#40P Evolutionary trajectories and clonal migration underlying tumor progression and lymph node metastasis in resectable lung cancer

Rong Yin[1*], Siwei Wang[1], Cheng Wang[2], Jingyuan Zhang[3], Ming Li[1], Feng Jiang[1], Xiaojun Fan[4], Min Wu[4], Hua Bao[4], Ruoying Yu[4], Xue Wu[4], Yang Shao[4,5], Lin Xu[1*]

[1]Department of Thoracic Surgery, Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China; [2]Department of Epidemiology and Biostatistics, International Joint Research Center on Environment and Human Health, Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, China; [3]Department of Pathology, Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China; [4]Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China; [5]School of Public Health, Nanjing Medical University, Nanjing, China. * Corresponding authors.

Background

- Progression and metastasis of early-to-mid stage lung cancers exhibited great diversity and have not been systemically studied to date.
- Evolutionary genomics underlying lung cancer progression and metastasis may provide guidance for patient stratification and personalized disease management.

Methods

- We collected 160 primary tumors (PTs, 474 region) and 112 lymph node metastases (LNMs) from 125 patients with stage I-III resectable lung cancer and performed targeted sequencing.
- We reconstructed the sample phylogeny of each patient and investigated evolutionary subtypes of PTs and metastatic trajectories of LNMs at the clonal resolution.

Results

- In progressive clonal evolution of PTs, intratumor heterogeneity decreased with tumor growth while Ki67 index increased with tumor differentiation.
- We categorized lung adenocarcinomas (LUADs) into 7 evolutionary subtypes and elaborated their correlation with clinicopathological features.
- We identified *NF1* and *TP53* mutations as potent metastatic drivers and unfavored prognostic markers for metastasis-free patients (P = 0.021 and 0.0017, respectively).
- The majority of LNMs (67.9%) were seeded polyclonally, among which three cases showed profound evidence for LNM-mediated metastasis.
- Multiple metastases of distinct evolutionary origins indicated higher risk of relapse than those of common origins.

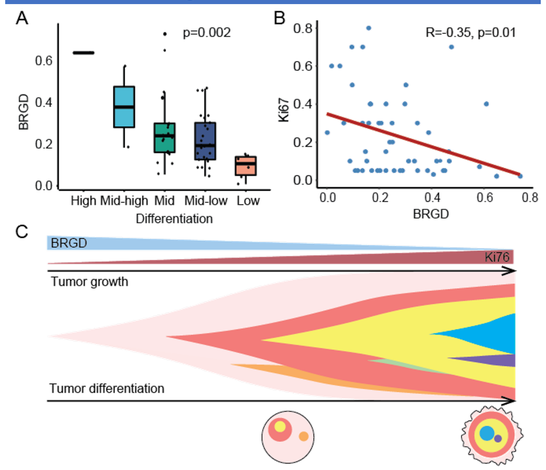
References

1. Roth, Andrew, et al. *Nature methods* 11.4 (2014): 396-398.
2. Niknafs, Noushin, et al. *PLoS computational biology* 11.10 (2015): e1004416.
3. Caravagna, Giulio, et al. *Nature methods* 15.9 (2018): 707-714.

Disclosure

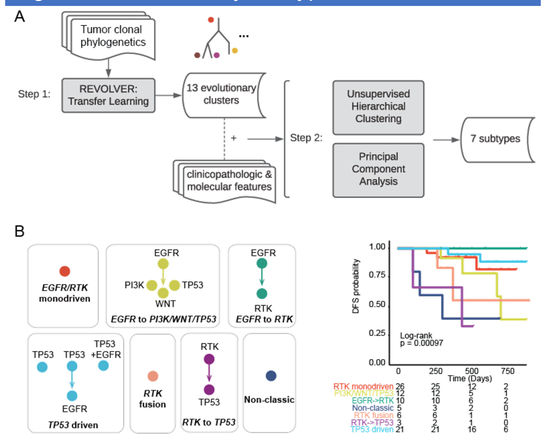
X.F., M.W., H.B., R.Y., X.W., and Y.S. are employees of Nanjing Geneseeq Technology Inc. All remaining authors have declared no conflict of interests.

