Publications

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RESEARCH ARTICLE

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YWHAG Deficiency Disrupts the EMT-Associated Network to Induce Oxidative Cell Death and Prevent Metastasis

Jeannie Xue Ting Lee, Wei Ren Tan, Zun Siong Low, Jia Qi Lee, Damien Chua, Wisely Duan Chi Yeo, Benedict See, Marcus Ivan Gerard Vos, Tomohiko Yasuda, Sachiyo Nomura, Hong Sheng Cheng, and Nguan Soon Tan**

Metastasis involves epithelial-to-mesenchymal transition (EMT), a process that is regulated by complex gene networks, where their deliberate disruption may yield a promising outcome. However, little is known about mechanisms that coordinate these metastasis-associated networks. To address this gap, hub genes with broad engagement across various human cancers by analyzing the transcriptomes of different cancer cell types undergoing EMT are identified. The oncogenic signaling adaptor protein tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma (*YWHAG*) is ranked top for its clinical relevance and impact. The cellular kinome and transcriptome data are surveyed to construct the regulome of *YWHAG*, revealing stress responses and metabolic processes during cancer EMT. It is demonstrated that a *YWHAG*-dependent cytoprotective mechanism in the regulome is embedded in EMT-associated networks to protect cancer cells from oxidative catastrophe through enhanced autophagy during EMT. *YWHAG* deficiency results in a rapid accumulation of reactive oxygen species (ROS), delayed EMT, and cell death. Tumor allografts show that metastasis potential and overall survival time are correlated with the *YWHAG* expression level of cancer cell lines. Metastasized tumors have higher expression of *YWHAG* and autophagy-related genes than primary tumors. Silencing *YWHAG* diminishes primary tumor volumes, prevents metastasis, and prolongs the median survival period of the mice.

1. Introduction

Metastasis is a multistep process resulting in cancer cell dissemination from the primary site to distal organs, along with metabolic adaptation toward prevailing oxidative stress, deprivation of oxygen, and nutrients of the microenvironment at the foreign site. It is often associated with end-stage cancers.[1] Metastasis begins with cancer cells at the primary site undergoing epithelial-mesenchymal transition (EMT) to breach the basal lamina and invade surrounding tissues, followed by the disruption of adjacent endothelial cells to enter the systemic circulation, evade immune recognition, and survive anoikis before landing on a suitable secondary site. Metastatic cancer cells adapt to the new microenvironment and proliferate to form micrometastases and secondary tumors.[2] These metastatic cancer cells are resistant to many chemotherapeutic drugs and other therapeutic modalities, such as chemotherapy and radiotherapy. The complex nature of metastasis makes it a difficult therapeutic target because of its multisystemic spread and enhanced resistance to many anticancer therapies.[3] With metastasis accounting for over 90% of cancer mortality,[4] effective cancer treatment largely depends on our capacity to intercept the metastatic process. Although these clinical realities have been acknowledged for a long period, our capability to manage metastasis remains unsatisfactorily deficient.

EMT is a series of energy-demanding events that culminate in the metastatic dissemination of carcinomas.[5] During

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