Macedonian pharmaceutical bulletin, 68 (Suppl 1) 595 - 596 (2022)
Online ISSN 1857 - 8969
DOI:10.33320/maced.pharm.bull.2022.68.03.285
Short communication

Current and future perspectives in laboratory analysis of Pituitary neuroendocrine tumors

Teodora Jovanova, Ivana Vichentijevikj*, Debora Petrevska, Elena Ilievska, Marija Hiljadnikova-Bajro

Faculty of Pharmacy, Ss Cyril and Methodius University in Skopje, Majka Tereza 47, 1000 Skopje, R.N. Macedonia

Introduction

Pituitary neuroendocrine tumors (PitNETs) are common, generally benign tumors with complex clinical manifestations related to hormone hypersecretion and/or growing sellar tumor mass. PitNETs do not only belong to a group of the most common intracranial neoplasms, accounting for approximately 15% of all intracranial tumors, but seem to be generally more common than has been thought and its incidence rate is increasing yearly. Since the symptoms of PitNETs may appear later on, a noninvasive specific biomarker is the instrumental key for timely diagnosis, precise prognosis, and monitoring of patient's response to the treatment. Only a particular group of selected biomarkers show promises in differentiating pituitary tumors, therefore, the most common and promising biomarkers and terms were analyzed, proposing the need for uniform design, application of methods and standardized criteria for correcting the interpretation of results. The new spectrum of biomarkers may shed light upon the pathogenetic mechanisms and also may serve as standardized diagnostic tool for daily pathologic practice.

Current practic

Current diagnostic laboratory analysis of pituitary tumors is based on evaluating the hypersecretion or hyposecretion of hormones produces by the gland or the dynamic of production over time. These hormones are used as tumor markers for pituitary tumors, but they can easily lead to wrong diagnosis or misreading of results, hence other tumor markers are currently used with predictive value (Kaltsas et al., 2005).

Proliferative Marker Ki-67- Antigen KI-67 is a nuclear protein that is associated with cellular proliferation. Several studies have suggested that Ki-67 values greater than 3% predict more aggressive tumor behavior (Sav et al., 2012).

Apoptosis - Apoptosis, or programmed cell death, is characterized by a rapid sequence of events aimed at destruction of damaged cells. In neoplasmas apoptosis is generally suppressed to allow tumor growth. In their article from 2012, Sav et al. have brought out several studies about the significance of apoptosis in PitNETs diagnostic. Most apoptotic activity was observed in corticotrope adenomas. Also hormone-secreting adenomas had higher apoptotic indices than non-functioning tumors. The highest apoptotic indices were observed in thyroid-stimulating hormone (TSH)-secreting adenomas, followed by growth hormone (GH)-, prolactin (PRL) - and mixed GH/PRL-secreting adenomas (all adenomas mentioned are PitNETs types).

p53- Expression of *p53* gene products is important for tumor biology. Although a p53 mutation has not been documented in PitNETs, *p53* immunoreactivity has been found to correlate with tumor invasiveness. A significantly higher p53 expression is reported for 'aggressive-invasive' tumors compared with those with less aggressive behavior (Sav et al., 2012).

In spite of their usefulness, these tests are usually invasive and we can't rely only on them. Therefore, in the next section we will present some new, still in development, tumor markers that have a great potential.

Novel tumor markers

DNA methylation abnormalities are pervasive in PitNETs. Grayson A. Herrgott (2022), suggested that similar to other CNS tumors, PitNETs release tumor-related information in the blood that allows the identification of clinically relevant methylation signatures specific to patients with PitNETs. For instance, a recent study has demonstrated the ability to detect somatic gene variants using plasma cfDNA in PitNETs, despite the rarity of somatic mutations in these tumors. Results provide evidence that PitNETs release DNA methylation markers

*ivana_vicentijevic@yahoo.com

in the serum/plasma and that blood-based liquid biopsies constitutes a reliable approach for the noninvasive detection of clinically relevant epigenetic signatures specific to PitNETs.

Micro-RNAs (miRNAs) are short, non-coding RNAs, which intercept mRNA transcripts and thus can disrupt protein translation. They are circulating in the plasma after leaking from PitNET and can be used in a liquid biopsy format. Several studies have reported the possible involvement of miRNAs in PitNETs tumorigenesis, invasion, and aggressiveness, demonstrating that some are able to behave as tumor suppressors and others as oncomiRs (microRNA (miRNA) that is associated with cancer), depending on the biological context, thus considering them to be possible therapeutic agents (Gossing et al., 2020; Donati et al., 2021).