Figure 1. Intratumor clonal heterogeneity decreased during tumor differentiation



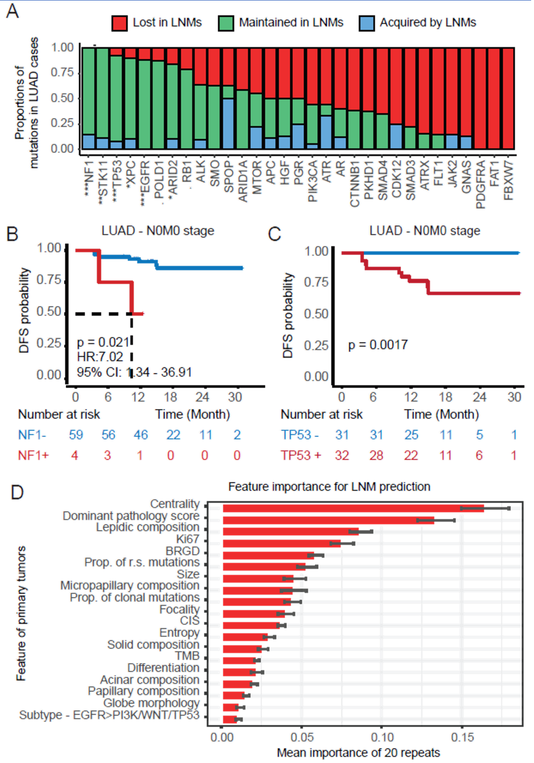
A). Between-region genetic divergence (BRGD) of LUADs of different differentiation grades. B). Correlation of Ki67 index and BRGD in LUADs. C). Schematic diagram illustrating the trend of BRGD and Ki67 during tumor differentiation.

Figure 2. Evolutionary subtypes of LUADs



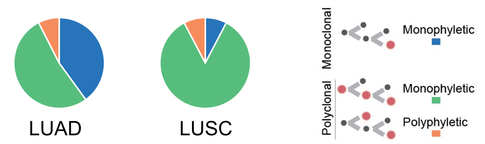
A). Workflow for evolutionary subtype inferences.[1,2,3] B). Disease-free survival analysis of LUAD patients stratified by seven evolutionary subtypes.

Figure 3. Potent metastatic drivers in LUADs



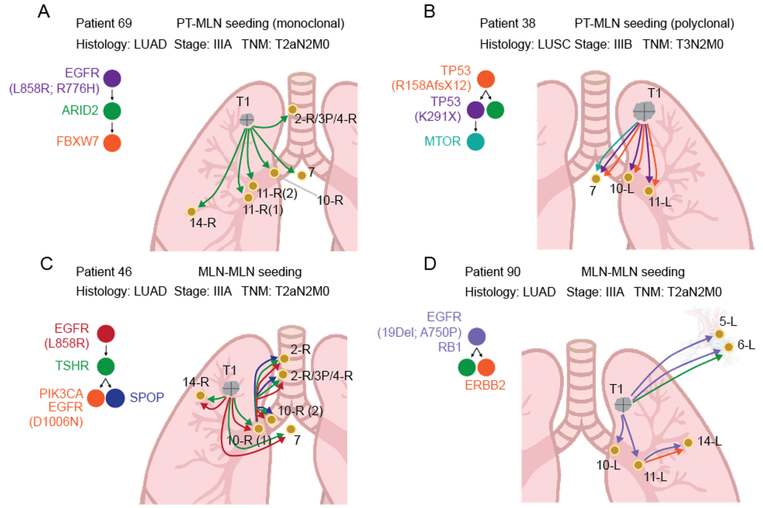
A). Mutations that were more prevalent in LNMs. B-C). Disease-free survival analysis of N0 stage patients stratified by *NF1* (B) and TP53 (C) mutations. D). Importance of clinicopathological and genomic features for predicting LNM status through a machine learning algorithm.

Figure 4. Clonality patterns of LNMs



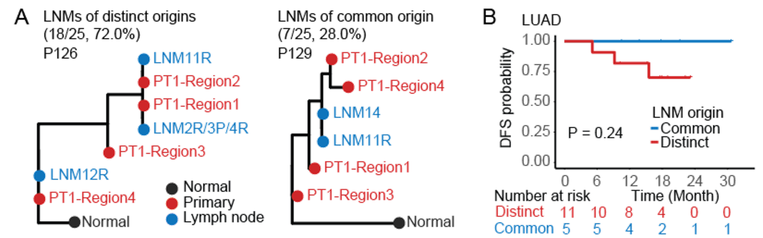
Proportions of LNMs that originated from mono- and poly-clonal seeding in LUAD and LUSC cases

Figure 5. Representative cases of LNM patterns



A). Representative case of monoclonal seeding from LUAD. B). Representative case of polyclonal seeding from LUSC. C-D). Representative cases of LNM-mediated metastasis.

Figure 6. Prognostic indication of multi-LNM cases



A). Representative cases of multiple LNMs that originated from distinct (P126) and common (P129) phyletic origins. B). Disease-free survival analysis of multi-LNM LUAD cases stratified by modes of phyletic origins.

Conclusions

- Our results depict the evolutionary patterns of PTs and LNMs in patients with resectable lung cancers. Features such as evolutionary subtypes of PTs and phylogenetic origins of LNMs may serve as prognostic markers, highlighting the clinical significance of evolutionary genomics in the understanding of tumor progression and disease management.