

Link between hypercholesterolemia and bladder cancer aggressiveness

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Hypercholesterolemia is a metabolic disorder commonly found in people with obesity. It has been reported as a risk factor in the development of the cancers derived from steroid-targeted tissues, such as breast and prostate cancer. However, little is known about the effects of hypercholesterolemia on non-steroid-targeted cancers, such as bladder cancer.

In a study published in *Cancer Research*, a team of researchers led by Yan Jun from Fudan University, Huang Ruimin from Shanghai Institute of Materia Medica of the Chinese Academy of Sciences, and by Guo Hongqian from Drum Tower Hospital, Medical School of Nanjing University, has revealed a novel mechanism on how hypercholesterolemia-induced oxidized low-density lipoprotein (ox-LDL) promotes bladder cancer aggressiveness.

The researchers, using two different hypercholesterolemia mouse models, validated that the elevated cholesterol could enhance bladder cancer progression via regulating cancer stemness. In line with this notion, the inhibition of intestinal cholesterol absorption by Ezetimibe reversed diet-induced hypercholesterolemia and cancer stemness, suggesting that the elevated cholesterol was the primary cause of bladder cancer aggressiveness.

Then, they analyzed the main components in hypercholesterolemic sera, and found that ox-LDL was the key factor. Mechanistically, by binding with its receptor CD36 on cytomembrane, ox-LDL enhanced the interaction of CD36 and JAK2, induced phosphorylation of JAK2 and subsequently activated STAT3 signaling, the well-known signaling mediating cancer stemness. Increase of ox-LDL levels in serum further indicated worse clinical outcomes in UBC patients.

This study first established the link between hypercholesterolemia and bladder cancer. It showed that elevated ox-LDL may serve as a risk factor for bladder cancer, hypercholesterolemia-induced ox-LDL in serum was a key factor to promote cancer stem-like cells, providing an example for the tumor macroenvironment on regulating cancer stemness, and lowering serum ox-LDL or targeting the CD36/JAK2/STAT3 axis might serve as a potential therapeutic strategy for bladder cancer patients with hypercholesterolemia.

More information: Lin Yang et al, Oxidized low-density lipoprotein links hypercholesterolemia and bladder cancer aggressiveness by promoting cancer stemness, *Cancer Research* (2021). **DOI:** [10.1158/0008-5472.CAN-21-0646](https://doi.org/10.1158/0008-5472.CAN-21-0646)

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