The Role Of Macrophage Metabolism In Promoting Tumour Growth And Metastasis In Pancreatic Ductal Adenocarcinoma

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Abstract
Pancreatic Ductal Adenocarcinoma (PDAC) is the fourth leading cause of cancer death worldwide. Patients show poor survival due to its exceptionally high metastatic rate. Despite pronounced epithelial-to-mesenchymal transition (EMT) observed at inflammatory foci within the tumor, the immunological basis for the extensive tumor dissemination is unclear. While it is well established that tumor cells preferentially use glycolysis for energy production, it is unknown if immune cells also exhibit Warburg metabolism. We, therefore hypothesized that tumor infiltrating macrophages exhibit altered metabolic profile in PDAC, conferring a pro-metastatic phenotype.

We generated macrophages in vitro by culturing human monocytes with conditioned-media from either normal pancreatic or PDAC cell lines to obtain steady-state and tumor-associated macrophages (TAMs) respectively. Compared with steady-state macrophages, TAMs augmented vascular network formation, promoted extravasation of tumor cells out of blood vessels, and induced higher levels of EMT. This pro-metastatic phenotype correlated with a heightened glycolytic signature. Inhibiting glycolysis in TAMs with 2-deoxyglucose (2DG), a competitive inhibitor to Hexokinase II (HK2), was sufficient to disrupt this pro-metastatic phenotype, reversing the observed increases in TAM-supported angiogenesis, extravasation, and EMT.

Our results indicate a key role for metabolic reprogramming of tumor-infiltrating macrophages in PDAC metastasis, and highlight the therapeutic potential of using pharmacologics to modulate these metabolic pathways.

About Our Speaker
Wong Siew Cheng obtained her PhD from University College London, UK in 1999 under the supervision of Prof Elizabeth Shephard. She then returned to Singapore for her post-doctoral training in Prof Lam Kong Peng’s lab at the Institute of Molecular and Cellular Biology (IMCB) working on mouse adaptive immunity through the generation of knock-out mouse model. In 2006, she joined Prof Philippe Kourilsky’s lab in Singapore Immunology Network (SIgN) and subsequently set up her own lab in 2012 to work on innate immunity, focusing on monocytes and macrophages biology. The lab has utilised system approaches like transcriptomics and proteomics to characterize monocyte subsets in humans. Her current research interests also include deciphering the role of myeloid cells in tumour progression and metastasis.