Discovery of new molecular targets to stop breast cancer metastasis

With the support by the National Natural Science Foundation of China, the research team led by Prof. Han WeiDong (韩卫东) at Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, and Prof. Zhou YuBin at the Institute of Biosciences and Technology, College of Medicine, Texas A&M University, recently reported a protein called TRIM59, as a key determinant of the migration mode, favors the breast cancer survival and metastasis, which was published in *PLoS Biology* (2018, 16(11): e3000051).

Change of cell morphology is critical for cancer cell motility and metastasis, which requires spatiotemporal control of the turn-over or stabilization of cell polarity signaling components. The tripartite motif (TRIM) family proteins, most of which have E3 ubiquitin ligase activity, play crucial roles in regulating the stability of critical proteins involved in cell migration. TRIM59 was reported to promote the progression of prostate, lung and gastric cancer. While these earlier studies are primarily centered on establishing the correlations of TRIM59 with cancer hallmarks such as cell cycle progression and apoptosis, the direct targets of TRIM59 and the molecular mechanisms underpinning the pro-oncogenic role of TRIM59 in breast cancer, particularly its involvement in advanced stages of malignant transformation (cancer invasion and metastasis), remain largely unexplored.

By combining the Cancer Genome Atlas (TCGA) data and cancer patient samples, Dr. Han and Dr. Zhou's group found that TRIM59 is frequently overexpressed in metastatic breast cancer, which is correlated with advanced clinical stages and reduced survival among breast cancer patients. *TRIM59* knockdown promoted apoptosis and inhibited tumor growth; while TRIM59 overexpression led to the opposite effects. Importantly, they uncovered TRIM59 as a key regulator of cell contractility and adhesion to control the plasticity of metastatic tumor cells. At the molecular level, they identified PDCD10 as a target of TRIM59. TRIM59 stabilized PDCD10 by suppressing RNFT1-induced K63 ubiquitination and subsequent p62-selective autophagic degradation. TRIM59 promoted PDCD10-mediated suppression of RhoA-ROCK1 signaling to control the transition between amoeboid and mesenchymal invasiveness. PDCD10 overexpression or administration of a ROCK inhibitor reversed *TRIM59* loss-induced contractile phenotypes, thereby accelerating cell migration and invasion, and tumor formation. These findings highlight the rationale for targeting deregulated TRIM59/PDCD10 to treat breast cancer.

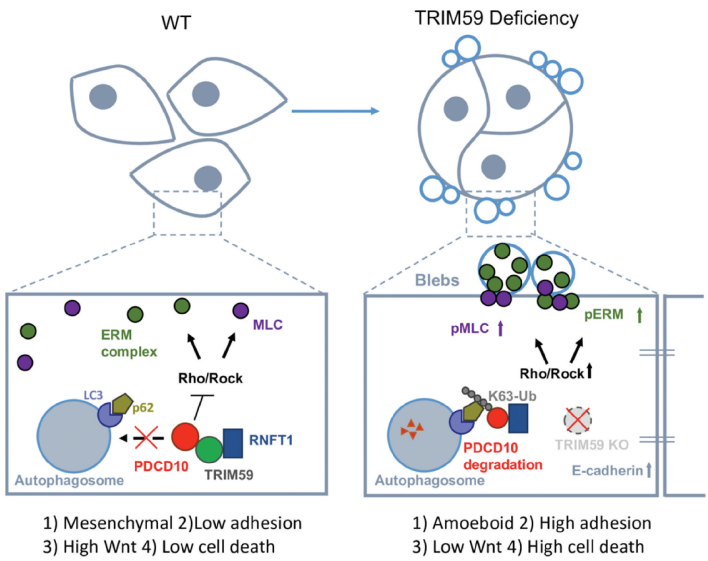

Figure TRIM59 depletion attenuates breast cancer cell survival and metastasis.