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Hemodynamic Effects on Tumor Cell Arrest at Microvascular Intersections

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INTRODUCTION

Tumor metastasis, the spread of malignant cells from primary tumors to distant organs, is the major cause of cancer mortality and is a complex multistep process. One critical step of tumor metastasis is arrest of blood-borne metastatic tumor cells in the microvasculature of a target organ (Talmadge and Fidler 2010). Previous studies have found that physical trapping due to size restriction in the narrow part of the microvasculature, blood flows at the branches and turns of the microvessels, and cell adhesion molecules at circulating tumor cells and at the microvascular endothelial cells of target organs, all play a role in tumor cell arrest and adhesion (Fokas et al. 2007; Mook et al. 2003; Yan et al., 2012). However, how and how much each factor contributes to the tumor arrest is not clear. Therefore, the objective of this study is to elucidate the mechanical mechanisms by which the hydrodynamic factors, mechanical properties (stiffness) of tumor cells and cell adhesion molecules contribute to tumor cell arrest and adhesion. Our results will suggest more efficient ways to stop tumor metastasis.

MATERIALS AND METHODS

All experiments were performed on SD rats (250-300g). After anesthesia, 3ml 5 million/ml fluorescently labeled human breast carcinoma cells MDA-MB-231 (~14 μm diameter) or rigid microbeads (~10 μm diameter) were injected into the blood circulation via the carotid artery of a rat in ~3 min; cell and bead arrest patterns in the microvasculature of mesentery were recorded up to 3 h. From the recorded images, we quantified the numbers of tumor cells or microbeads arrested in arterioles, at arteriole-capillary intersections, in capillaries, at capillary (or postcapillary venule)-postcapillary venule intersections, and in postcapillary venules. We also measured the vessel diameter, the blood flow velocity in each vessel, as well as the angle between two vessels at the intersections where the cells or beads prefer to adhere. To investigate the hemodynamic effects on the tumor cell arrest, we used a commercial software FLUENT to simulate the flow and force distributions at these intersections.

RESULTS AND DISCUSSION

We found that 93% rigid microbeads (without cell adhesion molecules) were arrested either at arteriole (~18 μm diameter, mean velocity 2.2 mm/s)-capillary (~9 μm diameter, 1 mm/s) intersections (56%) or in capillaries (<10 μm diameter) (37%). Only 3% was at the capillary-postcapillary venule intersections and in postcapillary venules. In contrast, most of the flexible tumor cells (with cell adhesion molecules at surface) were either entrapped in capillaries (43%) or at capillary or postcapillary venule (~13 μm diameter, 0.6 mm/s)-postcapillary venule (~28 μm diameter, 1 mm/s) intersections (27%), and 15% in post-capillary venules. Only 12% of tumor cells were arrested at the arteriole-capillary intersections. $\chi 2$-test yielded a p value < 0.001 for these distributions, indicating a differential adhesion of tumor cells and microbeads in the microvasculature. Our numerical simulation further elucidates the mechanical mechanisms behind this observed differential adhesion. It shows that at turning points of both types of intersections, there are higher vorticity and higher shear stress regions compared to other regions in the vessels. The higher vorticity brings microbeads and tumor cells to the turning points of the arteriole-capillary intersections. The majority of rigid microbeads (56%) are arrested at the intersection if the capillary is smaller than 10 μm due to size restrictions, while most of tumor cells (85%) can squeeze themselves into capillaries and 42% of them can further move downstream to capillary-postcapillary venule intersections and postcapillary venules. Due to higher vorticity at the capillary-postcapillary venule intersection, escaped tumor cells can be brought to the turning points of the intersection. The higher shear stress at the turning points can activate endothelial cells and increase the possibility of tumor cell adhesion at the intersection. The cell adhesion molecules at tumor cells and endothelial cells forming the vessel wall should be responsible for the final 15% tumor cells adhering in postcapillary venules.

CONCLUSION

Our *in vivo* experiment demonstrates differential arrest patterns of rigid microbeads without cell adhesion molecules and flexible tumor cells with cell adhesion molecules in the microvasculature. Although size restriction contributes the most to the rigid bead (or stiff tumor cells) arrest, numerical simulation reveals that hydrodynamic factors, combined with the cell adhesion molecules, play an essential role in tumor cell arrest and adhesion in the microcirculation.

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