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

S. Wang1, C. Wang2, J. Zhan3, M. Li4, F. Jiang5, X. Fan3, M. Wu6, H. Hao7, R. Yu8, X. Wu9, Y. Shao10, L. Xu11, R. Yin12

1Department of Thoracic Surgery, Jinqiao Key Laboratory of Molecular and Translational Cancer Research, Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China; 2Department 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; 3Department of Pathology, Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China; 4Department of Research and Development, Nanjing Geneseeq Technology Inc., Nanjing, China

Background: Progression and metastasis of early-to-mid stage lung cancers exhibited great diversity and have not been systematically 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 regions) 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 clonal diversity increased with tumor differentiation. NF1 and RB1 mutations were selected during clonal sweep. We categorized lung adenocarcinomas into 7 evolutionary subtypes and elaborated their correlation with clinicopathological features. Some with late-acquired TP53 mutations indicated worse DFS than those initiated by TP53 mutations (HR = 7.98; P = 0.0070). We further identified NF1 and TP53 mutations as potent metastatic drivers and unfavored prognostic markers for metastasis-free patients (P = 0.021 and 0.0017, respectively). An overall trend of sequential metastatic spreading was observed, on the basis of which we envisaged fine classifications of seeding modes by clonality and trajectories. The majority of LNMs (67.9%) were seeded multyclonally, among which three cases showed profound evidence for LN-mediated metastasis. Moreover, multiple metastases of distinct evolutionary origins indicated higher risk of relapse than those of common 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 for optimal treatment in lung cancer patients. Our study highlights the clinically significant identification of evolutionary genomics in the understanding of tumor progression and disease management.

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41P Testosterone level and severity of COVID-19 infection in ambispective cohorts: The TESTOVID study

J. Noel1, A. Sabouret1, E. Auclin1, J.B. Arlet1, B. Hermann2, J.L. Diehl2, J.S. Hulot3, C. Wang2, J. Zhang3, M. Li1, F. Jiang1, A. Blanchard3, S. Brabant2, C. Wang2, J. Zhang3, M. Li1, F. Jiang1, A. Blanchard3, S. Brabant2

1Oncology, Hospital European George Pompidou, Paris, France; 2Intensive Care, Hospital European George Pompidou, Paris, France; 3Centre d’Investigations Cliniques, Hospital European George Pompidou, Paris, France; 4Vascular Medicine, Hospital European George Pompidou, Paris, France; 5Maladies Infectieuses, Hospital European George Pompidou, Paris, France; 6Biostatistics, Hospital European George Pompidou, Paris, France; 7Physiology, CHU Lille, Lille, France; 8Oncology, APHP Hospital European George Pompidou, Paris, France; 9Nephrology, Hopital Necker, Paris, France; 10Epidemiology, Hopital Bichat, Paris, France; 11INSERM, Hopital Bichat, Paris, France; 12Recherche Clinique, Institut Pasteur, Paris, France; 13Medical Oncology, Hospital European George Pompidou, Paris, France

Background: Lower risk of COVID-19 was reported in men with prostate cancer receiving androgen deprivation therapy while low levels of testosterone (T) were associated with a more severe disease and poor clinical outcomes in COVID-19 male patients (pts). In the latter case, it is unclear whether low levels of T and dihydrotestosterone (DHT) are risk factors or consequences of COVID-19. Here, we investigated T and DHT levels impact on COVID-19 severity in ambispective cohorts of symptomatic SARS-CoV-2 infected males.

Methods: Both prospective (European Hospital Georges Pompidou patients, P-cohort) and retrospective (French COVID-19 cohort, Réalising project, R-cohort) cohorts included male pts admitted for severe COVID-19. The P-cohort included pts admitted in a medical unit (non-ICU) or in ICU immediately (ICU-I). The R-cohort included pts admitted to a medical unit, ICU or to ICU secondarily (ICU-S). The size of ICU-S pts group in P-cohort was insufficient to include their data in the analysis. We collected information on pts demographics and COVID-19-related outcomes. T, DHT levels and inflammation markers were measured. Wilcoxon-Mann-Whitney test and chi²-test (or Fisher’s exact test, if appropriate) were performed. All tests were two-sided at 0.05 significance level.

Results: The P-cohort included 71 pts (median age: 64 years) and the R-cohort 89 pts (median age: 62 years). The median duration between admission and measurement of hormone levels was 2 days (range: 0-16) and 0.5 days (range: 0-11) respectively. T and DHT levels were low in all pts as compared to standards and even lower in ICU pts (Table). In the R-cohort, T and DHT lowest values were observed for ICU-I pts and median values for ICU-S pts.

| Hospital stay (days) | Death (%) | T (nmol/l) | DHT (nmol/l) |
|----------------------|-----------|-----------|--------------|
| Non-ICU          | ICU-I     | P         | Non-ICU      | ICU-I     | P      |
| n=22             | n=49      | p         | n=44         | n=24      | p    |
| 7.23              | 25.71     | 0.001     | 8.26         | 15.5      | 0.001 |
| 22                | 37.5      | 0.002     | 2.27         | 19.05     | 0.002 |
| 5.55              | 2.36      | 0.001     | 6.28         | 2.59      | 0.011 |
| 0.5               | 0.25      | 0.012     | 0.75         | 0.34      | 0.56  |
| 0.045             |           |           |              |           |       |

Conclusion: Low T and DHT levels were associated with the severity of the disease and the poorest clinical outcomes in males with severe COVID-19. This suggests that COVID-19 may cause a rapid and profound decrease in androgens levels and that T and DHT serum levels may be used as prognostic markers.

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42P Analysis of canonical uveal melanoma aberrations in murine uveal melanocytes

Y. Sayegh1, J.N. Kuznetsoff, S. Kurtenbach, J.J. Dollar, J.W. Harbour

Ophthalmology, University of Miami, Bascom Palmer Eye Institute/Sylvester Comprehensive Cancer Center, Miami, FL, USA

Background: Uveal melanoma (UM) is the most common cancer of the eye. Previous research has identified three key driver mutations in UM tumorigenesis: 1) gain of function GNAi2 signaling pathway mutations, 2) BAP1 loss of function mutations, and 3) aberrant expression of PRAME. However, the combined impact of these aberrations is not known. The purpose of this study was to characterize the phenotype of uveal melanocytes harboring one or more of these aberrations.

Methods: Uveal melanocytes were isolated from adult and neonatal murine choroid and were genetically engineered to express one or more of the three canonical aberrations. Phenotypic and transcriptional assays were performed to assess phenotypic changes.

Results: The stepwise addition of these aberrations resulted in progressive deregulation of transcriptome, morphology, and growth properties resembling findings in human uveal melanoma.

Conclusions: This unique genetically engineered mouse uveal melanocyte model will be invaluable for understanding how the progressive genetic evolution of human uveal melanoma results in increased malignant propensity.

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