Editorial

MiR-20a loaded with nanoparticles helps in the reduction of colorectal liver metastasis

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One of the foremost and worldwide leading cause of death is cancer. The molecular modifications or alterations in the genome leads to the cancerous condition. Many other factors are responsible for the cause of the disease such as lifestyle, age, gender, ecological factors, race, food and heredity (1). Among all the cancers, colorectal cancer is the third most often occurring cancer and responsible for the millions of deaths worldwide. According to WHO report, in 2018, around 1.8 million new cases from 25 countries were reported (https://www.wcrf.org/dietandcancer/cancer-trends/colorectal-cancer-statistics). The survival rate in case of colorectal cancer depends on the diagnostic stage, early diagnosis can lead to the survival while diagnosis at later-stage has lesser survival rate. For the screening of colorectal cancer sigmoidoscopy and coloscopy is generally used (https://www.who.int/cancer/detection/colorectalcancer/en/). In spite of undue advances in treatment possibilities for colorectal metastasis, patients might still not have access to effective treatments.

Many research groups are still in the race and trying hard to find out the treatment and diagnostic approaches for the disease. The anatomic position and the nature of receiving dual blood from a portal vein and hepatic artery makes liver one of the most common metastatic target organs (2). Nowadays many therapies and surgeries which specifically aimed at the liver like radiofrequency ablation, transcatheter arterial chemoembolization, and chemotherapy (3) etc. are in use for the treatment of disease, but having lots of side effects. Despite all the therapies, the role of micro-RNAs has come into the picture which is exclusive among all. The exclusivity of miRNAs has already been reported as a diagnostic biomarker for the various diseases and helps in the embryonic development as well as in the physiological processes (4). The differential expression level of miRNAs aids in the identification as well as enhancement or reduction of metastasis.

As microRNAs grip a prodigious promise in the field of cancer research, a recent study has been done by Marquez *et al.* in which they have analyzed the role of miRNAs in LSECs (liver sinusoidal epithelial cells) activation during liver metastasis progression (5). During colorectal cancer, the phenotypic transformation of liver sinusoidal epithelial cells into metastatic cells occurs. When the hepatic sinusoids (the first hepatic cell line) interact with the metastatic cells, LSECs initiate the production of proinflammatory chemokines that produce a favorable situation for the growth of tumor (6). This whole genome study has revealed that the miR-20a expression plays a very decisive role in the colorectal metastasis. To evaluate the expression of miRNA in the normal healthy and metastatic condition they developed a colorectal cancer liver metastasis model and isolated the LSECs from them. During the microarray analysis, it was seen that the miR-20a has shown the greatest alterations. The expression of cellular proteins changed during the metastatic progression. In healthy condition, the miRNA blocked the proteins which support the phenotypes of LSECs and at the time of its activation, the miRNAs get downregulated which leads to the overexpression of premetastatic proteins which leads to the enhancement of metastasis (*Figure 1*). Additionally, with the help of miRbase (microRNA database) it was identified that in the tumor-colonized LSECs among 713

