NPC1 in cancer cell metastasis that has not been previously explored, and identifies cholesterol uptake as a targetable dependency in TNBC.

Adrenal

ADRENAL - TUMORS

Increased Telomere Length in Adrenocortical Tumors Is Associated with Abnormal Expression of Chromatin Remodelling Factors

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Background: The pathogenesis of adrenocortical tumors (ACTs) in the pediatric population is partially known, and few prognostic factors have been identified in this age group. Recently, ATRX and DAXX have been implicated in the pathogenesis and prognosis of a variety of cancers. Their altered function has been shown to affect telomere length through a telomerase-independent mechanism.

Objective: To investigate *ATRX* and *DAXX* gene expression, ATRX and DAXX protein expression, and telomere length, as well as their clinical significance, in ACT samples from pediatric patients.

Methods: The records of 110 pediatric patients with available ACT samples were reviewed. *ATRX*, *DAXX*, *TERT* and *TERC* gene expression was assessed by qPCR (n = 100 ACTs; n = 12 normal adrenals). ATRX and DAXX protein expression was assessed by IHC (n = 45 ACTs). Telomere length was assessed by qPCR (n = 64 ACTs). For survival analysis, Kaplan-Meier curves were obtained. For association analysis, simple linear regression models were adjusted.

Results: Most patients were female (70.9%) and harbored germline *TP53* mutations (90.2%). Median age at diagnosis was 21.1 months (2.1 – 199). Younger patients (< 3 years) had better survival ($p < 0.01$), while those with metastasis at diagnosis and carcinomas (classified by the Wieneke score) had worse survival ($p < 0.01$). *ATRX* gene expression was decreased ($p < 0.01$), while *DAXX* gene expression was increased ($p < 0.01$) in ACTs, compared to normal adrenals. *ATRX* gene expression was even lower in the context of the germline *TP53* (R337H) mutation ($p < 0.01$). *TERT* expression was not detected in ACTs or normal adrenals, and *TERC* expression was not altered ($p = 0.69$). ATRX protein expression was lost in the majority of ACTs (95.6%), while DAXX was lost in a minority (21.1%). There was no association between gene or protein expression and disease-free or overall survival. There was a significant association between decreased *ATRX* and *DAXX* gene expression and increased telomere length ($p < 0.01$ and $p = 0.03$, respectively).

Conclusion: In pediatric ACTs, decreased *ATRX* and *DAXX* gene expression was associated with increased telomere length, independently of *TERT* or *TERC* expression. In these tumors, *ATRX* gene expression was decreased and ATRX protein expression was overall lost, while *DAXX* gene expression was increased and DAXX protein expression was overall retained. No significant association between these alterations and prognosis was found in this cohort. These findings suggest that ATRX and DAXX altered function may be more involved in the pathogenesis of pediatric ACTs than in the prognosis of the affected patients.

Thyroid

THYROID AUTOIMMUNITY AND BENIGN THYROID DISEASE

Thyroid Function Test Abnormalities Secondary to Immune-Checkpoint Inhibitors: A Marker of Survival?

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Immune-checkpoint inhibitors (ICI) are monoclonal antibodies which target molecules to enhance antitumor response. Several adverse events have been described and the major ICI-related endocrinopathies are thyroid dysfunction and hypophysitis. Its occurrence has been associated with increased survival.

A retrospective study of adult patients treated with ICI between March 2014 and September 2019 at an oncologic centre was performed to evaluate the impact of thyroid function test abnormalities (TFTA) in their prognosis. We excluded patients without regular monitoring of thyroid function, with previous thyroid or pituitary disease (including medical and surgical treatments), previous head/neck radiotherapy and who performed only one ICI cycle. Clinical data of all patients were examined independently by two Endocrinologists. Survival analysis was performed using the Kaplan-Meier method. Cox regression was used to evaluate associations between the occurrence of TFTA and the outcome of overall survival (OS). It was adjusted for sex, age, primary neoplasm, tumor staging and ICI. All analyses were performed using IBM-SPSS v.25 and a level of significance α=0.05 was noted.

We included 161 of 205 patients, with a median age of 65 years [Interquartile range (IQR) 15] and 67% male. Most patients had melanoma (52%) and lung cancer (43%). Globally, 86, 59 and 25 patients were under pembrolizumab, nivolumab and ipilimumab, respectively. Median duration of ICI treatment was 4.4 months (IQR 7.7) and median total follow-up was 11.4 months (IQR 11.2). New onset TFTA was diagnosed in 18% of patients, at median age of 65 years (IQR 20) and 55% male. Almost half (45%) had primary hypothyroidism, 28% had central hypothyroidism and 13.8% had biphasic thyroiditis and thyrotoxicosis,