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RAPID COMMUNICATION

Aberrant cholesterol metabolism in colorectal cancer represents a targetable vulnerability

Colorectal cancer (CRC) is the second most deadly adult cancer in men and women combined, accountable 9.2% of all cancer deaths.[1] Drug resistance to chemotherapies, such as 5-FU-related regimens, remains a major cause of cancer recurrence and death in patients with CRC. Aberrant metabolic changes in cancer cells are a significant cancer hallmark.[2,3] We hypothesize that elevated cholesterol synthesis represents a targetable vulnerability in CRC.

To test this hypothesis, we first evaluated the cancer recurrence risk of CRC patients with high (n = 103) *vs.* normal (n = 489) cholesterol synthesis in cancer tissues using the CRC cohort (n = 592) from The Cancer Genome Atlas (TCGA) program.[4] We detected the total cholesterol levels (see Supplemental Materials) in the collected CRC tissues, and determined whether cholesterol-related gene expression is associated with cholesterol levels. We found that elevated expression of at least three cholesterol-related genes (HMGCS1, HMGCR, SREBF2, SOAT1, and ACAT1) relative to matched normal colon tissues was associated with a high level of cholesterol in CRC tissues (Fig. S1A, B).[5] Based on these results, we divided colorectal cancer patients in the TCGA CRC cohort into a high cholesterol metabolism group (high cholesterol level was indicated by high expression of the above genes relative to diploid samples) and a normal cholesterol metabolism group (Fig. S1). A Cox proportional hazards model was used to adjust the effects of age, race, ethnicity, and cancer stage. Kaplan–Meier survival analysis with log-rank test was used to compare cancer recurrence between the high and normal cholesterol synthesis groups. We found that patients with high expression of cholesterol genes in CRC tissues demonstrated a significantly higher risk of cancer recurrence (19.35%) compared with patients with average cholesterol metabolism (6.67%; $P < 0.003$) (Fig. 1A). These results suggest that high cholesterol metabolism may be a risk factor for CRC recurrence. In the TCGA cohort, the adjusted hazard ratio of the high cholesterol synthesis group was 4.35 (95%CI: 1.82–10.39, Fig. S2), which was the highest score in the analysis (Fig. S2) of all factors, including cancer stage. For example, we observed that those patients with stage II and III CRC have worse survival compared to those patients with stage I disease, with adjusted hazard ratios of 2.45 (95%CI: 0.68–8.77), and 2.49 (95%CI: 0.67–9.28), respectively (Fig. S2). These findings indicate that high cholesterol metabolism represents a significant risk factor for cancer recurrence, with the highest hazard ratio of all the known cofounding factors, including cancer stage.

Next, we tested whether cholesterol-lowering atorvastatin effectively resensitizes treatment-resistant CRC cells to chemotherapeutic agents. Because most CRC patients receive chemotherapy after diagnosis, cancer recurrence is likely a result of drug resistance in cancer cells. Using 5-FU-resistant CRC cell line LoVo-R, we tested whether cholesterol-lowering atorvastatin is associated with an enhanced effect of 5-FU on cancer cells. Using BLISS independence model, we found that a combination of atorvastatin and 5-FU had a synergistic effect on cancer cell killing (Fig. 1B). In addition, we tested other CRC cells for the role of atorvastatin in drug sensitivity and found that cancer cells with high expression of cholesterol-related genes are more sensitive to the combined treatment of atorvastatin and chemotherapy (Fig. S1C, D). This analysis indicates that atorvastatin sensitizes colon can-

