AB008. Activated pathways of Thymic Epithelial Tumors: a RYTHMIC study

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Background: Thymic epithelial tumors (TETs) are rare malignancies of the anterior mediastinum with a high histopathological diversity from thymoma A to thymic carcinoma (TC). The biology of TETs is poorly understood and knowledge of the transcriptomic fingerprint of thymoma and TC is limited. Up to 30% of patients will develop associated autoimmune disorders, mainly myasthenia gravis (MG). We aimed to characterize main cancer activation pathways of TET subgroups.

Methods: We selected a representative balanced set of thymoma and TCs to analyze 24 main cancer activation pathways using gene expression throughout Oncology biomarker panel (2,562 genes). Tumor representative paraffin-embedded blocks were macrodissected. Then, we merged data with The Cancer Genome Atlas (TCGA) data (profiles with >30% tumor cellularity kept). We correlated epidemiologic, clinical and pathological characteristics of patients with genes expression based on cancer Hallmarks and immunedeconv (v2.0.4).

Results: Three hundred and fourteen patients were included, including 120 from TCGA. Median-age at diagnosis was 52 (10–84). Fifty two percent were women. Eighty four out of 314 (26.7%) reported MG, mostly in thymoma B2 (11,4%) and B3 (8%) but none for TC. AB was the most frequent thymoma subtype (n=70, 22.3%), followed by B2, B1, B3, A and TC. RNA expression analysis identified 3 main molecular subgroups or clusters, distribution of histological subtypes among them was diverse (P<0.0001). Cluster 1 was represented meanly by thymic carcinoma, cluster 2 was associated to thymoma type B and Cluster 3 to thymoma type A and AB. Activated pathways of histological subtypes were as follows: thymoma A showed activation of angiogenesis, Hedgehog and Notch hallmarks, as for thymoma AB; thymoma B1 and B2 showed cell cycle checkpoint factors activated pathway; thymoma B3 protein secretion pathway and; TC Epithelial to mesenchymal transition (EMT), MTOR1 and MYC pathways. Then, we analyzed activated pathways of the 3 molecular subgroups: cluster 1, with the worst prognostic, was associated to inflammatory signaling, MTOR1, KRAS and EMT pathways; cluster 2, with the best prognostic, showed activated cell control transcription factors hallmark and; cluster 3, showed cell differentiation activated pathway. We found a difference in the presence of B and T-cells among clusters and thymoma subtypes. Cluster 1, thymoma A and TC showed higher representation of B-cells (P<0.0001, respectively) and regulation T-cells (Treg) (P<0.0001, respectively); in contrast, cluster 2 and thymomas AB and B a higher proportion of CD8+ T-cells (P<0.0001, respectively). Interestingly, non-regulatory CD4+ T-cells did not show significantly results in any subset. Of note, Macrophages M1 were presented in cluster 1 and M2 in cluster 3 (P<0.0001, respectively). Median follow-up was 35 months [95% confidence interval (CI): 27.03–42.96 months]. Median-OS was 350 months (NR-NR). Cluster 1 showed a poorer prognostic (median-OS of 74 months vs. NR and NR; P<0.0001) comparing to cluster 2 and 3, respectively.

Conclusions: We describe differential molecular characteristics among histological subgroups in 3 molecular subgroups. Clusters were significantly associated to survival outcomes and showed distinguish activated cancer pathways. The analysis suggests new therapeutic venues.

Keywords: Thymoma; thymic carcinoma (TC); molecular subtypes

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-22-ab008/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

doi: 10.21037/med-22-ab008

Cite this abstract as: Benitez JC, Job B, Thomas de Montpréville V, Florez-Arango J, Lacroix L, Saulnier P, Arana R, Lambotte O, Mussot S, Mercier O, Fade E, Scoazec JY, Molina T, Girard N, Besse B. AB008. Activated pathways of Thymic Epithelial Tumors: a RYTHMIC study. Mediastinum 2022;6:AB008.