Letter to the Editor

Targeting liver sinusoidal endothelial cell activation during angiogenesis using miRNA: a new therapeutic approach against liver metastasis

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Colorectal cancer is the third most frequently occurring cancer and a common cause of cancer-related death worldwide (1). The most common metastatic target organ of colorectal cancer is the liver (2). The first interaction between colon cancer cell and liver occurs in the liver sinusoid. The narrow fenestrated capillaries of the hepatic tissue (3). The tumor cell is trapped in this space and start the interaction between metastatic cell and host organ. The first liver cell that commences the interaction is the endothelial cell of the liver sinusoid also called liver sinusoidal endothelial cell (LSEC). This cell expresses adhesion molecules such as ICAM-I and VCAM-I and reinforce the interaction between both cells (4). After this first step, the active endothelial cell produces proinflammatory chemokines that generate a propitious environment for metastatic cell progression. This environment is also known as tumor microenvironment. In this scenario, other cells such as Kupffer cell and hepatic stellate cell are activated and support the tumor. In such favorable situation the metastatic tumor continue growing until it is so huge that need more oxygen and nutrients. The oxygen and nutrient requirement is satisfied recruiting new blood vessels, this is the angiogenesis process. To produce the angiogenesis, tumor cell secrets signals to the liver sinusoidal endothelial cells to produce the intracellular signals to proliferate and move them to the tumor mass. There are many signals involved in the angiogenic process but the most relevant is the vascular endothelial growth factor (VEGF). This molecule is produced by tumor cells and result in endothelial cell growth. The role of the VEGF has been described as crucial for the angiogenic process and for this reason; it has been used as therapeutic target (5). It is the case of bevacizumab, an antibody that interact with the VEGF receptor and block the signal. Unfortunately, this drug is not very efficient and in many cases, the tumors can produce angiogenesis despite the anti-VEGF treatment. The reasons of the failure can be multiple; from a different VEGF isoforms produced by the cancer cell to other signals different to the VEGF produced by the tumor cells in the secretome. The casuistic could be huge and it could be different from tumor to tumor. The intertumor and intratumor heterogeneity is so high that it could be difficult to design a multitarget drug able to block all the signals that are producing tumor endothelial cells growth and migration.

Due to all aforementioned mechanisms, we decided to change the therapeutic perspective. Instead of focusing in the activation signals, we moved to the endothelial cell intracellular signals involved in the activation process. Although the extracellular signals could be very heterogeneous and different, the intracellular mechanism can be more conserved. From all possible molecules we selected the miRNAs; small, versatile and multitarget molecules able to regulate the cell behavior. In a comparative study between tumor colonized LSEC with healthy LSEC we identified upregulated and downregulated miRNA. If we had selected the upregulated miRNA in the tumor colonized cells, the strategy would had been focused

on blocking the miRNA, but we chose the downregulation option. We decided because of replacement of a missing element is easier that a complete blocking of a molecule. We detected many downregulated miRNA and worked *in silico* to select the best candidate. miRNA-20a is a well-known molecule described in tumor progressions, embryonic development and Wnt signaling (6-8). In this case, the selection of miR-20a was motivated because two potential targets were detected in the proteomic study; ARHGAP1 and E2F1. Two molecules related with cell cycle and migration. These two molecules appear in the metastasis process in LSEC and provoke cell proliferation and migration. MiR-20a replacement in LSEC during tumor colonization stop the LSEC growth and migration (9). Consequently, metastasis size was decreased 80%.

In conclusion, this new therapeutic approach is focused on reverting the endothelial cell phenotype to reduce the angiogenic status of the metastatic tumor to weaken the cancer cells. This reversion is based on replacement of key miRNAs. The strategy is focused on reverting the crucial miRNA expression level to a physiological condition. For this replacement a suitable sorbitan ester based nanoparticle has been developed to interact exclusively with LSEC, another key point of the strategy. The ubiquity of the miRNA is a dangerous characteristic that has to be controlled in therapeutic activities. MiRNA can produce one specific effect in one cell type and just the opposite in another cell type, for this reason the importance to control the delivery of the miRNA. The success in a mice model open the possibility to develop a real treatment for humans; in another hand, the approach can be moved to other cancer and metastasis types changing the nanoparticle delivery molecules and key miRNA.

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Footnote

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Ethical Statement: The author is 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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