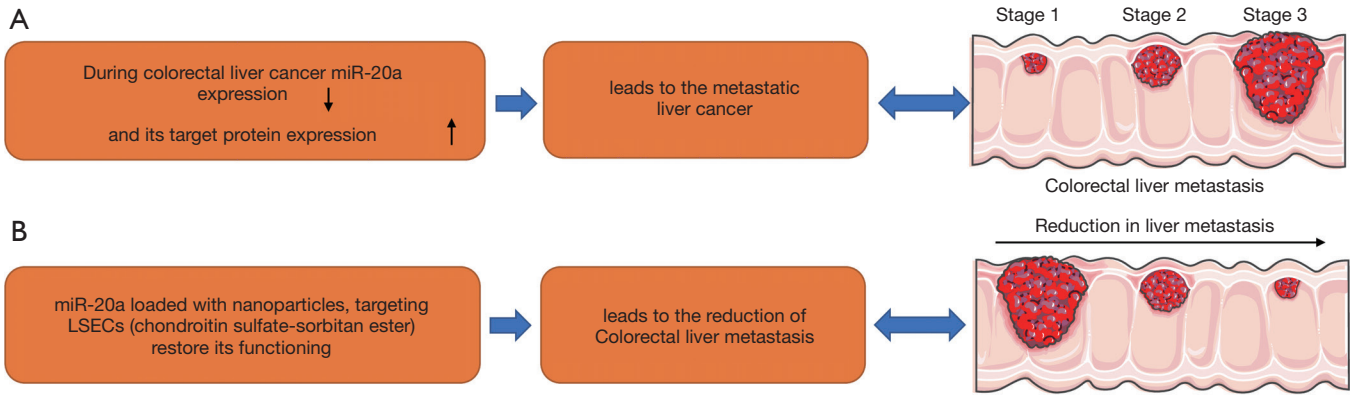

Figure 1 Schematic representation showing the stages of colorectal cancer (A) during colorectal liver metastasis, miR-20a expression gets downregulated which leads to the growth of tumor (B) when the miR-20a conjugated with nanoparticles (SP-OA-CS) the activity of the miR-20a get restored which leads to the reduction in tumor growth.

protein target candidates, 5 protein targets were seen to be overexpressed i.e., JAK1, ARHGAP1, ACSL4, DECR1, and E2F1. Among these 5, 2 protein targets ARHGAP1 (Rho GTPase activating protein (7) and E2F1(transcription factor involved in cell cycle processing (8) have shown the direct correlation between tumor-activated expression and miR-20a. In the current study, it was observed that the E2F1 and ARHGAP1 expression levels were upregulated in tumor-activated LSECs.

The researchers hypothesized that the restoration of normal mir-20a levels in these cells induced downregulation of its protein targets. So, to achieve this restoration, the exogenous miR-20a (multi-target nature), requires an efficient delivery system for its targeted delivery into the LSECs. Based on the previously designed nanoparticle sorbitan ester (9), researchers have developed a nanoparticle chondroitin sulfate-sorbitan ester which then conjugated with miR-20a (5). The modified nanoparticles have polysaccharide chondroitin sulfate (CS) (functional moiety), hence creating span, oleylamine and chondroitin sulfate based nanoparticles (SP-OA-CS) and it is biocompatible and biodegradable in nature. For the clearance of the functional moiety (hyaluronic acid and chondroitin sulfate), key scavenger receptor, HARE (hyaluronic acid receptor for endocytosis) also known Stabilin-2 is primarily expressed on the sinusoidal endothelial cells of the lymph nodes, liver, and spleen (10). Further, the efficiency of nanoparticle delivery was evaluated in LSEC by *in vivo* and *in vitro* analysis. The nanoparticle was then incorporated with EGFP plasmid for the efficient transfection and expression of GFP protein followed by fluorescence labeling at the target cell. It shows that the miRNA coated with modified nanoparticle was efficiently uptaken by the reticuloendothelial system (RES), which encompasses phagocytic cells and results in the short circulation life of the Nanosystem. However, the anionic nature of Nanosystem shows LSEC-specific internalization instead of Kupffer cell.

Expressed CD31 collected from *in vivo* liver metastasis murine model and treated with miR-20a conjugated with nanoparticles brought out a significant reduction of CD31-positive LSEC infiltration into tumor foci. The restoration of miR-20a prevent the increased migratory capacity of LSECs cells linked with tumor-induced activation. It is directly correlated with the above-mentioned multiple protein targets which help in the reduction of a metastatic tumor occupied area. However, miR-20a injection leads to E2F1 and ARHGAP1 depletion, which are associated with cell cycle, metabolism, migration, and differentiation. miR-20a level restoration shows that the activation of LSECs leads to the passable reduction of neoangiogenesis and vascular support to tumors.

It is still a mystery why early activation of LSECs induces miR-20a depletion? Numerous researchers are still working on it to reveal the facts behind the story. This new therapeutic strategy might be a valuable mode to inhibit the progression of liver metastasis.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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