NANYANG TECHNOLOGICAL UNIVERSITY

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Cancer, cellular transformation, cancer stem cell

The role of cytoplasmic EZH2 in cancer stem cells

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Co-supervisor/ Collaborator(s) (if any):

Project Description

a) Background:

We have reported that the histone methyltransferase, EZH2, controls leukocyte migration through interaction with the cytoskeleton remodeling effector, VAV, and direct methylation of the cytoskeletal regulatory protein, Talin[1]. However, it is unclear whether this extra-nuclear, epigenetic-independent function of EZH2 has a profound impact on the initiation of cellular transformation and metastasis.

Our recent data showed that cytosolic EZH2 was enriched in breast cancer stem cells and overexpression of EZH2 promoted adhesion turnover and tumorigenesis in a VAV interaction-dependent manner[2]. This transforming capacity was abolished by targeted disruption of EZH2 interaction with VAV[2]. Collectively, our results suggest a critical role for the VAV interaction-, Talin1 methylation-dependent, extra-nuclear action of EZH2 in neoplastic transformation.

b) Proposed work:

To further investigate the subcellular distribution of EZH2 in primary human cancers, determine the mechanisms controlling the cytosolic localization of EZH2 in breast cancer stem cells and develop novel therapeutic strategies for cancer by targeting cytosolic EZH2, we proposed 3 complementary specific aims, which will make use of cell-biological, structural, biochemical and proteomic approaches, *in vitro* culture systems and *in vivo* mouse models.

Specific Aim 1: To establish the relevance of cytoplasmic EZH2 in primary cancer stem cells

Specific Aim 2: To determine the molecular mechanisms governing subcellular localization and functions of EZH2 in breast cancer stem cells

Specific Aim 3: Targeted disruption of VAV interaction-dependent oncogenic activity of EZH2

Here, we aim to provide mechanistic basis for developing novel therapeutic intervention strategies in the treatment of human cancers.

References:

1. Gunawan, M. et al. The methyltransferase Ezh2 controls cell adhesion and migration through direct methylation of the extranuclear regulatory protein talin. *Nat Immunol* **16**, 505-16 (2015).
2. Venkatesan, N. et al. EZH2 promotes neoplastic transformation through VAV interaction-dependent extranuclear mechanisms. *Oncogene* **37**, 461–477 (2017).

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