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# 'Yapping' with extracellular vesicles in fatty liver metastasis

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Liver metastasis is a major cause of death in patients with colorectal cancer (CRC). A recent study by Wang et al. has deciphered unprecedented prometastatic and immunosuppressive properties of the tumor microenvironment (TME) mediated by hepatocyte-derived extracellular vesicles (EVs) in fatty liver, paving the way for therapeutic innovations to treat patients with CRC and liver metastasis.

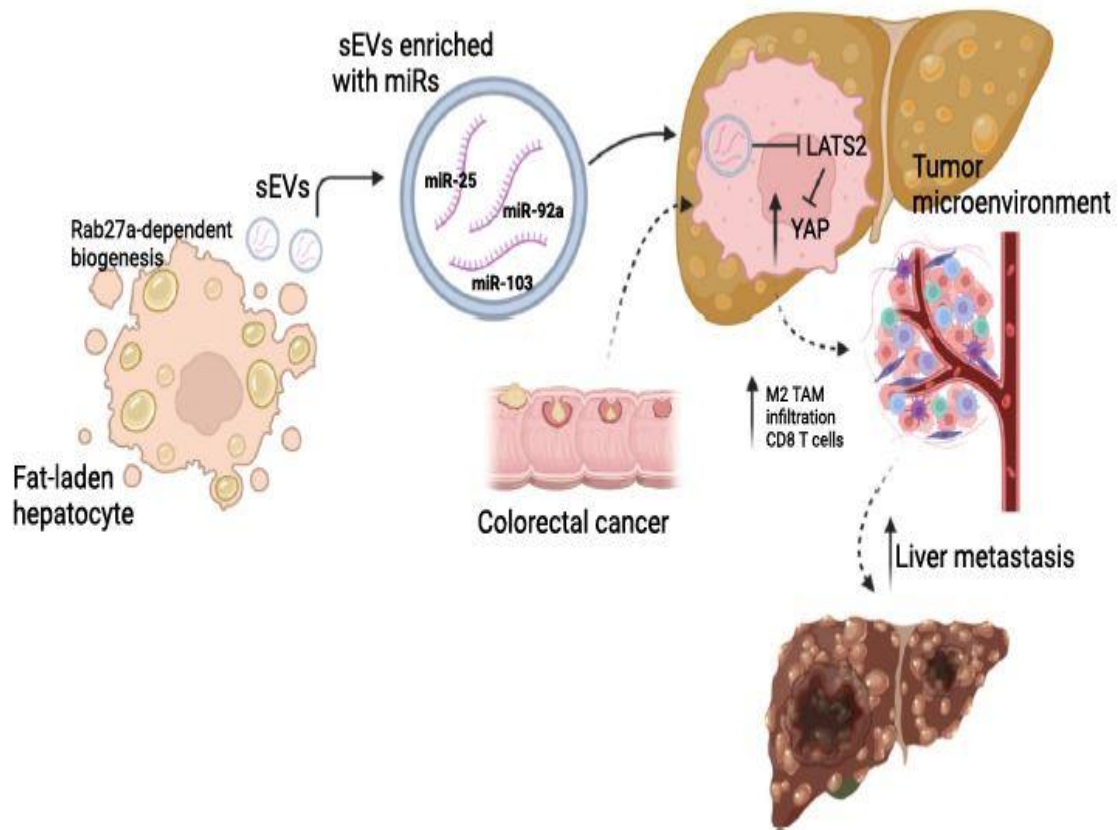
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Epidemiological data suggest that obesity is associated with an increased risk of CRC [1]. Several biological factors such as insulin resistance, the associated increased production of insulin growth factor 1, endothelial growth factors, and several adipokines, as well as intestinal dysbiosis, may explain the role of obesity in the development and outcome of CRC [2]. Obesity and fatty liver during non-alcoholic fatty liver disease (NAFLD) increase the occurrence of CRC liver metastasis and local recurrence following resection of CRC liver metastases, thereby worsening prognosis [3]. Furthermore, the TME – a highly complex and heterogenic local environment that includes primary tumor cells and stromal, immune, and hepatic cells – influences liver metastasis. Understanding the molecular mechanism of metastasis in patients with fatty liver remains a crucial strategy to manage patients with CRC and to develop innovative therapeutic approaches.

EVs, including both large vesicles (IEVs), and small vesicles (sEVs), convey fundamental information between cells that leads to liver disease in the context of NAFLD, as well as to tumor growth and metastasis, and they also participate in the aggressiveness of TME [4–6]. EVs from circulating and tumor cells contain microRNAs (miRNAs), proteins, and lipids with immunological and cancer growth, invasion, and metastatic activities. Thus, EVs might be active in the formation of a pre- and prometastatic liver environment that predisposes to CRC liver metastasis. sEVs can be released via different Rab family proteins that mediate the transport, docking, and fusion of multivesicular bodies with the plasma membrane. Wang et al. now provide evidence that fatty liver enhances the production of hepatocyte-derived EVs, especially sEVs, and promotes the progression of CRC liver metastasis via Yes-associated protein (YAP) signaling and an immunosuppressive TME [7].

