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REVIEW

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The effect of cytokines on neuroendocrine differentiation in prostate cancer

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Abstract

Prostate cancer is an androgen dependent cancer that can initially be effectively treated with androgen deprivation therapy (ADT). However, during the treatment process, most prostate cancer patients eventually develop drug resistance and gradually progress to castration resistant prostate cancer. Among them, neuroendocrine prostate cancer (NEPC) is the most difficult to treat and different from *de-novo* NEPC and small cell cancer of prostate. With the decrease of androgen levels in cancer cells after castration treatment, the differentiation of cells with neuroendocrine phenotype increases, promoting cancer cell growth in the form of paracrine secretion. The factors that affect this mechanism include loss of *RB1* (Retinoblastoma 1) and *TP53* (Tumor Protein 53) gene expression, changes in epigenetic factors, and swelling changes in tumor microenvironment, *etc*. Within the tumor microenvironment, cytokines such as interleukin-6 and interferon have the greatest impact. The author of this article aims to explore new strategies for delaying the progression of NEPC by elucidating the latest research progress on the mechanism of cytokines in neuroendocrine differentiation of prostate cancer.

Keywords

Prostate cancer; Neuroendocrine differentiation; Cytokine

1. Introduction

Prostate cancer is one of the malignant tumors with a high incidence rate among men in the world, ranking second in the world, especially in developed countries such as Europe and the United States. In recent years, the incidence rate and death rate of prostate cancer in Chinese men have also increased year by year due to the incontinence of diet and aging population. Prostate cancer is an androgen dependent tumor [1], and in addition to surgical treatment, the current standard first-line treatment is androgen deprivation therapy (ADT). Generally speaking, in the early stage of ADT, prostate cancer patients can achieve good clinical efficacy, with significant improvements in prostate-specific antigen (PSA) and imaging as well as novel treatments. However, most patients experience a decrease in efficacy and inevitable drug resistance after approximately 13.1 months of treatment, gradually developing into castration resistant prostate cancer (CRPC) with a poor prognosis [2]. The reasons and mechanisms of NEPC are currently not clear worldwide. We have been engaged in research in this area for a long time and researchers could pay attention to our papers, as well as consult relevant literature. NEPC has high invasiveness and a higher incidence of NEPC in prostate cancer patients, it is one of the important molecular subtypes of CRPC, and the difficulty and significance of studying it could be imagined.

In recent years, a highly malignant type has been discovered in the study of CRPC resistance mechanisms, which does not rely on classical androgen receptor (AR) related pathways. This type of prostate cancer cells lose their typical epithelioid morphology and are induced during ADT treatment to form neuroendocrine (NE)-like structures. Neuroendocrine prostate cancer (NEPC) is characterized by a distinct neuroinflammatory branch with secretory elements that can produce androgens to supply tumor cell growth and is not antagonized by anti-androgen drugs. It is known as neuroendocrine prostate cancer (NEPC) and has a very poor prognosis [3]. In NEPC, NE cells can be recognized through the expression of a series of NE markers, such as chromogranin A (CgA), neuron specific enolase (NSE), and synaptophysin [4]. There are currently many studies on the formation mechanism of NEPC. Studies [5, 6] have shown that the deletion of tumor suppressor genes *RB1* and *TP53* is a key promoting factor for NE cell differentiation, through specific epigenetic changes such as overexpression of the *Zeste* gene enhancer homolog 2 (EZH2) and DNA methylation, driving tumor cell proliferation, downstream neuron and neuroendocrine pathway expression; In these pathways, transcription factors SRY (Sex-determining Region Y) box transcription factor 2 (SOX2) and *Achaete* scute family bHLH transcription factor 1, *etc*, are all play a certain role. Advanced prostate cancer now has molecular subtyping and the role of cytokines is significant. In addition,

recent studies [7] have shown that the tumor microenvironment also plays an important role in the mechanism of NEPC formation. The tumor microenvironment contains both cellular and non-cellular components, including tumor cells, immune cells, tumor associated fibroblasts, and vascular endothelial cells. These cells produce cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), growth factors, and interferon (IFN), which can mediate intercellular signaling to promote tumor cell differentiation, growth, and progression [8]. The author of this article provides a review of the research progress of relevant cytokines in the differentiation mechanism of NEPC.

