Understanding the biomechanics of colon metastasis-competent CTCs using microchips mimicking microcapillaries of the bloodstream

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Background & objectives

Metastatic progression is the deadliest feature of cancer. Cancer cell growth, invasion, intravasation, circulation, arrest/adhesion, and extravasation require certain cell-mechanical properties in order to survive and complete the metastatic cascade. During metastasis, circulating tumor cells (CTCs) come into contact with capillary beds when they begin their extravasation and intravasation processes. Moreover, uncertainty exists regarding the behavior of CTCs in the bloodstream and even more specifically in the micro capillaries. Thus, our project objective is to investigate the behavior of colon metastatic-competent CTCs in the microcirculation by passing through the microchannels of microchips, which mimic blood capillaries with different channel sizes.

Methods

Our group established the first permanent colon CTC line from a patient with metastatic colorectal cancer before treatment initiation (CTC-MCC-41) [1] and 8 other CTC lines (CTC-MCC-41.4, CTC-MCC-41.5A-G) during progression and after different therapies [2]. The survival behavior of these more aggressive colon CTCs in the microcirculation was observed by calcein staining by passing through dedicated microfluidic device with different confinement sizes (26µm, 6µm and 3µm) and were compared with those of the primary HT-29 and the metastatic SW620 colon cell line.

Results

We observed that cells that passed through the 26µm- and 6µm-microchips, had no influence on cell viability. However, when the more drastic 3µm-confined microchannel chip was used, CTC lines obtained after treatment resistance (CTC-MCC-41.5A-G) are still viable after 24 hrs compared to CTC lines obtained before treatment resistance (CTC-MCC-41, CTC-MCC-41.4), primary HT-29 and metastatic SW620 colon cell lines. More interestingly, among the CTC lines CTC41.5A-G that survived therapies, we observed a higher survival rate of CTC-MCC-41.5A, B, F and G cell lines that are actively released by liver metastasis as they express all ALDOB [3].

Conclusion

Our preliminary findings provide the key message that selected CTC clones that developed drug resistance and were released by secondary liver metastases are more likely to survive in very small capillaries. More in-depth analysis is being conducted to understand the gene expression induced by these confinements as well as to identify one or several pathway(s) involved in this CTC adaptation strategy to withstand the capillary confinement.

References

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