Chenyi Liu et al., J Cancer Sci Ther 2016, 8:9(Suppl)
http://dx.doi.org/10.4172/1948-5956.C1.084



## H3K4-specific histone methyltransferase *MLL3* regulates EMT in pancreatic cancer cells

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Pancreatic cancer is among the most devastating cancers with 5-year survival rate under 5%. Metastasis occurs in the majority of pancreatic cancer patients at the time of diagnosis, however, it is not clear what triggers metastasis. Currently, there is virtually no effective medicine for the disease. In addition to genetic alterations, epigenetic mechanisms have also been reported to play critical roles in tumourigenesis. *MLL3*, a histone methyltransferase, is a component of the ASCOM complex, which specifically di and tri-methylates lysine 4 of histone 3. The methylation is involved in the regulation of gene transcription and more specifically, tri-methylated H3K4 is a sign of active gene transcription. Sequencing projects find *MLL3* gene mutated at frequencies ranging from 1% to over 25% in 8 different cancer types including human pancreatic cancer and it is thus considered as a bona fide new cancer gene. A recent study finds that pancreatic cancer patients who have mutations in the ASCOM genes have poorer survival. In addition, *MLL3* is also shown to play roles in metastasis of esophageal squamous cell carcinoma. Using RNAi techniques to knockdown *MLL3* expression, we observed EMT-like morphological change in pancreatic cancer cell lines, which was confirmed by their enhanced mesenchymal marker vimentin expression. Flow cytometry analysis showed a clear negative correlation between vimentin and *MLL3* expression. Further, gene expression profile analysis with microarray showed that at least two other mesenchymal cell markers N-cadherin and Snail2 were also upregulated; meanwhile, an epithelial marker E-cadherin was downregulated. Furthermore, time-lapse wound-healing assay showed that those mesenchymal cells acquired enhanced migration ability. Very interestingly, using the list of over 1300 genes whose expression was found by the microarray to be up- or down-regulated in two or more folds after *MLL3* knockdown, to do a gene set enrichment analysis against normal stem or cancer stem cell signature expression gene sets, the gene list was found to be enriched for 3 types of stem cells, embryonic stem cell, embryonal cancer cell and hematopoietic stem cells. Since both EMT and the reverse MET are believed to be required for metastasis to occur, the stemness shown by cells subsequent to *MLL3* knockdown raises a possibility that tumor cells in patients acquire stemness through *MLL3* mutations which endows cells with flexibility to go through both EMT and MET, which in turn lead metastasis to occur. The stemness needs more study to be confirmed. Put together, alterations in *MLL3* may be one of mechanisms of cancer metastasis and further investigation may lead to discovery of new therapy targets for various cancers.

### Biography

Chenyi Liu has graduated with a BSc in Biochemistry from Fudan University, China and then worked in Shanghai Medical University. He has obtained his MSc in Medical Microbiology and BSc in Computer Science from University of Manitoba, Canada. He has also worked in Canadian Federal Government Laboratories for a few years. He is currently studpursuing PhD in the Department of Molecular Genetics of University of Toronto under supervision of Drs. Lincoln Stein and Andrew Emili.

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