THE UNIVERSITY OF HONG KONG
SCHOOL OF BIOLOGICAL SCIENCES

Postgraduate Student Public Seminar

"TUMOR MICROENVIRONMENTAL REGULATION OF MIR-199A-3P AND FUT5 IN SHEAR STRESS MEDIATED OVARIAN CANCER METASTASIS"

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Abstract

Ovarian cancer is the most lethal gynecological malignancy worldwide. The fatality of the disease is mainly due to late detection, resulting in patients being diagnosed at an advanced stage with widespread peritoneal dissemination of cancer cells and accumulation of ascitic fluid. The tumor microenvironment in malignant ascites is actively involved in cancer progression and is becoming an attractive therapeutic target. It is increasingly clear that both biotic and abiotic factors in the microenvironment play a crucial role in disease progression. Using a three-dimensional microfluidic platform that mimics the peritoneum, we previously demonstrated that physiologically relevant shear stress (1) induces chemoresistance and stemness in ovarian cancer cells, and (2) mediates tumor-mesothelial adhesion through P-selectin and its ligand sialyl-Lewis^x (sLe^x). Shear stress stimulated chemoresistant, stem-like ovarian cancer cells also showed a downregulation of microRNA(miR)-199a-3p, suggesting a previously unknown mechanosensitive property of this miRNA. In testing other microenvironmental factors known to be involved in ovarian cancer progression in the regulation of miR-199a-3p, we found that hepatocyte growth factor (HGF), which is abundant in malignant ascites, could decrease miR-199a-3p expression in a similar manner as shear stress. Both shear stress and HGF induced this downregulation through a transcriptional regulation of primary miR-199a-1, but not primary miR-199a-2, via c-Met/PI3K/Akt signaling pathway. Further, ectopic overexpression of miR-199a-3p could sensitize ovarian cancer cells to cisplatin, decrease their ability to form multicellular spheroids, and reduce tumor burden in an in vivo xenograft model of ovarian cancer, confirming a role for this miRNA in chemoresistance, stemness, and metastasis of ovarian cancer. Moreover, in clinical samples, a higher proportion of miR-199a-3p-high patient samples were sensitive to chemotherapy and patients stratified into high-risk groups had lower expression of miR-199a-3p and higher expression of Akt.

In order to elucidate the important determinants of tumor-mesothelial adhesion, the expression of sLe^x was compared in our in-house metastatic-(M-) and non-metastatic cancer stem cells (NM-CSCs), and it was found that M-CSCs exhibited a higher expression of sLe^x. This was associated with increased expression of sLe^x-synthesizing enzymes B4GALT4, ST3GAL3, ST3GAL4, and FUT5. Among these, FUT5 was found to be crucial for adhesion and its knockdown decreased the ability of ovarian cancer cells to adhere to P-selectin and mesothelial cells, and reduced peritoneal tumor burden in mice. Moreover, patient samples with higher expression of FUT5 had lower probability of survival, suggesting that it could serve as a prognostic factor in ovarian cancer. Taken together, these findings provide a mechanistic insight of shear stress mediated chemoresistance and tumor-mesothelial adhesion in ovarian cancer, and illustrates that miR-199a-3p and FUT5 are key mediators of the process.

--- ALL ARE WELCOME ---