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Sex-related differences in estrogen receptors and tumor proliferation factors in macroprolactinomas

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Prolactin-producing tumors represent nearly half of all pituitary tumors. The noticeable rate of aggressive clinical behavior in males with macroprolactinoma necessitates identifying novel genes and proteins which play a role in the process of tumorigenesis, tumor invasion to adjacent structures and resistance to medical treatment. ERα36 expression which is a novel splice variant of traditional ERα66 receptor has not been evaluated in the pituitary gland which is highly responsive to estrogen. In this cohort study, tumor samples from 62 patients with prolactinoma who underwent surgery during a period of eight years were evaluated for immunohistochemistry. ERα36, ERα66, Ki67 and p53 were measured by semi-quantitative immunoreactive score. A wide expression of ERα36 even more than ERα66 was found in normal pituitaries. This may imply the importance of non-genomic signaling pathway of estrogen in the pituitary. The scoring results of Ki67 showed that tumor proliferation rate was higher in males. Males also showed a greater mitotic count than women. Males presented larger and invasive tumors. There were no significant sex-related differences in the expression of the estrogen receptors and p53. Taken together, the results indicate that Macroprolactimomas in males are more aggressive than females. However, there were no significant difference in ERα36 and ERα66 expression between males'and females' tumors.

Introduction:

Epidemiological data indicates the tumors such as lung cancer, hepatocarcinoma, and melanoma have a worse prognosis in men when compared to women. This observation is also true for both metastatic and primary brain tumors including gliomas, meningiomas, and a subset of pituitary tumors that produce prolactin. These latter tumors defined as pituitary lactotroph tumors that are larger in men than in women and less sensitive to dopamine agonists. And their proliferative activity is reported to be higher in men and older women (>40 years of age) than in young women. The longer diagnostic delay in men cannot solely explain the sex related differences in lactotroph tumors. Indeed in a large surgical series of patients with lactotroph tumors. We previously demonstrated that the increased aggressiveness of this type of tumor related to a higher proliferative index among men. More recently we confirmed the sexual dimorphism that exists in lactotroph pituitary tumors by demonstrating that low expression of estrogen receptor alpha (ERα) is more frequently observed in men and that are further associated in both sexes with high-grade lactotroph tumors that are resistant to therapeutic treatments. Besides the sex specificity that exists in terms of hormone regulation and secretion the most evident differences between men and women lie in their epigenome and the existence of X and Y sex chromosomes. Among X located genes the androgen receptor (AR), glucose metabolic enzymes, proteins of the apoptotic cascade are expressed in normal tissues and modified in various tumors.

Moreover, other X-located genes as cancer-testis antigens are expressed in numerous tumors. While in normal tissues the expression of most of them remains restricted within the testis and the placenta. Expression of cancer-testis antigens is regulated by epigenetic mechanisms and could be associated with the tumor progression. By increasing the data also support the role of genes located on the Y chromosome such as the candidate tumor suppressor TMSB4Y a hypothesis further confirmed by the loss of the Y chromosome that is observed in cancers. A little is known about the molecular mechanisms that drives the sexual dimorphism observed in pituitary lactotroph tumors and studies comparing gene expression between tumors in men and women are lacking.

Here we addressed these questions in order to delineate the mechanisms in orders to identify the genes that drive the sex specificity that exists in aggressive lactotroph tumors. While our data confirm the implication of estrogen signaling in the sexual dimorphism observed in these tumors it further highlights a number of candidate genes and pathways that could represent appealing targets contributing to sex-related differences in lactotroph tumors.

Materials and Methods:

Human Pituitary Tumors, Transcriptomic Analysis, RNA Amplification, Array Hybridization and Processing, Microarray Data Analysis, Quantitative Gene Expression Analysis Through qRT-PCR, Comparative Genomic Hybridization (CGH) Analysis, Copy Number Alterations (CNA) Analysis.

Results:

A wide expression of ERα36 even more than ERα66 was found in normal pituitaries. This may imply the importance of non-genomic signaling pathway of estrogen in the pituitary. The scoring results of Ki67 showed that tumor proliferation rate was higher in males. Males also showed a greater mitotic count than women. Males presented larger and invasive tumors. There were no significant sex-related differences in the expression of the estrogen receptors and p53. Taken together, the results indicate that Macroprolactimomas in males are more aggressive than females. However, there were no significant difference in ERα36 and ERα66 expression between males'and females' tumors.

Discussion:

We have previously reported that the lactotroph tumors that develop in men are of a higher grade and are resistant to the treatment and men have an overall worse prognosis compared to the women. Despite this evident sexual dimorphism there have been few studies carried out to compare gene expression between the sexes. Here we used a comparative set of analysis involving transcriptomic and CGH experimental data obtained from lactotroph tumors from 20 men and 10 women to undertake such an analysis. We paid a particular attention to the importance of the estrogen signaling pathway in sex-specific behavior due to our previous identification of a reduced ERα protein expression in male lactotroph tumors and the well-established correlation between the grade of malignancy and low ERα protein expression that exists in breast tissues and bladder tumors.