Medical Xpress

CAR-like membrane protein determines all-trans retinoic acid response in colorectal cancer

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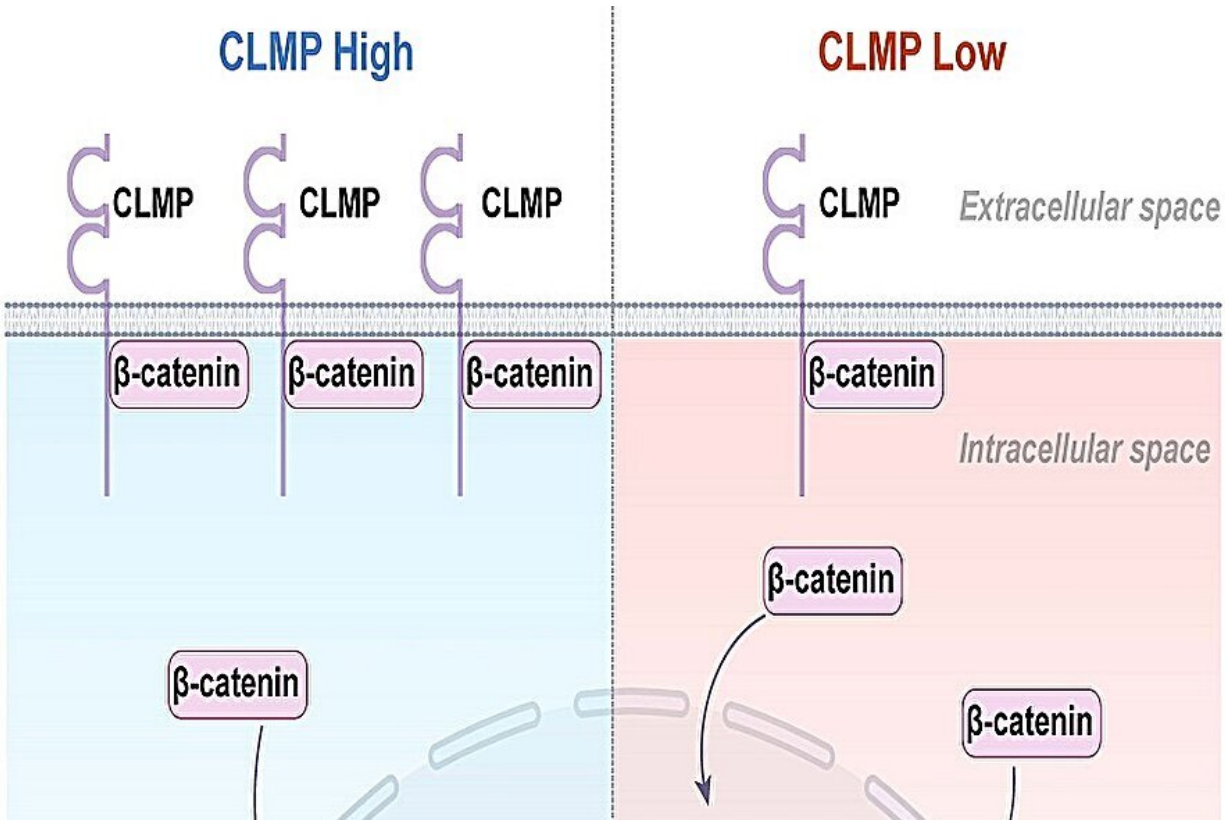

CLMP regulates ATRA response via Wnt/β-catenin signaling in CRC. Credit: Bu Pengcheng's group

Researchers led by Prof. Bu Pengcheng from the Institute of Biophysics

of the Chinese Academy of Sciences and their collaborators have revealed that the CAR-like membrane protein (CLMP) is a tumor suppressor and determines all-trans retinoic acid response in colorectal cancer (CRC).

The study was published in *Developmental Cell* on Nov. 8.

CLMP is dramatically overexpressed in intestine. In congenital short-bowel syndrome (CSBS), CLMP mutations are observed in the intestine, indicating that CLMP plays a critical role in intestinal development. However, its function in CRC remains unidentified.

All-trans retinoic acid (ATRA), the major biological active metabolite of vitamin A, has shown substantial effect for the treatment of patients with acute promyelocytic leukemia, and has also been under an increasing number of clinical trials against various types of cancer. However, the effect of ATRA is controversial in CRC, as some CRC respond to ATRA, some do not, and the mechanism that regulates the response of ATRA on CRC has not been elucidated.

The researchers analyzed the expression of CLMP in CRC tissues in The Cancer Genome Atlas (TCGA) database. Results showed that CLMP was downregulated in CRC and was associated with CRC progression. Then they generated CLMP conditional knockout mice in intestinal epithelial cells. Loss of CLMP enhanced intestinal carcinogenesis in both azoxymethane/dextran sodium sulfate (AOM/DSS) and $Apc^{Min/+}$ mouse models.

To reveal the molecular mechanism of how CLMP regulates tumorigenesis and growth of CRC, the researchers examined proteins interacting with CLMP by co-immunoprecipitation and mass spectrometry. CLMP interacted with β-catenin, recruiting β-catenin to the cell membrane and suppressing Wnt/β-catenin signaling.

Cytochrome P450 hydroxylase A1 (CYP26A1) was found to be targeted by the Wnt/β-catenin pathway and significantly upregulated in CLMP null tumors. CYP26A1 is the key enzyme that degrades retinoic acid into a less bio-active retinoid. CLMP knockdown increased CYP26A1 expression in CRC57 cells and resulted in the cells resistant to ATRA.

Notably, the cells became sensitive to ATRA when CYP26A1 was knocked down, demonstrating that CYP26A1 was required for CLMP knockdown-mediated cell proliferation. Furthermore, CLMP expression is negatively associated with nuclear β-catenin and CYP26A1 expression in clinical CRC samples.

The combination of ATRA and CYP26A1 inhibitor suppressed CLMP downregulation-mediated CRC tumorigenesis and growth in $Apc^{Min/+}$, AOM/DSS and orthotopic CRC mouse models.

More information: Zhenzhen Wu et al, CLMP is a tumor suppressor that determines all-trans retinoic acid response in colorectal cancer, *Developmental Cell* (2023). DOI: 10.1016/j.devcel.2023.10.006

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