A closer look at esophageal cancer through different lenses

De-Chen Lin
Department of Medicine, Cedars-Sinai Cancer, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA

ARTICLE INFO

Article History:
Accepted 9 August 2021
Available online xxx

Esophageal squamous cell carcinoma (ESCC) is highly aggressive and lethal, and yet it is understudied compared with other common cancers. Genome-guided therapies are still unavailable for ESCC patients, who suffer extremely poor clinical outcomes with a 5-year survival rate lower than 20% [1]. Undoubtedly, an urgent need exists for ESCC tumors at the transcriptional level. As an attempt to understand the most conserved and common alterations in ESCC, the researchers first performed integrated analysis of expression profiling of 718 ESCC patient samples from multiple published studies, representing the largest combined cohort so far. A total of 112 common differentially expressed genes were identified. This list of genes provides an important resource for the ESCC research community, given their robustness and reproducibility across different cohorts and platforms. In order to test functional essentiality of these dysregulated genes, the authors analyzed the dependency profile from ESCC cell lines using genome-wide CRISPR-Cas9 loss-of-function data from the DepMap database. A number of novel functional candidates were uncovered by this approach, such as HEATR1, TIMELESS, DTL, GINS1, RUVBL1, and ECT2, which warrant future experimental validations. In addition, enriched biological pathways were presented. Together, these results likely reflect the most conserved and common alterations in ESCC tumors at the transcriptional level. As an attempt to understand epigenetic mechanisms underlying the conserved transcriptional changes, ATAC-seq was conducted on 6 samples with matched RNA-seq data. However, likely owing to the limited size of ATAC-seq samples, only a small fraction of dysregulated genes showed expected changes in chromatin accessibility.

Having shown the converged and shared transcriptomic changes in ESCC, the authors next studied the other side of the coin: inter-tumor heterogeneity and its clinical significance. Using LASSO Cox regression analysis, Prognosis-related Subtype Classifier (PrSC) was generated which identified two subtypes in ESCC displaying distinct survival probabilities. Notably, the more aggressive subtype-1 (S1) tumors exhibited prominent signatures of stromal activation, with high scores in pathways such as TGF-beta signaling pathway, vascular smooth muscle contraction, angiogenesis, as well as fibroblast TGF beta response signature. Moreover, S1 tumors were more EMT-like, possibly due to the TGF-beta signaling pathway, a prominent EMT inducer.

To further understand the biology of S1 tumors, random forest analysis was performed which pinpointed the TNS1 gene as the top contributor to the survival classification. In line with the finding that S1 tumors had activated stromal signature, TNS1 was predominantly expressed in fibroblasts and smooth muscle cells. The authors further confirmed this using published single-cell RNA-Seq data of an ESCC mouse model [5]. Moreover, the percentage of Tns1+ fibroblasts was increased during the development of the murine ESCC, implying that Tns1+ fibroblasts might have pro-tumor functions. Encouraged by this result, the authors performed multiplex fluorescent immunohistochemistry on ESCC patient samples to investigate TNS1+ fibroblasts in the context of tumor microenvironment. Interestingly, patients with a higher proportion of TNS1+ fibroblasts in the stroma had lower infiltration of CD8+ T cells in the tumor parenchyma and showed an immune exclusion phenotype. Spatially, TNS1+ fibroblasts resided near CD8+ T cells in the stroma, implying possible crosstalk between these two types of stromal cells in the ecosystem of ESCC.

Finally, the researchers sought to associate subtype-specific transcriptomes to drug sensitivity, hoping to provide mechanistic basis for the development of personalized treatment strategies. To achieve this, a ridge regression model was employed to mathematically infer the ESCC tumors’ sensitivity to libraries of drugs based on the transcriptomic and drug screen data from public databases. As a result, 15 and 40 inhibitors were predicted to be more effective against S1 and S2 tumors, respectively. Interestingly, Nintedanib, which has anti-angiogenic and anti-fibrotic activities [6], was the most significant S1-specific drug, congruent with the above results that S1 tumors showed increased activities of angiogenesis and fibroblast cell infiltration. Finally, a couple of the predicted chemicals were experimentally validated using ESCC cell lines in vitro.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.1035510.
E-mail address: De-Chen.Lin@cshs.org

https://doi.org/10.1016/j.ebiom.2021.103545
2352-3964/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
To sum up, by integrating over 700 transcriptomes of patient tumors, this work identified highly conserved and common gene expression changes in ESCC. On the other hand, taking advantage of this large cohort, the researchers investigated inter-tumor heterogeneity and revealed two subtypes with distinguishing biological features, survival probabilities as well as sensitivities to various inhibitors. Focusing on the more aggressive subtype, a novel population of TNS1+ fibroblasts was uncovered which might play a role in the tumor microenvironment via crosstalk with CD8+ T cells. Clearly, these results bring several interesting questions which require future studies. For example, is TSE1 a functional driver or a biomarker for TSE1+ fibroblasts? What is the biological basis of the interplay between TSE1+ fibroblasts and CD8+ T cells? Are TSE1+ fibroblasts also present in other cancer types? What is the mechanism underlying the differential responsiveness of S1 and S2 tumors to different drugs? Addressing these questions will have significant implications in both basic and translational research in the field of ESCC.

Declaration of Competing Interest

I declare no conflicts of interest.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30. doi: 10.3322/caac.21590.
[2] Hao JJ, Lin DC, Dinh HQ, Mayakonda A, Jiang YY, Chang C, Jiang Y, Lu CC, Shi ZZ, Xu X, Zhang Y, Cai Y, Wang JW, Zhan QM, Wei WQ, Berman BP, Wang MR, Koefler HP. Spatial intratumoral heterogeneity and temporal clonal evolution in esophageal squamous cell carcinoma. Nat Genet 2016;48:1500–7. doi: 10.1038/ng.3683.
[3] Lin DC, Wang MR, Koefler HP. Genomic and epigenomic aberrations in esophageal squamous cell carcinoma and implications for patients. Gastroenterology 2017. doi: 10.1053/j.gastro.2017.06.066.
[4] Li Y, Fengkai X, Chen F, Chen Y, Ge D, Zhang S, Lu C. Transcriptomics based multi-1 dimensional characterization and drug screen in esophageal squamous cell carcinoma. EBioMedicine. 2021. doi: 10.1016/j.ebiom.2021.103510.
[5] Yao J, Cui Q, Fan W, Ma Y, Chen Y, Liu T, Zhang X, Xi Y, Wang C, Peng L, Luo Y, Lin A, Guo W, Lin L, Lin Y, Tan W, Lin D, Wu C, Wang J. Single-cell transcriptomic analysis in a mouse model decipheres cell transition states in the multistep development of esophageal cancer. Nat Commun 2020;11:3715. doi: 10.1038/s41467-020-17492-y.
[6] Yamasaki Y, Kuwana M. Nintedanib for the treatment of systemic sclerosis-associated interstitial lung disease. Expert Rev Clin Immunol 2020;16:547–60. doi: 10.1080/1744666X.2020.1777857.