Gut Bacteria Discovery Holds Promise for Future Cardiovascular Drugs

Swedish researchers connect the dots linking gut microbiota influence on cholesterol via the bile acid regulation process.

By Joanna Cosgrove, Online Editor

The body of research regarding the influence of gut bacteria on human health and disease is growing at an exponential rate. Researchers at the Sahlgrenska Academy, University of Gothenburg, Sweden, recently published a study that found cholesterol metabolism to be regulated by bacteria in the small intestine—findings they believe could be important for the development of new drugs for cardiovascular disease.

The study was published in the journal *Cell Metabolism* and was led by Fredrick Bäckhed, professor at the Sahlgrenska Academy, University of Gothenburg. Dr. Bäckhed's research group has been at the forefront of investigating how gut bacteria are linked to lifestyle diseases such as obesity, diabetes and cardiovascular disease.

Among this latest study's topline findings was that gut microbiota is capable of reducing bile acid pool size and composition; that gut microbiota activates farnesoid X receptor (specific proteins also known as FXR) by alleviating receptor antagonism; and that tauro-conjugated muricholic acids are naturally occurring FXR antagonists.

Pointing to cholesterol as the top risk factor for cardiovascular disease, the researchers explained that cholesterol—which is mainly synthesized in the body but also obtained from dietary sources—is converted to bile acids in the liver, which are then secreted into the intestine and either removed from the body or recycled back to the liver. In their study, the Swedish researchers posited that gut bacteria was capable of reducing bile acid synthesis in the liver by signaling through the FXR receptor in the small intestine.

"Bile acids are synthesized from cholesterol in the liver and further metabolized by the gut microbiota into secondary bile acids," they wrote. "Bile acid synthesis is under negative feedback control through activation of the nuclear receptor farnesoid X receptor (FXR) in the ileum and liver."

The researchers profiled the bile acid composition throughout the enterohepatic system in germ-free (GF) and conventionally raised (CONV-R) mice.

"We confirmed a dramatic reduction in muricholic acid, but not cholic acid, levels in CONV-R mice," they wrote. "Rederivation of FXR-deficient mice as GF demonstrated that the gut microbiota regulated expression of fibroblast growth factor 15 in the ileum and cholesterol 7a-hydroxylase (CYP7A1) in the liver by FXR-dependent mechanisms. Importantly, we identified tauroconjugated beta- and alpha-muricholic acids as FXR antagonists. These studies suggest that the gut microbiota not only regulates secondary bile acid metabolism but also inhibits bile acid synthesis in the liver by alleviating FXR inhibition in the ileum."

"Drugs that reduce cholesterol levels have, in recent years, greatly reduced deaths from cardiovascular disease," said Sama Sayin, medical doctor and PhD student at the Sahlgrenska Academy, University of Gothenburg, and the study's primary author. "Our study is a step forward because we have shown how gut bacteria regulate the formation of bile acids from cholesterol."

The FXR receptor not only affects cholesterol metabolism but is also involved in the body's sugar and fat metabolism. "If future research can identify the specific bacteria that affect FXR signaling in the gut, this could lead to new ways to treat diabetes and cardiovascular disease," said Dr. Bäckhed.

The study, "Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-betamuricholic acid, a naturally occurring FXR antagonist," was conducted in collaboration with researchers from VTT in Finland, the Karolinska Institute and AstraZeneca in Mölndal.