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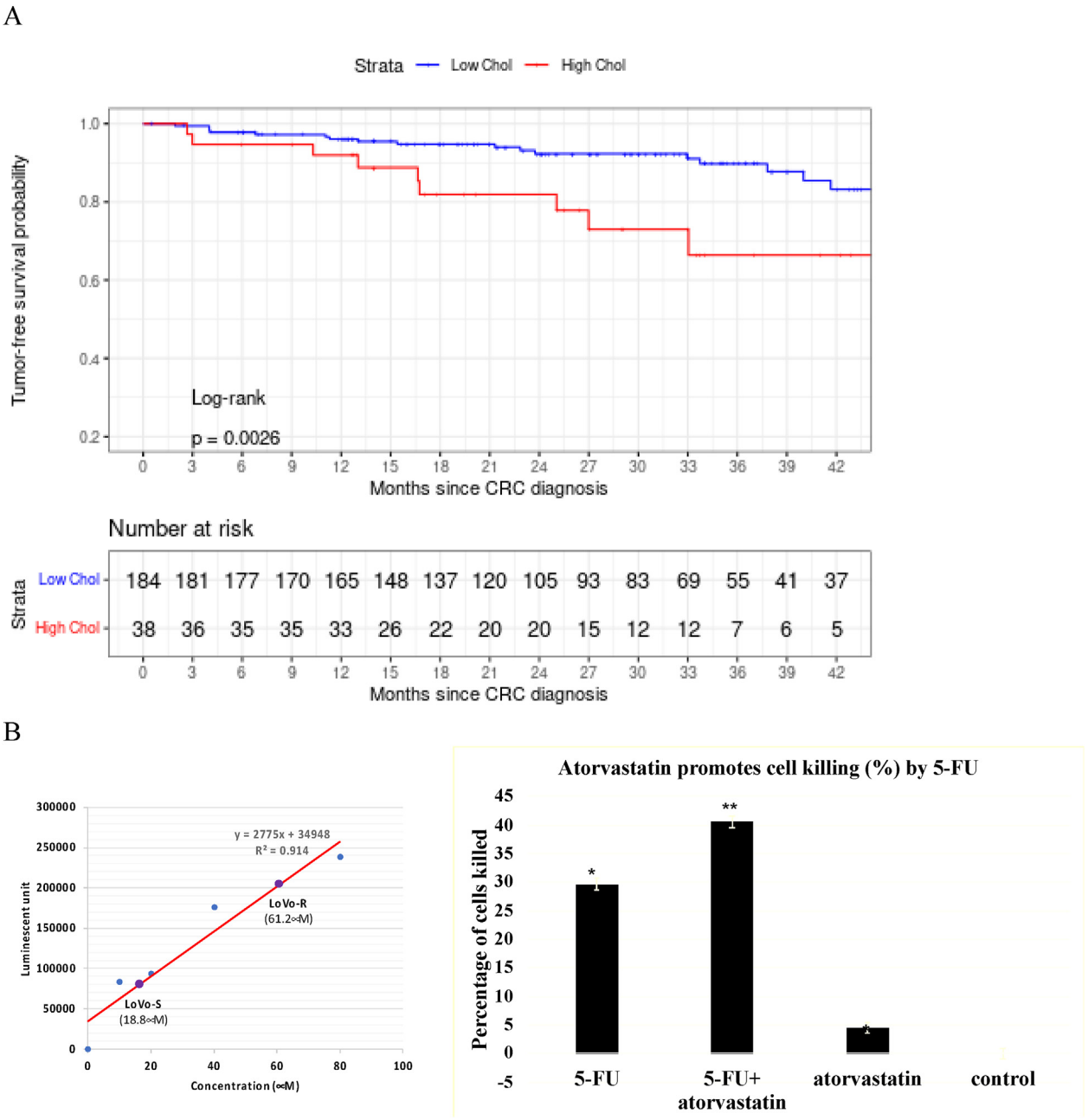

Figure 1 Cholesterol metabolism in colorectal cancer tissues and tumor-free survival and drug resistance. **(A)** Kaplan–Meier tumor-free progression in patients with high or low cholesterol metabolism in the cancer tissues as indicated by expression of HMGCS1, HMGCR, SREBF2, SOAT1, and ACAT1 in the cancer tissues ($P = 0.0026$). **(B)** 5-FU resistant LoVo cells have a high cholesterol level (left) and are susceptible to the combined treatment of 5-FU and atorvastatin (right). * indicates $P < 0.05$; ** indicates synergy between two drugs (via the Bliss independence model, see Supplemental Materials).

cer cells to chemotherapy, consistent with a previous report on statin effects.[5]

In summary, we found that CRC with high cholesterol synthesis activity had a high chance of cancer recurrence and worse tumor-free survival. Our results also suggest that atorvastatin sensitizes CRC cells with high cholesterol levels to 5-FU. Thus, elevated cholesterol synthesis in

CRC tissues represents a targetable vulnerability for treatment.

Author contributions

XJ, JS and KH initiated and supervised the research. CMN and JX performed analyses and the experiments respectively. AT, HN, TFI and MH provided expertise comments and data interpretation. XJ and JS prepared the manuscript. All authors have reviewed and approved the final version of this manuscript.

Conflict of interests

The authors declare no conflict of interests.

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Data availability

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.06.002.

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