The comprehensive molecular and clinical characterization of Crooke's cell corticotroph pituitary neuroendocrine tumors

In the intricate landscape of endocrine disorders, pituitary neuroendocrine tumors (PitNETs) emerge not only due to their prevalence but also because of their complex nature. They account for nearly a fifth of all tumors found within the skull in adults. These tumors originate from the hormone-secreting cells of the pituitary gland and are classified based on their cellular origin and the hormones they impact. Among these diverse types, Crooke's cell corticotroph pituitary neuroendocrine tumors (CC-PitNETs) present a particularly daunting challenge. Making up a small fraction (1%) of all pituitary tumors, CC-PitNETs are characterized by their aggressive behavior and poor prognosis, frequently leading to rapid progression and high recurrence rates that defy standard treatments, resulting in severe health outcomes for affected patients. They are especially dangerous because they secrete adrenocorticotropic hormone (ACTH). This causes adrenal glands to secrete cortisol, leading to changes in body fat distribution, increased blood pressure, diabetes, heart disease, and mood disorders. These symptoms are also known as Cushing's disease, and CC-PitNETs are known to cause a particularly severe and relentless form of this disease.

Despite their significant impact, CC-PitNETs remain poorly understood, largely overshadowed by more prevalent types. The limited research on these tumors hampers effective diagnosis and treatment, leaving many aspects of their pathophysiology a mystery. By examining 32 samples of CC-PitNETs with three state-of-the-art techniques, we hope to map out the genetic and epigenetic alterations that drive these tumors. Here's what we're diving into:

RNA Sequencing: This technique is akin to a set of microphones that record instruments in the philharmonic. We can measure which instruments (genes) were played too much or too little, leading to the imbalanced symphony (CC-PitNET development). Like in a symphony, one can decide to focus on similar instruments, in RNA sequencing sets of genes that do certain things (e.g. make cells divide) can be examined together. We call this pathway analysis or gene set enrichment analysis and it is complementary to measuring each gene signal separately.

DNA Methylation Profiling: Like a conductor of the orchestra can make some instruments play quietly, a methyl group, added to the cytosine, can bring down gene expression. This molecular mechanism is utilized by many organisms (from bacteria to humans). Because DNA methylation is rather stable and not affected by temporary changes, it is often utilized to classify tumor samples into groups similar to each other (clusters).

Copy Number Abnormalities Analysis: In the musical analogy DNA copy number changes are similar to musicians losing their notes. The cell (orchestra) cannot perform properly when the instruction for making the genes (notes) go missing. This data is particularly useful in determining the order of events, leading to cancer development (which notes are lost first in the process of playing symphony out of tune).

The data from these analyses will not only be compared internally but also matched against a comprehensive database of nearly 700 molecularly profiled PitNETs from various subtypes, enhancing the understanding of how CC-PitNETs differ from or resemble other pituitary tumors. This database is available publicly, thanks to a commitment to open science in the pituitary research community around the world. Data generated in this project will be shared with the broader scientific audience freely but also responsibly (considering privacy concerns of the patients), as was done by our research team previously.

The potential impacts of this research are profound. By elucidating the molecular basis of CC-PitNETs, the study aims to identify novel biomarkers that could significantly improve diagnostic accuracy and prognostic assessments. Moreover, understanding the molecular pathways in depth may open new avenues for targeted therapies, offering hope for more effective treatment options tailored to the specific molecular characteristics of these tumors. Additionally, this project has the potential to redefine clinical approaches to managing PitNETs, advocating for more personalized and precise interventions based on genetic and epigenetic profiles.

Continued efforts of surgeons, neuroendocrinologists, pathologists, and molecular biologists led to the establishment of a first biobank, comprehensive enough to enclose 32 cases of CC-PitNETs. Never before have we faced a similar opportunity to characterize these tumors, answer why they are so notorious clinically, and if the mechanisms of aggressiveness are similar to these in other neoplasms. Ultimately, this project is more than a scientific endeavor; it represents a beacon of hope for patients grappling with a rare yet formidable opponent – the Crooke's cell corticotroph pituitary neuroendocrine tumor.