Medical & healthcare, Drug development, Cancer treatment

The novel strategy targeting tumor vessels in any types of cancer

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Abstract

Tumor vessels, which has irregular dilatation and fragility, are seemed to become a novel target on cancer therapy via 'normalization'. We revealed that cancer-secreted exosome effected endothelial cells, and the specific microRNAs in that exosome increased transparency via decrement of cell adhesion molecules, VE-cadherin and ZO-1. These tumor endothelial cells (TEC) had a high glycolysis ability and effected tumor growth. Regulation of the glycolysis in TEC induced 'normalization' of vessels and decrements of tumor growth. This could be a reliable target of cancer therapy especially in highly diverse tumors.

Background & Results

Recently, a main cancer treatment was shifting from cytotoxic agents to molecular target therapy via understanding cancer itself mechanism, 'Precision Medicine.' Cancer genome analysis permitted this 'Precision Medicine' but its also revealed the high diverse in cancer; inter-individuals, heterogeneity, cancer evolution by treatment or metastasis. Tumor vessels are consisted by tumor endothelial cells, which would be raised from normal endothelial cells and may contribute as a novel target on cancer therapy, via simple mechanism, because there would be no genetic modification. In this study, we showed that cancer with high metastatic ability could give transparent morphology with less cell adhesion molecules, VE-cadherin and ZO-1, to normal endothelial cells, via exosome from the cancer cells (Fig. 1). A part of microRNAs from the exosome, miR-638, miR-663a, miR-3648, and miR-4258 directly changed cell features like transparency (Fig. 1). In addition to this insight, we revealed that these tumor endothelial cells (TEC) had a high phosphofructokinase-2/fructose-2, 6-bisphosphatase 3 (PFKFB3)(Fig.2A), which was a key molecule of glycolysis, with high production of ATP and lactate, and had s different functional features from normal endothelial cells (sFig.1A). TEC induced high progression of tumor growth and regulation of PFKFB3 by the specific inhibitor PFK15 or siRNA of PFKFB3 contributed to decrease the production of ATP and lactate (Fig.2B), growth of tumor vessels (sFig.1B), and tumor growth (Fig.2C). After clinical analysis regarding these molecules, these basic data were compatible. Taken together, cancer changed the features of endothelial cells via exosome, and control of the metabolism at TEC may become a novel and simple target of cancer therapy, even in high diverse cancers.

Significance of the research and Future perspective

Even though the cancer genome analysis provided the chance of 'Precision Medicine,' actionable targets were less, and un-developed target for the mutation seemed to be extravagant. On the contrary, cancer stroma cells would not have a huge genetic change and might be more easily controlled than cancer itself. In this study, we targeted tumor endothelial cells and revealed that the origin of tumor endothelial cells (TEC) were normal endothelial cells, and cancer-associated exosome changed normal cells to TEC, and regulation of metabolism could contribute 'normalization' of TEC. This procedure would expand to other cancer stromal cells, like as cancer-associated fibroblast and tumor infiltrating lymphocytes.

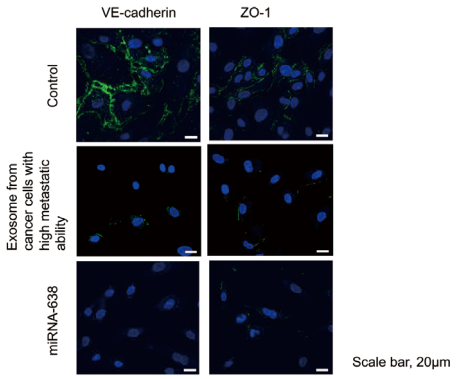


Figure 1

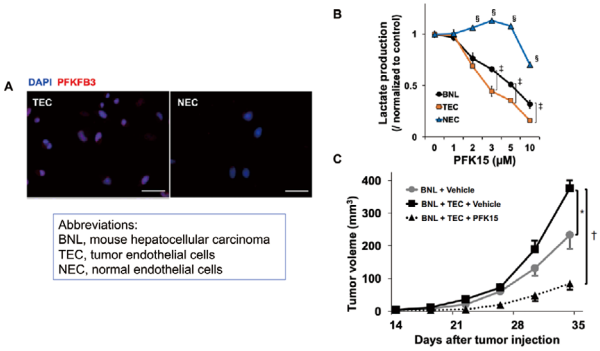
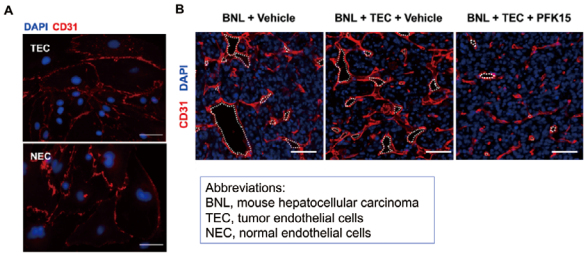


Figure 2



Supplementary Figure 1

Patent
Treatise
Matsumoto, Kenichi; Noda, Takehiro; Kobayashi, Shogo et al. Inhibition of glycolytic activator PFKFB3 suppresses tumor growth and induces tumor vessel normalization in hepatocellular carcinoma Cancer Lett. 2021, 500, p. 29-40. doi: 10.1016/j.canlet.2020.12.011
Yokota, Yuki; Noda, Takehiro; Okumura, Yuichiro; Kobayashi, Shogo et al. Serum exosomal miR-638 is a prognostic marker of HCC via downregulation of VE-cadherin and ZO-1 of endothelial cells Cancer Sci. 2021, 112(3), p. 1275-1288. doi: 10.1111/cas.14807
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