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Lipid droplets may lay a spacial foundation for vasculogenic mimicry formation in hepatocellular carcinoma

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ABSTRACT

Vasculogenic mimicry is a highly patterned vascular channel distinguished from the endothelium-dependent blood vessel. Vasculogenic mimicry is lined by highly aggressive tumor cells, and is associated with tumor grade, invasion and metastasis, and poor clinical prognosis. Much attention has been focused on the signaling pathways and the tumor microenvironment needed for vasculogenic mimicry formation, however, the studies on the spacial foundation for vasculogenic mimicry formation are limited. There are many lipid droplets in hepatocellular carcinoma due to steatosis, while increased numbers of lipid droplets also have been reported in many other neoplastic processes. The role of lipid droplets in tumor is still unclear. Based on the similar structural and morphological characteristics between vasculogenic mimicry and lipid droplet, we speculate that the lipid droplets may lay a spacial foundation for vasculogenic mimicry formation by a way of "space placeholder" in HCC. Experimental data and limited clinical literatures support the hypothesis to a certain degree. This hypothesis may provide a new idea for the study of vasculogenic mimicry and also provide a new direction for the functional study of lipid droplets in tumor.

Background

Blood supply plays a critical role in tumor growth and metastasis, and most attention has been focused on endothelium-dependent blood vessels [1]. In 1999, Maniotis et al. [2] discovered a new type of blood supply channels in uveal melanomas. This channel is lined by aggressive tumor cells in the absence of endothelial cells and is composed of a basement membrane that stains positive with the periodic acid-Schiff (PAS) reagent. There are red blood cells and blood plasma flowing through these channels, suggesting that they are functional blood supply channels. For emphasizing its formation differences from angiogenesis, this channel is termed as vasculogenic mimicry (VM). Since then, VM has been reported in several malignant tumor types, such as liver cancer, glioma, ovarian cancer, astrocytoma, and prostate cancer [3–7]. Furthermore, the presence of VM is associated with tumor grade, invasion and metastasis, and poor clinical prognosis [8,9]. The study has been focused on the tumor-cell plasticity, signaling pathways and tumor microenvironment needed for vasculogenic mimicry [10–12]. However, the studies on spacial foundation for vasculogenic mimicry formation are limited.

Hepatocellular carcinoma (HCC), one of the most common malignancies worldwide, is the leading cause of death for cancer patients in South Eastern Asia, especially in China [13]. The death rates of most cancers have been declining slightly in recent years, whereas the death rates of HCC have been increasing [14]. These epidemiologic data is enough to raise our attention for HCC. Steatosis is one of the pathological morphological characteristics of HCC. Frequently, there are large lipid droplets accumulation in HCC due to steatosis [15]. The fatty change of HCC is closely related to the tumor size and histological grade, and the number of lipid droplets in HCC changes with the tumor progression [16,17]. Interestingly, it is found that steatosis can promote angiogenesis in chronic hepatitis C [18,19]. Furthermore, lipid droplets have been reported in several other tumor types [20]. However, there are limited reports focusing on the association between lipid droplets and angiogenesis in tumor.

The hypothesis

Based on the similarity of structural and morphological characteristics between vasculogenic mimicry and lipid droplet and the limited clinical literatures, we speculate that the lipid droplets may lay a spacial foundation for vasculogenic mimicry formation by a way of "space placeholder" in HCC, especially for those located

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in the distal area of endothelium-dependent blood vessel. If this hypothesis is correct, it may be a new function of lipid droplets in HCC, and it also may be a new mechanism of vasculogenic mimicry formation in HCC.

Evaluation of the hypothesis

The classic theory of tumor angiogenesis

Tumor cells mainly get the nutrients and oxygen by diffusion in the early stage of tumorigenesis, which is restricted when tumors grow to a certain size [21]. Under hypoxic condition, tumor cells generate and secrete the angiogenic factors such as VEGF, thereby forming a concentration gradient of angiogenic factors toward hypoxic center. The blood vessels in adjacent normal tissue are stimulated by the angiogenic factors, and subsequently the endothelial cells secrete some enzymes such as MMP to degrade the basement membrane of blood vessels. The endothelial cells invade through the gap of basement membrane by morphologic change and proliferation. Then, the endothelial cells grow into the tumor tissue following the angiogenic factors gradient by aggressive proliferation and migration. Meanwhile, the E-cadherin mediates the adhesion between adjacent newborn endothelial cells. The tumor cells in hypoxic area get the nutrients and oxygen by the endothelium-dependent blood vessels [22].