2. Interleukin

2.1 IL-6

IL-6 is a multifunctional cytokine mainly expressed in the basal cells of prostate epithelium and is also commonly present in glandular cells of advanced prostatic intraepithelial neoplasia and prostate cancer. In the tumor microenvironment, IL-6 affects the occurrence and development of tumors by regulating tumor cell proliferation, apoptosis, differentiation, metabolism, angiogenesis, and metastasis processes. Research [9] has shown that the expression level of IL-6 is elevated in CRPC patients with drug resistance and metastasis, which is associated with poor prognosis and reduced survival rate in prostate cancer patients. Downregulation of IL-6 expression level suggests a good prognosis. The method of obtaining NE like cell lines cultured *in vitro* can be obtained not only through the commonly used ADT therapy induction, but also through IL-6 overexpression stimulation. In the past, most researchers believed that the role of IL-6 in NEPC differentiation was mediated by its involvement in related signaling pathways such as Janus kinase/signal transducer and transcription factor 3 (JAK/STAT3) pathway, phosphatidylinositol 3-kinase/protein kinase B (PI3K/PKB) pathway. The pathways of mitogen activated protein kinases/extracellular regulated protein kinases (MEK/ERK) and mitogen activated protein kinases/extracellular regulated protein kinases (MAPKs) have been studied, the results are correlated and show that IL-6 participates in the process of inducing NEPC. However, with further research, it has been found that in addition to the functions of these signaling pathways, IL-6 itself has the ability to induce NE like differentiation. Natani *et al*. [10] found that the AMP activated protein kinase/silencing information regulator of transcription 1 (AMPK/SIRT1) signaling pathway, mediated by p38 mitogen activated protein kinase (p38MAPK), can induce NE like differentiation of LNCaP (Lymph node-derived carcinoma of the prostate) prostate cancer cells under reduced androgen conditions. The relationship between IL-6 (interleukin-6 AMPK) and AMPK (adenylate activated protein kinase) is mainly reflected in their synergistic effect on metabolic regulation, especially in the interaction between skeletal muscle glucose metabolism and fat breakdown processes. Antiandrogenic drugs activate tumor macrophages during treatment, leading to increased secretion of IL-6 and inducing NEPC. IL-6 can also participate in the activation of the JAK-STAT3 pathway through autocrine or paracrine mechanisms, increasing its own expression to induce NEPC differentiation [11]. In the latest study, Ji *et al*. [12] found *in vitro* experiments on NEPC mouse models that the antihistamine drug ketotifen reverses lineage switching by targeting the IL-6/STAT3 pathway, effectively inhibits NE differentiation, and reduces tumor cell viability.

Research has found that in addition to the aforementioned stimulus induced mechanisms, IL-6 can also regulate transcription factors to achieve NE differentiation. Suppressoreelement-1-silencing transcription factor (REST) is a silencing transcription factor that can inhibit NE gene expression. Zhu *et al*. [13] found that IL-6 can inhibit the expression of REST and degrade and inactivate REST to eliminate factors that hinder NE cell differentiation. In addition, autophagy regulation, which has attracted much attention in prostate cancer ADT and chemotherapy resistance, has an impact on IL-6 induced NE differentiation. Chang *et al*. [14] found through cell counting and Western blot analysis that treating LNCaP cells with IL-6 not only induced NE like differentiation of tumor cells, but also activated a specific autophagy pathway, which was further silenced by Beclin1 and Atg5.

The MTT (Methylthiazolyldiphenyl-tetrazolium bromide) colorimetric assay confirmed that the autophagy pathway reduces apoptosis in NE-like cells. If the autophagy pathway is inhibited, the number of apoptotic NE-like cells significantly increases, indicating that autophagy is the fundamental cause of chemotherapy resistance in NE-like cells. In summary, it further proves that IL-6 is one of the important cytokines that induce NE differentiation in prostate cancer cells.

