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2. Title
   Development of On-chip Model with Perfusion System for Hematogenous Cancer Metastasis and Its Application to Analysis of Influences of Smoking-related Substances

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4. Summary

   Hematogenous metastasis is the most life-threatening aspect of human cancer, which is responsible for vast majority in patients with refractory solid cancer. Intravasation of cancer cell is the first critical step of the metastatic processes. However, it remained unclear whether smoking could be one of the risk factors for hematogenous cancer metastasis. To clarify influences of vascular flow and smoking on cancer intravasation, in this study, we firstly developed an on-chip model for cancer hematogenous metastasis, in which three-dimensional vascular network of human umbilical vein endothelial cells was induced in the extracellular matrices (ECM) on microfluidic device and cancer cell (HT1080) spheres embedded into the avascular area in the ECM were cultured with or without vascular flow. By using this model, we found that vascular flow enhanced cancer cells invasion into the surrounding ECM from embedded spheres, and increased invasion rate across the vascular wall. The vascular flow-dependent enhancements of interstitial invasion and intravasation were weakened in β_1 and β_3 double knock-downed cancer cells. We further found frequent site in which cancer intravasation takes place. The frequent site is where the vasculature is exposed to relatively slower vascular flow. These results suggest that vascular flow at appropriate range of flow speed could be a promoting factor of cancer cell intravasation, and also suggest that cell adhesion via integrins might at least partially contribute to the promotion. The developed on-chip model is a useful tool to dissect the mechanisms underlying vascular flow-dependent metastatic intravasation of cancer cells. Influences of smoking on cancer cell intravasation remained unresolved in this study.