

CHARACTERIZATION OF ALTERED IMMUNITY IN ANAPLASTIC THYROID CANCER

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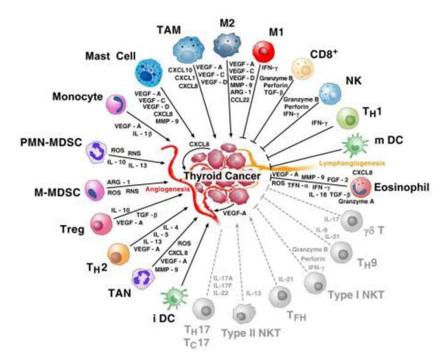
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Background

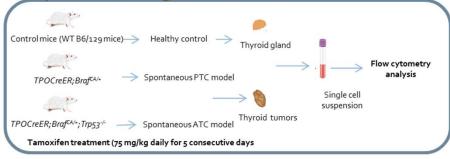
- Anaplastic thyroid cancer (ATC) occurs in less than 2% of all thyroid cancer cases, and it is almost uniformly lethal with an average median survival of 6 months (Manikas et al; JAMA Oncol, 2020)
- ATC is very aggressive and spreads rapidly within the neck and metastasizes to distant parts of the body, which makes it resistant to standard therapy (surgery, radioactive iodine therapy and chemotherapy) (Zhang et al; EJMC, 2022)
- The mutational landscape of ATC is very complex compared to other forms
 of thyroid cancer, including Papillary (PTC) and Follicular (FTC), due to
 multiple mutations in oncogenes and tumor suppressors (Cancer Genome
 Atlas Research N; Cell, 2014; Landa et al; JCl, 2016)
- Thyroid cancers are rich in immune cells, making them a reasonable candidate for immunotherapies (Varrichi et al; IJMS 2019)
- To develop new therapeutic strategies, further studies determining the immune cell composition of ATC that favors tumor progression are required



Hypothetical scheme of immune contexture of thysoid cancer (Varrichi et al; IJMS 2019)

Results

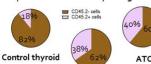
Experimental design



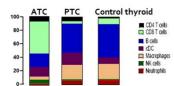
Cellular composition of ATC tumors

Hematopoietic cell distribution in ATC and PTC tumors compared to thyroid gland

· Higher infiltration of lymphoid immune cells in ATC and PTC compared to normal thyroid gland



Immune cell composition in thyroid tumors



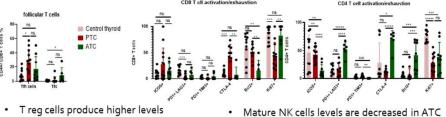
Percentage of immune cells among hematopoietic cells (CD45+)

Immune microenvironment in ATC

Lymphocyte subsets

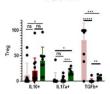
Higher infiltration of follicular CD8+ T cells (PD1+ CXCR5+) in ATC compared to PTC and normal glands

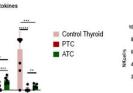
• Exhaustion markers (PD1+, LAG3+ and CTLA4+) expression is increased in CD4+ T cells in ATC

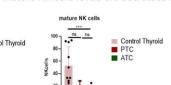


· T reg cells produce higher levels of IL17 in ATC







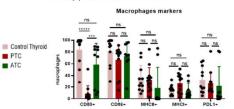


Myeloid subsets

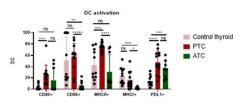
Percentages of hematopoietic (CD45.2+) and non hematopoietic

(CD45.2-) cells among total live cells

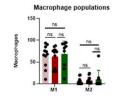
· Myeloid cells expressed decreased levels of T-cell activation molecules and increased levels of the suppressor factor PDL1

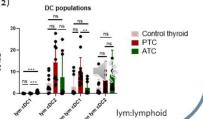


■ PTC



· ATC enriched in suppressor myeloid cells (cDC2 and M2)





Summary

- ATC tumor microenvironment is highly enriched with exhausted CD4+T cells expressing PD-1, LAG3 and CTLA-4
- ATC tumors are infiltrated with immunosuppressive myeloid cells, cDC2 and M2 macrophages, expressing high levels of PDL1
- Treg cells changed phenotype towards inflammatory Th17 cells in ATC

Future directions

- Assess the contribution of immune cells to ATC pathogenesis
- Evaluate the efficacy of cell-targeted and immune checkpoint blockade therapy in ATC model



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