Editorial

Genomic lesions drive the metastasis of esophageal squamous cell carcinoma

De-Chen Lin[1,2], H. Phillip Koeffler[1,2,3]

[1]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, USA; [2]Cancer Science Institute of Singapore, National University of Singapore, Singapore; [3]National University Cancer Institute, National University Hospital Singapore, Singapore

Correspondence to: De-Chen Lin. Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, USA. Email: De-Chen.Lin@cshs.org.

Provenance: This is an Invited Editorial commissioned by Section Editor Dr. Di Lu (Department of Thoracic Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China).

Comment on: Dai W, Ko JMY, Choi SSA, *et al*. Whole-exome sequencing reveals critical genes underlying metastasis in oesophageal squamous cell carcinoma. J Pathol 2017;242:500-10.

Submitted Aug 19, 2017. Accepted for publication Sep 05, 2017.
doi: 10.21037/jtd.2017.09.58
View this article at: http://dx.doi.org/10.21037/jtd.2017.09.58

Esophageal cancer ranks sixth in terms of cancer-associated mortality (1). The majority (over 80%) of esophageal cancers are squamous cell carcinomas (ESCC) (2), which is the leading cause of cancer-related death in its epidemic regions, such as northern China. Even with the advent of modern therapeutic approaches, the 5 years survival of ESCC (<20%) has not significantly improved in the past few decades. These facts necessitate the need for better characterization of the molecular basis of ESCC pathogenesis.

The dissemination and seeding of cancer cells from primary tumors to distant tissues is a complex, multi-step process. Clinically, tumor metastasis is, by and large, incurable and accounts for the majority of cancer-associated deaths. ESCC is no exception, in that the great majority of ESCC-associated deaths are caused by distal metastasis. Although the exome of more than 700 primary ESCCs have been sequenced over the years (3-8), genomic lesions associated with ESCC metastasis have not been systematic profiled. In a recent study (9), Dai *et al.* performed whole-exome sequencing to compare the genomic alterations between primary ESCCs and matched metastatic lesions in lymph node (LN), representing an initial effort to understand the genomic basis underlying ESCC metastatic process.

Not surprisingly, overall, more than half of the mutations in primary tumors were retained in the LN metastatic samples. These included known driven genes, including *TP53*, *KMT2D*, *RB1*, *CDKN2A*, *ZNF750*, *NOTCH3* and *TET2*. This is consistent with our recent finding that the majority of these significantly mutated genes (SMGs) tend to arise as early events during clonal evolution of esophageal tumorigenesis, albeit our results were based on a multi-region profiling in primary cases and computational modeling (10). We also suggested that a few activating mutations, such as those in *PIK3CA* and *NFE2L2*, might reinforce subclonal diversification in ESCC. However, due to the limited number of LN samples, Dai *et al.* did not observed such features in their cohort.

Notably, Dai and colleagues observed that mutations in *ZNF750* appeared more frequently in metastatic tumors than the primary ones. In addition, in silico analysis showed that ESCC individuals with *ZNF750* mutations were more likely to present LN metastasis, and to have shorter disease-free survival compared with those without *ZNF750* mutations. *ZNF750* is a novel tumor suppressor identified by our lab and others (5,11,12), and it exhibits frequent loss-of-function mutations and genomic deletions across different types of squamous cell carcinomas in a lineage-specific fashion. In vitro experiments have shown that *ZNF750* regulates the proliferation, differentiation, adhesion and migration of squamous cells, supporting its putative role in tumor metastasis.

Another interesting finding from this study is the metastatic-specific deletion of chromosome 6p22 in ESCC. The authors further showed that genes involved

in nucleosomal assembly were highly significantly enriched in this genomic segment. In addition, loss of these genes appeared to correlate with the survival time of ESCC patients. Considering that a few genes involved in nucleosomal assembly were found to contribute to the metastasis in other cancer types (13,14), these results warrant further investigations to establish the biological significance of the process of nucleosomal assembly in ESCC metastasis.

In summary, Dai and colleagues demonstrated a number of noteworthy genomic lesions associated with ESCC metastasis to the LN, which provides insights into the molecular changes during regional metastasis this cancer. Clearly, both larger number of samples and epigenomic approaches (15) are needed to further establish the biological, as well as clinical significance of these alterations. More importantly, samples from matched primary and distal metastatic tumors are required to dissect the biological features associated with the distant metastasis of this aggressive malignancy.

Acknowledgements

Funding: This work is supported by the National Research Foundation Singapore under its Singapore Translational Research Investigator Award (NMRC/STaR/0021/2014) and administered by the Singapore Ministry of Health's National Medical Research Council (NMRC), the NMRC Centre Grant awarded to National University Cancer Institute, the National Research Foundation Singapore and the Singapore Ministry of Education under its Research Centres of Excellence initiatives to HP Koeffler and DC Lin is supported by Tower Cancer Research Foundation.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241-52.
3. Gao YB, Chen ZL, Li JG, et al. Genetic landscape of esophageal squamous cell carcinoma. Nat Genet 2014;46:1097-102.
4. Song Y, Li L, Ou Y, et al. Identification of genomic alterations in oesophageal squamous cell cancer. Nature 2014;509:91-5.
5. Lin DC, Hao JJ, Nagata Y, et al. Genomic and molecular characterization of esophageal squamous cell carcinoma. Nat Genet 2014;46:467-73.
6. Sawada G, Niida A, Uchi R, et al. Genomic Landscape of Esophageal Squamous Cell Carcinoma in a Japanese Population. Gastroenterology 2016;150:1171-82.
7. Cancer Genome Atlas Research N, Analysis Working Group: Asan U, Agency BCC, et al. Integrated genomic characterization of oesophageal carcinoma. Nature 2017;541:169-75.
8. Lin DC, Wang MR, Koeffler HP. Genomic and Epigenomic Aberrations in Esophageal Squamous Cell Carcinoma and Implications for Patients. Gastroenterology 2017. [Epub ahead of print].
9. Dai W, Ko JMY, Choi SSA, et al. Whole-exome sequencing reveals critical genes underlying metastasis in oesophageal squamous cell carcinoma. J Pathol 2017;242:500-10.
10. Hao JJ, Lin DC, Dinh HQ, et al. Spatial intratumoral heterogeneity and temporal clonal evolution in esophageal squamous cell carcinoma. Nat Genet 2016;48:1500-7.
11. Zhang L, Zhou Y, Cheng C, et al. Genomic analyses reveal mutational signatures and frequently altered genes in esophageal squamous cell carcinoma. Am J Hum Genet 2015;96:597-611.
12. Hazawa M, Lin DC, Handral H, et al. ZNF750 is a lineage-specific tumour suppressor in squamous cell carcinoma. Oncogene 2017;36:2243-54.
13. Kaur E, Gupta S, Dutt S. Clinical implications of MTA proteins in human cancer. Cancer Metastasis Rev 2014;33:1017-24.
14. Wang Y, Zhang H, Chen Y, et al. LSD1 is a subunit of the NuRD complex and targets the metastasis programs in breast cancer. Cell 2009;138:660-72.
15. Jiang YY, Lin DC, Mayakonda A, et al. Targeting super-enhancer-associated oncogenes in oesophageal squamous cell carcinoma. Gut 2017;66:1358-68.

Cite this article as: Lin DC, Koeffler HP. Genomic lesions drive the metastasis of esophageal squamous cell carcinoma. J Thorac Dis 2017;9(10):3523-3524. doi:10.21037/jtd.2017.09.58