2.2 IL-8

IL-8 is a cytokine secreted by Th1 cells, which can be highly expressed in various human tumor cells. It can act on different cells, promote inflammatory response, stimulate blood vessel formation, promote mitosis, regulate host immune function, *etc*. It is closely related to the occurrence and development of various inflammatory diseases, tumors, and immune diseases. In prostate cancer patients, serum IL-8 levels increase with disease progression [15]. Patel *et al*. [16] found that IL-8 was not expressed in the prostate cancer cell line LNCaP but was expressed in cell lines cultured in androgen deficient medium, suggesting a preliminary association between IL-8 and prostate cancer drug resistance. There are two types of epithelial cell populations in prostate cancer: (1) secretory tumor cells, which account for the majority of tumor cells; (2) a few scattered NE cells. After hormone therapy, the number of NE cells increases, especially when prostate cancer is in the androgen dependent phase. These NE tumor cells may contribute to the androgen independent growth of prostate cancer. In 2004, Lee *et al*. [17] further explored the expression and effects of IL-8 in LNCaP cells. Through cell migration and chromatin immunoprecipitation methods, they found that IL-8 is a promoter of androgen independent transformation in prostate cancer cells and may be related to IL-8-induced tyrosine kinase signaling and androgen receptor activation, but the specific mechanism is still unclear. The main binding receptor of IL-8 is CXC chemokine receptor 1 (CXCR1).

CXCR1 and CXC chemokine receptor 2 (CXCR2), two

IL-8 receptors widely expressed in various types of prostate cancer cells, among which CXCR2 is expressed in Purkinje cells and various neurons in the human body, and plays an important role in promoting neuronal proliferation and migration when combined with IL-8. In 2005, Huang *et al*. [18] further demonstrated that NE cells are an independent source of IL-8 in prostate cancer. When combined with CXCR2, NE cells induce androgen independent proliferation of tumor cells through autocrine effects and stimulate more NE cell differentiation. This conclusion was once again validated in the study by Li *et al*. [19] in 2013. According to reports, activation of the MAPK/ERK pathway in the tyrosine kinase signaling pathway of LNCaP cells can induce NE differentiation and increase NSE expression. IL-8 is one of the upstream regulatory factors of this pathway [20], but there is still no direct evidence to suggest the specific role of IL-8 on the MAPK/ERK pathway in prostate cancer cells. Forkhead box A1 (FOXA1) is a transcription factor. In 2017, Kim *et al*. [21] found that FOXA1 can inhibit the MAPK/ERK pathway by reducing ERK phosphorylation, thereby preventing NE like differentiation of prostate cancer cells. At the same time, gene expression analysis and Western blot analysis showed that the binding of FOXA1 to the IL-8 promoter sequence knocked out the expression of FOXA1, which may be one of the mechanisms by which IL-8 participates in causing NEPC.

3. Growth factors

3.1 Epidermal growth factor (EGF)

EGF is one of the important mitogenic factors in prostate cells, which is overexpressed in tumor cells to promote proliferation, differentiation, and metastasis. Its specific binding receptors include not only EGFR (Epidermal Growth Factor Receptor), but also members of the ErbB receptor family, such as ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). DiLorenzo *et al.* [22] observed increased expression of EGF and EGFR in prostate cancer cells. Research [23] found that overexpression of EGF increased the expression of NSE. This indicates that EGF may induce increased differentiation of NE-like cells in prostate cancer cells, but there are few studies reporting the direct mechanism of EGF action. Most of them induce NE differentiation by binding to receptors and enhancing their expression. Research [24] has shown that using the PI3K/Akt (Phosphatidylinositol 3-kinase/Protein Kinase B) inhibitor LY294002 to observe cell apoptosis in LNCaP cell lines through flow cytometry, the number of apoptotic cells decreased after the addition of EGF, and a sharp increase in ErbB2 levels was observed. After a period of time, LNCaP cells began to exhibit NE like differentiation, during which the levels of NE differentiation markers increased parallel to ErbB2 levels. This result indicates a clear positive correlation between EGF binding to ErbB2 overexpression and NE differentiation. Zhang *et al*. [25] also found that activating the EGFR/ERK signaling pathway can promote angiogenesis and gene mutation induced NEPC formation, increasing tumor metastasis and invasiveness.

