AB007. OS02.01. The integrated genomic landscape of thymic epithelial tumors: a report by the TCGA research network

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Background: Thymoma and thymic carcinoma are the most common malignancies of the anterior mediastinum. Additionally, thymoma has a unique association with autoimmune disorders, notably myasthenia gravis (MG). Histologic classification of thymic epithelial tumors (TETs) has been largely based on the gross description of the epithelial cell appearance and the relative abundance of associated lymphocytes. A comprehensive molecular analysis of TETs has not heretofore been conducted.

Methods: The TCGA Research Network conducted multi-platform analyses of 117 TETs (thymoma =105; thymic carcinoma =10 and micronodular thymoma =2), which included whole-exome, transcriptome, methylome and targeted proteome analysis. Patient characteristics: median age =60 years (range, 17–84 years); M:F (%) =52:48; Masaoka stage {I [36], IIA [39], IIB [19]; III [15]; IVA [1]; IVB [5]}; MG was present in 32 patients. No patient had prior therapy for metastatic disease, but 14 had prior chemotherapy and 39 had prior radiation therapy in the adjuvant setting. WHO histologic classification (blinded review) revealed A =10; AB =48, B1 =12, B2 =25, B3 =10, micronodular thymoma =2 and TC =10.

Results: Thymoma has the lowest tumor mutation burden among adult malignancies in the TCGA. A unique transcription factor, GTF2I, was the most commonly observed mutation in WHO Types A and A/B. All GTF2I mutations were exclusively at the amino acid 424 locus. This is the only tumor with this specific mutation within the entire TCGA database. Differential expression of the RNA and protein data revealed dysregulation of several oncogenic pathways in GTF2I mutants *vs.* wild-type. Oncogenic HRAS, NRAS and TP53 mutations were also observed, but at a lower frequency among all TETs. We further describe an MSI-unstable thymic carcinoma that was hyper-mutated. Using multi-platform analyses, four distinct molecular-driven subtypes of TETs were identified that strongly correlated with the current WHO histologic classification and were associated with survival. Genomic hallmarks of these subtypes were identified to aid pathologic diagnosis. Lastly, when comparing MG-positive *vs.* -negative thymomas, we observed increased aneuploidy and overexpression of muscle auto-antigens in MG-positive tumors, providing a pathophysiologic link between thymoma and MG.

Conclusions: Based on molecular analysis, four clusters were identified that correlated strongly with the current WHO Histologic Classification. Also identified was a unique mutation in GTF2I, which was associated with WHO Type A and A/B thymoma. Lastly, a molecular link between MG and thymoma characterized by increased aneuploidy and tumoral over-expression of muscle auto-antigens was observed.