Biophysical roles of pre-metastatic niche evolution on transport of circulating tumor cells

Physical Science in Oncology Project

Exploring the earliest events that promote circulating tumor cells (CTCs) to immobilize on blood vessel walls at future metastatic sites will expose new targets for rational prevention. Studies suggest that distant microenvironments are primed and ready to entrap CTCs, creating a pre-metastatic niche for initiating metastasis. In addition to biological mechanisms, the physical transport of CTC in blood vessels and biophysical interaction of CTC with the pre-metastatic niche can be regarded as key determinants of metastatic potential. Whereas biological effects of circulating platelet (PLT) on CTCs and PLT accumulating to primary and metastatic tumors to support tumor growth and invasion are known, the roles of PLT in the initiation and development of the pre-metastatic niche and biophysical effects of the PLT on transport of CTCs in blood vessels have not been reported.

Our objective is to elucidate and validate biophysical roles of the pre-metastatic niche initiated with PLT in the future metastatic site on CTC transport. We integrate orthotopic mouse tumor models using cell lines with different metastatic potentials, novel microfluidics pre-coated with or without PLT, and multiscale/multi-physics computational transport models. Our hypotheses are: 1) there is an organ- and time-dependent initiation/evolution of the pre-metastatic niche, wherein deposited and activated PLT on vessel walls in mice bearing primary tumors alters hydrodynamics of CTCs and their interactions; 2) only the pre-metastatic niche, which is sufficiently developed to significantly alter these biophysical parameters, promotes immobilization of CTCs on vessel walls; and 3) modulation of PLT functionality by anti-PLT reagents affects biophysical roles of PLTs on CTC transport and the prospect of metastasis. The multiscale/multi-physics transport modeling provides optimized parameterization of metastasis based on experimental results in vitro and in vivo to characterize transport phenomena of CTCs and phenotype pre-metastatic niches. The significance of this study will establish a scientific framework for understanding undiscovered biophysical roles of the pre-metastatic niche initiated with PLTs on transport of CTCs for rational prevention of metastasis using anti-PLT reagents.

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Dr. Yokoi is a Faculty and an Assistant Professor in Nanomedicine, Institute for Academic Medicine, Assistant Member, Houston Methodist Research Institute (HMRI). He has a background in surgical oncology and cancer biology. His expertise includes the establishment and therapy of various primary and metastatic mouse tumor models, as well as biological, molecular biological, and proteomic analysis of tumor specimen and cancer cell lines. He has extensive experiences in histological, immunohistochemical and immunofluorescence analysis of tumor sections. Since moving to the Department of Nanomedicine at HMRI from the Department of Cancer Biology, UT MD Anderson Cancer Center, he has focused research on tumor microenvironments and its roles on the transport of various mass and therapeutics using various orthotopic tumor mouse models. For these purpose, he has utilized various imaging techniques including confocal microscopy, and Intravital microscopy.

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Dr. Qin is a Professor at HMRI, and he directs the Methodist Hospital Biomicrofluidics laboratory. Dr. Qin has more than ten years of experience in microfluidics and nanotechnology research, which include high throughput cell deformability analysis by using microfluidic chips. Dr. Qin has developed innovative biotechnological tools with the use of polydimethylsiloxane (PDMS), glass, plastic, and silicon-based nanoelectronic/microfluidic devices. His research sponsors include NIH/NCI, NIDA, NIA, Alliance of Nanohealth, Cancer Prevention and Research Institute of Texas (CPRIT), Emily Herman Research Foundation, Golfers Against Cancer Foundation, and others. Dr. Qin's research team has demonstrated leadership in the field of microfluidics biotechnology and his research has been featured in journals including Nature Communications, Proceedings of the National Academy of Sciences, Science Advances, Journal of the American Chemical Society, Angewandte Chemie, Trends in Biotechnology, and others.

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Dr. Kojic is a professor and senior member at the Department of Nanomedicine, HMRI. He is the worldwide leading authority in Finite Element modeling with more than 30 years of research which spans form nonlinear analysis in solid mechanics and field problems to various topics in bioengineering and multiscale models. His previously positions include University of Kragujevac, Serbia (professor of Mech. Eng.), MIT (visiting scholar), ADINA R&D Software Company Boston (research engineer), Harvard University (senior research scientist), University of Texas Medical Center at Houston (research professor). Currently, Dr. Kojic works actively in development of multiscale model for biomedical and bioengineering applications, and focusing on drug/mass transport problems. His main scientific focus will be further developing and advancing novel multiscale and Finite Element models for the prediction of drug/mass transport in tumor microenvironment.

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