AB012. Transcriptional and chromatin profiling reveals the molecular architecture and druggable vulnerabilities of thymic epithelial tumors (TETs)

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Abstract: Thymic epithelial tumors (TETs) have been profiled to the present moment mainly through several analyses of FFPE samples. Despite the leap forward brought by the TCGA, several questions remain still unsolved. Among these, TETs are characterized by a strong component of immune infiltrate which makes the transcriptomic analyses conducted so far scarcely interpretable to profile stromal subpopulations constitutive of the tumor. Furthermore, rarely correspondent healthy tissue is available due to the lipomatous atrophy of aged thymi. Therefore, the recent report of (I) isolation, (II) propagation (III) and characterization of human thymic epithelial cells (TECs) and their capacity to reconstitute the functional organ *ex vivo* and *in vivo*, represents a novel approach to study the biology of both healthy and neoplastic thymi. Human thymic biopsies (both healthy and neoplastic) were digested and plated on a lethally irradiated murine feeder layer. Both RNA-Seq and CUTANDTAG were performed on cultivated TECs at different passages. Cultured TECs were injected with human thymic interstitial cells into rat decellularized scaffolds and cultivated for 10–12 days. sc-RNA Seq is currently being performed on both healthy and neoplastic thymic mini-organs and their correspondent primary tissues. We have successfully cultivated a cohort of 21 clonogenic TECs *in vitro* including adult neoplastic TECs, their non-tumoral counterpart and pediatric TECs. We show that at the transcriptome level each class of TECs clusters independently and that neoplastic TECs belong to the same cloud independently from thymoma histotype. Around 1,400 differentially expressed genes (DEGs) can be found when comparing adult neoplastic cells TECs and their non-neoplastic counterpart, among which around 70 are transcription factors. Importantly, we prove for the first time that clonogenic TECs derived from TETs can repopulate a decellularized rat scaffold and recreate a 3D architecture mimicking the primary tumor. This work demonstrates that this culture system allows the expansion of clonogenic TECs from both tumor samples and their non-tumoral counterpart. Those cells, when transplanted into decellularized thymi, reproduce the architecture of the primary tissue, showing that TETs contain progenitor/stem epithelial cells. We are currently characterizing TECs at the transcriptomic and epigenomic level with aim of identifying new druggable targets prior their entry into clinical trials.

Keywords: Thymoma; thymic epithelial cells (TECs); miniorgan; stem cells

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Footnote

Conflicts of Interest: PB and AG are named inventors of

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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.

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