Space–time barrier for endothelial vascular formation

The cells in solid tumor are closely packed, and there is extracellular matrix distributing in the intercellular space. Furthermore, the tumor tissues squeeze each other with adjacent normal tissues due to tumor size continuously increasing, leading a high pressure environment in the tumor tissues. However, the blood vessels mainly distribute in the peripheral area of tumors. Therefore, the barrier composed of tumor cells and extracellular matrix and the high pressure environment are the key factors for endothelial cells to overcome, because they need to migrate into the tumor tissues and to form the patterned channels for blood flow. Firstly, this microenvironment limits the speed of endothelial cells migration and proliferation. Secondly, this microenvironment affects the formation of blood supply channels and limits the pipe diameter of blood vessels. Thus, all of these events may prolong the time for tumor cells staying hypoxic status.

The discovery of vasculogenic mimicry

In 1999, an article entitled "Vascular channel formation by human melanoma cells *in vivo* and *in vitro*: vasculogenic mimicry," by Maniotis and colleagues, ignited a spirited debate for several years. Since then, many studies have found new evidences supporting the presence of VM in a variety of tumors [23]. The endothelial cells are not involved in vasculogenic mimicry formation, but the vasculogenic mimicry can connect with endothelium-dependent blood vessels. Therefore, the vasculogenic mimicry contributes to rapidly build the microcirculation network in tumor tissues [12]. The space–time barrier for endothelial vascular formation is solved indirectly. Furthermore, the vasculogenic mimicry and blood are separated by a layer of basement membrane, so that the tumor cells near this channel are easier to metastasis [12].

Where is the spacial foundation for vasculogenic mimicry formation from?

Endothelium-dependent blood vessels intrude into tumor tissue by the way of angiogenic sprouting, which suggests that continuous proliferation and migration of endothelial cells is the main driving force for angiogenesis [24]. By contrast, vasculogenic mimicry is lined by tumor cells. How do the tumor cells spontaneously make a highly patterned channel for blood flow? It is an interesting question. Shiwu Zhang et al. [25] reported a theory "linearly patterned programmed cell necrosis (LPPCN)" about vasculogenic mimicry formation. They speculated that under hypoxic conditions, some melanoma cells might undergo LPPCN, thus providing a spacial foundation for VM channel formation in melanoma [26]. This hypothesis is supported by the preclinical and clinical evidences of melanoma. However, some channels in tumors are not applicable for this theory, especially the vasculogenic mimicry with bigger diameter and regular shape. It raises a question "where is the spacial foundation for vasculogenic mimicry formation from?"

Can the space placeholder of lipid droplets evolve into vasculogenic mimicry?

Steatosis can promote angiogenesis in chronic hepatitis C [18,19]. By analyzing the figures provided by authors, we can find that the newborn blood vessels in figures have the regular shape and the similar structure with adjacent lipid droplets, suggesting that there may be a special relationship between lipid droplets and newborn blood vessels. Furthermore, by analyzing the figures related to tumor angiogenesis in published articles, we can find that the newborn blood supply channels, especially the vasculogenic mimicry, mostly have the regular shape in many neoplastic processes, either in animal experiments or clinical specimens [25,27–30]. Based on these findings, we speculate that lipid droplets in HCC may be related to vasculogenic mimicry formation. As follows, we have found these clinical evidences and experimental data supporting this speculation.

Firstly, in addition to HCC, increased numbers of lipid droplets have been reported in many other neoplastic processes, such as brain cancer, colon cancer, prostate cancer, and breast cancer [31–34]. However, few data are available on the role of lipid droplets.

Secondly, upregulated lipogenesis is a common phenotype of numerous human carcinomas such as breast, prostate and colon cancer [35]. While most normal human cells prefer exogenous sources, tumor cells synthesize fatty acid de novo. Fatty acid synthase as the sole mammalian enzyme capable of de novo fatty acid synthesis is highly expressed in most human carcinomas [36]. There are several reasons accounting for tumor cells selecting de novo fatty acid synthesis. (1) lipid synthesis may function as a carbon sink to sequester excess pyruvate and avoid lactate production to equilibrate the intracellular pH [33]; (2) lipid synthesis-derived $NADP^+$ could also increase the availability of cytoplasmic NAD^+ required to maintain glycolysis [37]; (3) fatty acids provide twice as much ATP as carbohydrates (six times more when comparing stored fatty acids to stored glycogen), and in turn they are the preferred nutrient for storage [38]. Once synthesized, fatty acids are used for biosynthesis of membranes and signaling molecules. However, the modulation of numerous lipogenic enzymes may be altered due to malignancy, so excessive synthesis of fatty acids is inevitable. Excessive fatty acids transform to triacylglycerols or sterol esters by esterification, and are stored in lipid droplets in case of lipotoxicity [39]. This is the premise for lipid droplets appearing.

Thirdly, steatosis mainly appeared in the early stages of HCC, and with tumor progression, the degree of steatosis has a tendency to alleviate [16,17]. Based on these data, it shows that the lipid droplets mainly form in the early stages of HCC and some lipid droplets are degraded by enzymes in the progression of HCC. The formation of lipid droplets in tumor tissues makes it possible to reserve space for vasculogenic mimicry formation. The distribution of blood vessels is related to the oxygen levels of different regions in tumor tis-