They first demonstrate that increased EV release by fatty liver enhances liver metastatic tumor growth. They used a CRC liver metastasis model, with or without fatty liver, involving splenic injection of MC38 CRC cells into lean or high-fat diet (HFD)- fed mice. An HFD increased the number and size of metastatic tumors and serum sEV levels. Furthermore, serum sEVs from HFD-fed mice enhanced the cancer aggressiveness of CRC cells. The pathophysiological relevance of this finding is highlighted by the fact that serum sEV levels in patients with NAFLD are greater than those in healthy controls, and this correlates with liver fat content and aggressive CRC. In vitro treatment of mouse hepatocytes with palmitate (PA) increased sEV release that can be taken up by CRC cells to induce their proliferation, migration, and invasion. Silencing the mechanisms leading to sEV biogenesis – that are regulated by Rab27a and an ECRT-dependent pathway – was found to inhibit sEV production by PA-stimulated hepatocytes and reduced metastatic liver tumor growth in HFD-fed mice. By contrast, Rab27a overexpression enhanced CRC liver metastasis, likely through Rab27a mediated sEV production. Detailed characterization of the relative contributions of the different EV subtypes released would be interesting because NAFLD/non-alcoholic steatohepatitis (NASH) is associated with markedly increased circulating levels of both IEVs and sEVs. In addition, functional miR-25, mir-92a, and mir103 were upregulated in hepatocyte-derived sEVs and in serum sEVs from a mouse CRC model, as well as in NAFLD patients. These miRNAs are oncogenic players in fatty liver and may be involved in the tumorigenic effects of sEVs on CRC cells. Wang et al. also found that the expression of LATS2, a negative regulator of YAP signaling, was downregulated, leading to increased YAP nuclear localization and activation in CRC cells treated with miR-25, mir-92a, and mir103 mimetics. In metastatic tumors, HFD feeding enhanced YAP signaling and the expression of its target genes, and downregulated the expression of Lats2. The effect of HFD feeding was reversed by in vivo silencing of Rab27a, suggesting that sEVs arising via a Rab27a-dependent mechanism regulate YAP activity in metastatic tumors. Silencing Yap1 in CRC cells reduced the ability of sEVs from fat-laden hepatocytes to induce in vitro protumorigenic effects, and also inhibited tumor growth and lowered oncogenic gene signatures in vivo. Yap1 knockdown in cancer cells reduced type 2 (M2) tumor-associated macrophage (TAM) infiltration, indicating that metastatic YAP activity may affect TAM infiltration and the polarization of M2 macrophages. The mechanism involves activation of CYR61 – a YAP target molecule with chemoattractant properties – in tumor liver tissues, and this was further increased in tumor fatty liver subsequent to sEV release. It is also possible that sEVs from TME cells and circulating cells might participate in this phenomenon.

They next bring evidence that fatty liver enhances the immunosuppressive TME, including M2-TAMs, scar- and lipid associated macrophages (SAMs/LAMs), and CD8 T cells, in part via tumor-derived YAP activity. Finally, the clinical implications of TME modifications were studied in tissue samples from patients with CRC liver metastasis with or without fatty liver. YAP activity in cancer cells increased CYR61 production in fatty liver, thus recruiting TAMs (including SAMs/LAMs) to cancer lesions and polarizing them to a M2 phenotype. Patients with NAFLD are therefore vulnerable to CRC liver metastasis, likely through TME modulation that favors metastasis in which YAP plays an important role in regulating the aggressiveness of metastatic tumors. It would be interesting to address EV enrichment in patient tissue samples, especially in hepatocytes, to establish a cornerstone for the involvement of different sEV subtypes. In addition, one must consider EVs not only from other tissues (e.g., adipose tissue) but also, most interestingly, from the microbiota. Indeed, bacterial and eukaryotic EVs are important players in the gut–liver axis leading to NAFLD [5,8], and they probably participate in TME phenotypes in CRC liver metastasis.



**Figure 1.** Fatty liver promotes liver metastasis via the release of small extracellular vesicles (sEVs). Fat-laden hepatocytes induce sEV release through a Rab27a-dependent mechanism. These sEVs are enriched in functional microRNAs that upregulate the YAP signaling pathway, decrease LAST2, and favor a metastatic tumor microenvironment. YAP activity in cancer cells thus increases TAM recruitment to cancer lesions and their polarization towards a M2 phenotype.

**Abbreviations,** LATS2, large tumor suppressor kinase 2; M2, type 2 macrophage; miR, microRNA; TAM, tumor-associated macrophage; YAP, Yes-associated protein.

These findings highlight a novel concept that pre- and prometastatic niches can be created by metabolic abnormalities in the metastatic organ itself through EV signaling, resulting in an immunosuppressive TME – a process in which YAP plays an important role (Figure 1). They underscore distinct liver TMEs in patients with and without fatty liver that may contribute to the aggressiveness of metastatic tumors and a reduced response to anticancer therapy.

### Declaration of interests

The authors declare no conflicts of interest.

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