Somatic driver mechanisms of pituitary neuroendocrine tumor pathogenesis have remained incompletely characterized; apart from mutations in the stimulatory Gα protein (Gαs encoded by GNAS) causing activated cAMP synthesis, pathogenic variants are rarely found in growth hormone-secreting pituitary tumors (somatotropinomas). The purpose of the current work was to clarify how genetic and epigenetic alterations contribute to the development of somatotropinomas by conducting an integrated copy number alteration, whole-genome and bisulfite sequencing, and transcriptome analysis of 21 tumors. Somatic mutation burden was low, but somatotropinomas formed two subtypes associated with distinct aneuploidy rates and unique transcription profiles. Tumors with recurrent chromosome aneuploidy (CA) were GNAS mutation negative (Gsp-). The chromosome stable (CS) - group contained Gsp+ somatotropinomas and two totally aneuploidy-free Gsp- tumors. Genes related to the mitotic G1-S-checkpoint transition were differentially expressed in CA- and CS-tumors, indicating difference in mitotic progression. Also, pituitary tumor transforming gene 1 (PTTG1), a regulator of sister chromatid segregation, showed abundant expression in CA-tumors. Moreover, somatotropinomas displayed distinct Gsp genotype-specific methylation profiles and expression quantitative methylation (eQTM) analysis revealed that inhibitory Gα (Gαi) signaling is activated in Gsp+ tumors. These findings suggest that aneuploidy through modulated driver pathways may be a causative mechanism for tumorigenesis in Gsp- somatotropinomas, whereas Gsp+ tumors with constitutively activated cAMP synthesis seem to be characterized by DNA methylation activated Gαi signaling. IMPLICATIONS: These findings provide valuable new information about subtype-specific pituitary tumorigenesis and may help to elucidate the mechanisms of aneuploidy also in other tumor types [1].

Feng et al. found that the Notch2/Delta-like Notch ligand 3 (DLL3) signaling pathway was active in GHoma tumorigenesis, progression, and invasion. The γ-secretase inhibitor DAPT is of potential use in GHoma treatment targeting Notch signaling [2].

The aim of a study was to evaluate the effects of some widely diffused pollutants (i.e. benzene, BZ; bis(2-ethylhexyl) phthalate, DEHP and polychlorinated biphenyls, PCB) on growth hormone secretion, the somatostatin and estrogenic pathways, viability and proliferation of rat GH-producing pituitary neuroendocrine tumor (GH3) cells. All the pollutants induced a statistically significant increase in GH secretion and interfered with cell signaling. They all modulated the expression of SSTR2 and ZAC1, involved in the somatostatin signaling, and the expression of the transcription factor FOXA1, involved in the estrogen receptor signaling. Moreover, all the pollutants increased the expression of the CYP1A1, suggesting AHR pathway activation. None of the pollutants impacted on cell proliferation or viability. Present data demonstrate that exposure to different pollutants, used at in vivo relevant concentrations, plays an important role in the behavior of GH3 pituitary neuroendocrine tumor cells, by increasing GH secretion and modulating several cellular signaling pathways. These observations support a possible influence of different pollutants in vivo on the GH-adenoma aggressiveness and biological behavior [3].

1)
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