Circulating tumor DNA (ctDNA) is a fragmented DNA released into the bloodstream by deceased tumor cells that retains all of its original genetic and epigenetic properties. There are specific driver mutations for PitNET-subtypes that can be used to identify the pituitary tumor's functioning or secretory subtype. USP8 mutations were discovered to be a key tumor-driving factor and highly specific for adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas. Genetic mutations in BRAF (17%) and USP48 (23%) associated with increased ACTH secretion have been discovered in corticotropic adenomas, but haven't been identified in other PitNET subtypes. Although studies have revealed that DNA carries a variety of information that may be beneficial in PitNET diagnosis, no studies have yet been undertaken to test these findings in ctDNA (Gossing et al., 2020).

CTCs (circulating tumor cells) are cells that have spread from the tumor tissue into the bloodstream. They are relatively uncommon in non-malignant conditions, as most PitNET are. CTCs can be found in stage 4 of cancer sample, while ctDNA can be identified from stages I to IV. As Wilhelm Gossing study group have suggest in their study (2020), the ctDNA mutational count in blood samples including CTCs was greater than in CTCs alone, the reason is because ctDNA was released from the original source itself, rather than from CTCs. Overall, the benefit of using CTCs for PitNET diagnoses is uncertain, while the comparison of ctDNA to CTCs implies that molecular markers can be discovered easily and at the earlier stage.

Microarray-Based Approach- Microarray technologies evaluate the simultaneous expression of thousands of genes and since thousands of gene fragments can be located on an array, it can provide a genome-wide view of gene expression in cancer. Several studies also compared microarray transcriptome characteristics between different PitNET types, to identify markers for each subtype. Raitis Peculis and the collaborators, have reviewed a study from Jintao Hu et al., from 2019 about identification of transcriptional metabolic dysregulation in subtypes of pituitary adenoma by integrated bioinformatics analysis where tumor subtype-specific differentially expressed genes were identified; 22 for somatotrophs, 1081 for lactotrophs, and 437 for NFPAs, whereas 217 DEGs were common to all PitNET types (Peculis et al., 2021).

Conclusion

The proposed approaches in laboratory analysis of PitNETs posess great potential for clinical application in differentiating, detecting and managing this tumours in practice. But, it remains necessary to understand how potential drivers in PitNETs and altered gene expression promote tumorigenesis, and find ways to target these mechanisms using novel therapies and use them for design of specific and sensitive diagnostic procedures. Future translational perspectives must expand with noninvasive marker analysis, such as the suggested miRNAs. Consequently, altogether with appropriate technological advancements, this approach could provide robust diagnostic markers and treatment management strategies for patients with PitNETs.

References

Donati, S., Aurilia, C., Palmini, G., Miglietta, F., Falsetti, I., Iantomasi, T., Brandi, M. L., 2021. MicroRNAs as Potential Biomarkers in Pituitary Adenomas. Non-coding RNA *7*(3), 55. https://doi.org/10.3390/ncrna7030055

Gossing, W., Frohme, M., Radke, L., 2020. Biomarkers for Liquid Biopsies of Pituitary Neuroendocrine Tumors. Biomedicines 8(6), 148. https://doi.org/10.3390/biomedicines8060148

Herrgott, G.A., Asmaro, K.P., Wells, M. et al., 2022. Detection of Tumor-specific DNA Methylation Markers in the Blood of Patients with Pituitary Neuroendocrine Tumors. Neuro-oncology, noac050. Advance online publication. https://doi.org/10.1093/neuonc/noac050

Kaltsas, G.A., Nomikos, P., Kontogeorgos, G., Buchfelder, M., Grossman, A.B., 2005. Diagnosis and Management of Pituitary Carcinomas, J. Clin. Endocrinol. Metab. 90, 3089–3099, https://doi.org/10.1210/jc.2004-2231

Peculis, R., Niedra, H., Rovite, V., 2021. Large Scale Molecular Studies of Pituitary Neuroendocrine Tumors: Novel Markers, Mechanisms and Translational Perspectives. Cancers 13(6), 1395. https://doi.org/10.3390/cancers13061395