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Critical Reviews in Oncology/Hematology 92 (2014) 11–24

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Neuroendocrine differentiation in prostate cancer: Current and emerging therapy strategies

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Accepted 16 May 2014

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Abbreviations: ABCG2, ATP-binding cassette sub-family G member 2; ADT, androgen deprivation therapy; AR, androgen receptor; CSC, cancer stem cells; CgA, chromogranin A; CRPC, castration resistant prostate cancer; EGFR, epithelial growth factor receptor; FDG, fluorodeoxyglucose; FISH, fluorescence in situ hybridisation; GH, growth hormone; GRP, gastrin releasing peptide; 5-HT, 5-hydroxytryptamine; hASH-1, human achaetescute homolog-1; KGF, keratinocyte growth factor; IGF-1, insulin growth factor-1; IHC, immunohistochemistry; IL, interleukin; mTOR, mammalian target of rapamycin; NE, neuroendocrine; NED, neuroendocrine differentiation; NEPC, neuroendocrine prostate cancer; NSE, neuron specific enolase; NET, neuroendocrine tumor; NF-kB, nuclear factor kappa B; OS, overall survival; PET, positron emission tomographic; PI3K, phosphatidylinositol 3 kinase; PFS, progression free survival; PSA, prostate specific-antigen; PTHrP, parathyroid hormone-related protein; SSTR, somatostatin receptor; VEGF, vascular endothelial growth factor.

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http://dx.doi.org/10.1016/j.critrevonc.2014.05.008

Abstract

Neuroendocrine differentiation (NED) secondary to androgen deprivation therapy (ADT) may be frequent in various stages of prostate cancer (PC), particularly in castration-resistant PC (CRPC). NED generally involves more aggressive PC clinical behavior and an unfavorable prognosis. The identification of neuropeptides secreted by NE cells and of different proliferative and anti-apoptotic pathways has led to attention being focused on probable diagnostic targets and therapeutic options for a subtype of PC. Emerging evidence suggests that the acquisition of epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC) phenotype are associated with the development of NED in PC, responsible for a complex interaction between ADT, the onset of CRPC and NED, in which EMT and CSC could play a central role, providing potential therapeutic targets. In this article, we review the pathogenetic, prognostic and predictive significance of NED in human PC, providing an insight into innovative agents capable of treating and perhaps preventing NED occurrence.

Keywords: Neuroendocrine differentiation; Prostate cancer; Androgen deprivation therapy; Chromogranin A; Cancer stem cells; Epithelial-mesenchymal transition; Somatostatin; Prognosis

1. Introduction

Increasing knowledge of the pathophysiology of prostate cancer (PC) has recently led to the identification of novel mechanisms of androgen independence and progression which, in turn, have allowed for numerous drug discoveries with an increasing therapeutic armamentarium for PC, particularly in the advanced stages. However, despite much progress, some aspects of PC – remain largely unknown. In recent years, increasing attention has been focused upon neuroendocrine differentiation (NED), above all for castration resistant prostate cancer (CRPC) patients, in which the identification of NED might be helpful mainly for tailoring therapeutic strategies, increasing survival rates and ameliorating quality of life.

2. Features of neuroendocrine differentiation in prostate cancer

NED is a common feature of prostatic adenocarcinomas. Pure neuroendocrine prostate cancer (NEPC) and a small cell PC represent rare and aggressive tumors, such as primary carcinoids, which are also very rare, but usually not aggressive. In most cancers, the NE component coexists with non-NE component, displaying a variable extension of the two components, potentially ranging from 1 to 99%. NE component usually occupies less than 5% of the overall tumor mass and, in general, in NEPC NE component varies usually between 5% and 30% of the tumor mass [1,2].

NED is usually determined by immunoreactivity for NE markers, such as chromogranin A (CgA), and neuron specific enolase (NSE). In NEPC, NE cells do not express usually nuclear androgen receptor (AR) and prostate specific-antigen (PSA) [3] compared to secretory epithelial cells. Normal NE cells do not show proliferative activity, they are post-mitotic cells and usually Ki-67 (MIB-1) antigen negative, even if PC with increased grade of NED has a high Ki-67 expression [4]. In addition, NE cells have raised anti-apoptotic activity through an overexpression of Bcl-2 [5] and frequently mutated p53 protein [6].

NE cells do not show distinguishing features on hematoxylin and eosin-stained sections under the light microscope but electron microscopy or immunohistochemical staining can help to identify with antibodies against NE markers or other specific NE products, such as somatostatin, serotonin (5-hydroxytryptamine, 5-HT), bombesin-like peptides, such as gastrin releasing peptide (GRP), calcitonin and parathyroid hormone-related protein (PTHrP) [7].

3. Pathogenetic mechanisms involved in neuroendocrine differentiation and progression in prostate cancer

NE cells of the prostate are widely distributed in normal prostatic acini and ducts. The origin of NE cells in PC is controversial. It is suggested that NEPC cells have the same origin as normal NE cells from neural crest and are differentiated from common pluripotent stem cells (as reported in the following paragraph). In fact, NE cells have some features of cancer stem cells (CSCs), such as the expression of CD44 and CD133, which may give resistance to hormonal therapy and lead to tumor recurrence [8,9]. Other studies show that NE-like cells in PC lesions are originated from cancerous epithelial cells under pathological conditions like androgen ablation and cytokines production, but not from normal NE cells, and should be defined as 'NE-like PC cells' [10].

NE cells express potent neuropeptides that activate different pathways and biological processes such as cell growth, differentiation and transformation.

Bombesin/GRP is a potent mitogenic neuropeptide through its ability to activate nuclear factor kappa B (NF-kB) and to induce fos and myc deregulating the cell [10]. 5-HT [12] and PHTrP [13] are also associated with tissue growth and malignant transformation through the stimulation of G-protein-coupled receptor; moreover, PTHrP has a further mitogenic effect by the regulation of the epithelial growth factor receptor (EGFR) and calcitonin may modulate tumor growth by stimulating PTHrP release [14].