting muscles in the future. In their study, they were able to reduce lactone's ability to interfere with mitochondrial function, which is early evidence that side effects could be prevented or reversed.

More information: *Cell Metabolism*, Schirris et al.: "Statin-Induced Myopathy Is Associated with Mitochondrial Complex III Inhibition" dx.doi.org/10.1016/j.cmet.2015.08.003

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