3.2 Transforming growth factor beta (TGF β)

The TGF β superfamily contains a group of structurally related cytokines, including TGF β, growth and differentiation factors (GDF), and bone morphogenetic protein (BMP). TGF β can be detected in almost all tumor cells and is involved in regulating various cell growth processes, including cell proliferation, invasion, apoptosis, epithelial mesenchymal transition, tissue homeostasis, immune suppression, and extracellular matrix remodeling. It is overexpressed under conditions of fibrosis, inflammation, cancer, and excessive proliferation, especially in glioblastoma where it is highly secreted and may be related to neuronal differentiation. In prostate cancer cells, TGF β transmits signals through the TGF β R II (type II receptor subunit) on the cell surface to mediate the phosphorylation of TGF β R I (type I receptor subunit), activating the classical TGF β SMAD2 pathway to control cell growth by inhibiting proliferation, inducing apoptosis, promoting migration and invasion [26, 27], and also obtaining lineage transformation ability by inducing demethylation of CD133 (Prominin-1) promoter. Dicken *et al*. [28] proposed that the interaction between TGF β signaling and AR signaling axis induces epithelial mesenchymal transition, interferes with the homeostasis of epithelial cell lines, and provides a key site for epithelial cell differentiation into tumor cells. At the same time, it increases the invasiveness and metastasis of the derived tumor, supports the later acquisition of NE phenotype by prostate tumor cells, increases castration resistance, and reduces the efficacy of drug therapy. Previous reports have shown that under IL-6 stimulation, cells can release a large amount of TGF β. Sagara *et al*. [29] added IL-6 to androgen deficient culture medium to cultivate LNCaP cells and release TGF β. Proteomic data and bioinformatics analysis revealed that TGF β SMAD2 signaling can activate p38MAPK to promote NED, while targeted TGF β therapy can prevent the progression of NED in LNCaP cells, suggesting that TGF β targeted therapy may become a new direction for NEPC treatment, but the relevant mechanisms still need further exploration.

4. IFN

There are two main types of IFNs, type I (IFN-α, IFN-β), and type II (IFN-γ). Type I IFNs mainly exert anti-tumor effects and are widely used in clinical treatment of various tumors. IFN-γ is a dimeric soluble cytokine and the only member of type II IFN. It is expressed at low levels in normal tissues and increases in expression under inflammation and tumor stimulation. Its expression is significantly increased in chronic inflammation, making it a typical pro-inflammatory factor. Long term chronic inflammation has been shown to be significantly associated with the occurrence and development of various cancers. In the short term, IFN-γ stimulation can inhibit cell growth, but chronic IFN-γ stimulation provides a favorable microenvironment for tumor growth; A study has found that IFN-γ expression exists in the basal cells of human prostate epithelium, and toxic/inhibitory T lymphocytes of prostate epithelial cells under inflammatory conditions are also one of the sources of IFN-γ [30]. It is suspected that IFN-γ is related to NE like differentiation of prostate cancer

cells. In order to explore this phenomenon, Untergasser *et al*. [31] conducted relevant research by stimulating early passaged epithelial and stromal cultures as well as tumor cell lines with different concentration gradients of 0.0001–0.01 $ng \cdot L^{-1}$. Afterwards, the apoptosis rate of tumor cells significantly increased; and by evaluating NE differentiation through the expression of NSE, it was found that the expression of NSE protein was upregulated in basal epithelial cells and androgen independent PC-3 cell lines after IFN-γ stimulation; Under a microscope, it was observed that some primary human prostate basal epithelial/precursor cells exhibited morphological changes resembling neurons/fibroblasts, which may be related to the local action of IFN-γ, while IFN-α and IFN-β did not have this effect. In addition, IFN-γ stimulation can significantly induce the expression of classic markers NSE and CgA in NE cells, indicating that further exploration is needed to investigate the effect of IFN-γ on NE like differentiation of normal prostate and tumor cells, in order to better provide therapeutic targets for future clinical treatment of focal NE differentiation in NEPC.

