SYSTEMATIC REVIEW

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Neuroendocrine differentiation in prostate cancer – a review

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Abstract: Objectives: This review aims to provide practicing clinicians with the most recent knowledge of the biological nature of prostate cancer especially the information regarding neuroendocrine differentiation.
Methods: Review of the literature using PubMed search and scientific journal publications.
Results: Much progress has been made towards an understanding of the development and progression of prostate cancer.
The prostate is a male accessory sex gland which produces a fraction of seminal fluid. The normal human prostate is composed of a stromal compartment (which contains: nerves, fibroblast, smooth muscle cells, macrophages) surrounding glandular acins – epithelial cells.
Neuroendocrine cells are one of the epithelial populations in the normal prostate and are believed to provide trophic signals trough the secretion of neuropeptides that diffuse and influence surrounding epithelial cells.
Prostate cancer is the most frequently diagnosed malignancy in men. In prostate cancer, neuroendocrine cells can stimulate growth of surrounding prostate adenocarcinoma cells (proliferation of neighboring cancer cells in a paracrine manner by secretion of neuroendocrine products).
Neuroendocrine prostate cancer is an aggressive variant of prostate cancer that commonly arises in later stages of castration resistant prostate cancer.
The detection of neuroendocrine prostate cancer has clinical implications. These patients are often treated with platinum chemotherapy rather than with androgen receptor targeted therapies.
Conclusion: This review shows the need to improve our knowledge regarding diagnostic and treatment methods of the Prostate Cancer, especially cancer cells with neuroendocrine phenotype.

Keywords: prostate cancer, neuroendocrine cells, neuroendocrine differentiation

INTRODUCTION

Prostate cancer is the most frequently diagnosed malignancy in men, majority of them are adenocarcinoma (derived from transformation of the glandular cells) [1]. The prostatic glands are under the influence of androgens. Prostatic adenocarcinoma cells present androgen receptors and relies on androgens for development and progression. That's why standard therapies for advanced and recurrent prostate cancer is based on two principles: block androgen synthesis (chemical or surgical castration)

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and inhibit androgen receptors [2][3].

Usually, this treatment provide clinical responses, but rarely eradicate all prostatic cancer cell populations and most patients after months/years develop resistance to these treatment – that means progression to castrate – resistant adenocarcinoma.

Neuroendocrine differentiation for most of the clinicians is associated with progression of prostate cancer to castrate – resistant disease.

NEUROENDOCRINE CELLS IN THE NORMAL PROSTATE

Neuroendocrine cells are found in many types of tissues, including in the normal prostate [4]. This cells secrete neuropeptides such as: serotonin, histamine, chromogranin A, calcitonin, bombesin, neuropeptide Y, vasoactive intestinal peptide, adrenomodulin [5],[6],[7],[8] and also growth factors (VEGF) [9]. The principal role is to maintain local homeostasis of the surrounding epithelial cells. Some of these neuropeptides have been found in seminal fluid, raising the idea that they may regulate sperm function [10][11].

Studies shows that neuroendocrine cells are present in all anatomic zones of the prostate and comprise less then 1% of benign prostatic glandular epithelium [12].

Neuroendocrine cells cannot be recognized on routine Hematoxilyn-Eosine staining. Ussualy this cells are found using immunohistochemistry with specific markers: chromogranin, synaptophysin, neuron specific enolase and CD 56 [13][14][15][16]. Other neuroendocrine cells markers reported in literature but not ussualy used in clinical practice include: cytochrome b561 [17], synaptic vesicle protein 2 [18][19], vesicular monoamine transporters [20].

NEUROENDOCRINE DIFFERENTIATION IN PROSTATE CANCER

Neuroendocrine prostatic carcinomas are often diagnosed on primary prostate needle biopsy with negative or low PSA level.

Neuroendocrine carcinoma of the prostate may be linked to resistance to androgen receptor signaling inhibition. Some prostatic tumors such as carcinoid tumor and small cell carcinomas are entirely composed by this type of cells with neuroendocrine differentiation. These tumors are aggressive and often present locally advanced or metastatic diseases with poor survival prognosis [21]. In general, these cells are negative for androgen receptor and PSA. Hormonal therapy is not effective while chemotherapy may have some value [22].

More frequently, prostatic tumors are composed by conventional adenocarcinoma with a small component of cells with neuroendocrine differentiation.

The neuroendocrine cells are indistinguishable from the normal adenocarcinoma cells on Hematoxilin-Eosine stained section under light microscope, and can be identified only by immunohistochemical stained using specific markers. Chromogranin A is the most used marker in clinical practice and is considered to be sensitive and specific [23].

Prostatic tumors with high grade or high stage and particularly in hormonal treated or hormone-refractory tumors, neuroendocrine differentiation is increased [24][25][26]. Also the level of serum chromogranin A are increased and is associated with tumor resistence to hormonal therapy [27]. In patients with hormone-refractory tumors, elevated serum chromogranin A level is predictor of poor prognosis, independent of PSA level [28].

NEUROENDOCRINE DIFFERENTIATION AND HORMONE-REFRACTORY PROSTATE CANCER

If the local curative treatments (radical prostatectomy, brachytherapy, radiotherapy) are no longer indicate for the patients with prostate cancer, androgen deprivation therapy is an effective therapy with significant symptomatic relief, suggesting that tumor growth is dependent on androgen receptors signaling. It is known that prostatic stromal cells support survival and proliferation of epithelial cells (paracrine secretion), that's why, it is possible that neuroendocrine cells (who do not express androgen

receptors and so are resistant to androgen deprivation) being capable to secrete neuropeptides and cytokines and so stimulate proliferation of adenocarcinomas cells. This situation suggest that androgen deprivation generally works, but eventually fails because neuroendocrine cells gradually substitute the function of stromal cells and so continued to stimulate the proliferation of prostate cancer cells.

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