5. Other

In recent years, scientists have continued to explore cytokines that are abnormally expressed in the NEPC tumor microenvironment, such as neurociliary protein-2 (NRP-2), vascular endothelial growth factor (VEGF), macrophage migration inhibitor (MIF), and interleukin-1 (IL-1), *etc*. NRP-2 was initially discovered during neural development and is believed to be one of the axonal guidance factor receptors for signaling proteins. It can also act as a VEGF receptor and bind to VEGF to promote cell development. Previous studies on NRP-2 have found low expression or absence in prostatic epithelial or intraepithelial neoplasia, but high expression in prostate cancer. Clinical data shows that NRP-2 expression is associated with Gleason grading and is an independent prognostic factor for poor prognosis [32]. Islam *et al*. [33] found that NRP-2 was significantly expressed in the tissues of NEPC patients. Through *in vitro* experiments and *in vivo* studies, it was confirmed that NRP-2 promotes the growth and survival of NE-like cells after chemotherapy treatment. In addition, Wang *et al*. [34] found that after knocking out NRP-2 using shRNA, the neural axons of NE-like cells were shortened and reduced and finally switched back to the AR positive luminal cell lineage of prostate adenocarcinoma cells. Therefore, they concluded that NRP-2 is crucial for maintaining the NE characteristics of NEPC cells. In the same year, another research team discovered that NRP-2 activates the VEGFR-2/STAT3/SOX2 pathway by binding to VEGF, driving NEPC differentiation and growth after AR activity and dependence decrease. The combination of the two can also maintain the expression of PD-L1 in prostate cancer, making it an effective target for activating anti-tumor immunity [35]. Therefore, targeting NRP-2 can not only reduce the occurrence of castration treatment resistance, but also improve the efficacy of immunotherapy, and may be a potential treatment strategy for future treatment or prevention of NEPC. MIF is a pro-inflammatory cytokine involved in the carcinogenic process, and serum levels of MIF are associated with the invasiveness of PCa (Prostate cancer). During the NE differentiation process, a significant increase in MIF release was observed, which in turn stimulated tumor cell proliferation and anti-apoptotic ability, but did not affect the expression of NE markers, only stabilizing the NE differentiation process.

6. Conclusion

NEPC is one of the most aggressive types of CRPC. Due to the limited treatment methods, cancer progression cannot be controlled, and patients often have poor prognosis and short overall survival. The treatment methods for prostate cancer include surgery, endocrine drug therapy, targeted drug therapy, immune drug therapy, radiotherapy, chemotherapy, *et al*. However, the treatment effect for early prostate cancer is generally good and can achieve a curative effect, while the treatment effect for late stage castration resistant prostate cancer is poor and requires active control of the development of the disease to prolong the patient's survival as much as possible. NEPC is a subtype of CRPC molecular typing, and it particularly lacks effective treatment methods. Many researchers have been actively exploring the mechanism of NE like differentiation. Although it has been found that it may be related to factors such as gene changes and transcriptional regulation, the specific therapeutic targets are still unclear and need to be explored. From the above summary, it can be seen that most cytokine types in prostate cells are associated with the formation of NEPC. These studies may reveal new therapeutic targets and combination therapies, with the hope of finding new directions for effective treatment.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

XZY—writing and revising the manuscript. ZML—literature review. JL—provided help and advice on the revision of the paper. PQY—literature review. ZZS—literature review and editing. BCL—literature review. JZG—comprehensive coordination and guidance.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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