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Review Article

Transcription factors Brn-3α and TRIM16 in cancers, association with hormone reception

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ABSTRACT

Sex hormones, regulating normal physiological processes of most tissues and organs, are considered to be one of the key factors in the development of hormone-dependent cancer and formation of the hormone-resistant tumor phenotype. Recently, the importance of the system for control of hormone receptors expression mediated by nuclear peptides became evident. This system is involved in the regulation of normal physiological processes, in the pathogenesis of many diseases as well as oncogenesis. In the review, we discuss the relationships of the two regulatory peptides – Brn-3α, TRIM16 with hormone receptors. The transcription factor Brn-3α is able to affect the transcription activity of androgen and estrogen receptors. It is observed the participation of TRIM16 protein in the pathogenesis of hormone-dependent tumors due to its "anti-estrogenic effect". Additionally, they are involved in the key intracellular processes, such as proliferation, cell differentiation, and programmed death - apoptosis. Thus, Brn-3α and TRIM16 are associated with cancer development and progression. By understanding these alterations, we can identify potential markers and novel biochemical therapeutic targets. It makes clear the association between classical hormone-dependent tumors and less sensitive ones with the modification in the level of hormone receptors.

1. Introduction

Hormones influence not only breast and prostate cancer, the two most common hormone-dependent cancers, but also have a major impact on less common hormone-sensitive malignancies (e.g. ovary, testes, endometrium) as well as human cancers recently discovered to be hormone sensitive (e.g. lung, liver) [1]. The failure in hormonal therapy, the hormone resistance development dictates the search for other factors that can influence the course of the hormone-dependent tumor (Fig. 1). Hormones bind with their steroid hormone receptors, a subset of proteins within the nuclear receptor superfamily that includes estrogen receptors (ER), progesterone receptors, glucocorticoids receptors, androgen receptors (AR) and mineralocorticoid receptor.

In common, they are nuclear factors that interact with others, targeting various processes in the cell. Data review allow us to identify the neurogenic factor Brn-3α and the anti-estrogenic protein TRIM16 possessing the numerous functions and involving in AR and ER expression regulation and cancers development [2].

However, in general, their significance in oncogenesis is more discussed as well. Transcription factors POU are proteins that are distributed into 6 classes: POU1-POU6. The abbreviation is a combination of the initial letters of nuclear proteins: Pituitary-specific, Octamer, the neurogenic factor Unc-86. POU4F1, also known as neurogenic factors of Brn-3 (Brain-specific homeobox/POU domain protein 3A) were identified originally in the nervous system [3, 4], but are also expressed in reproductive tract tissues (breast, ovary, cervix, prostate, testis, etc.) [2, 5, 6]. Multiple mechanisms of protein participation in the regulation of intracellular processes, in particular, apoptosis, cell proliferation, etc., have been identified.

TRIM16 (Tripartite Motif Containing 16) or EBBP (Estrogen-responsive B box protein) protein, consisting of 564 amino acids, belongs to the TRIM family of proteins, which includes 65 members. They are activated

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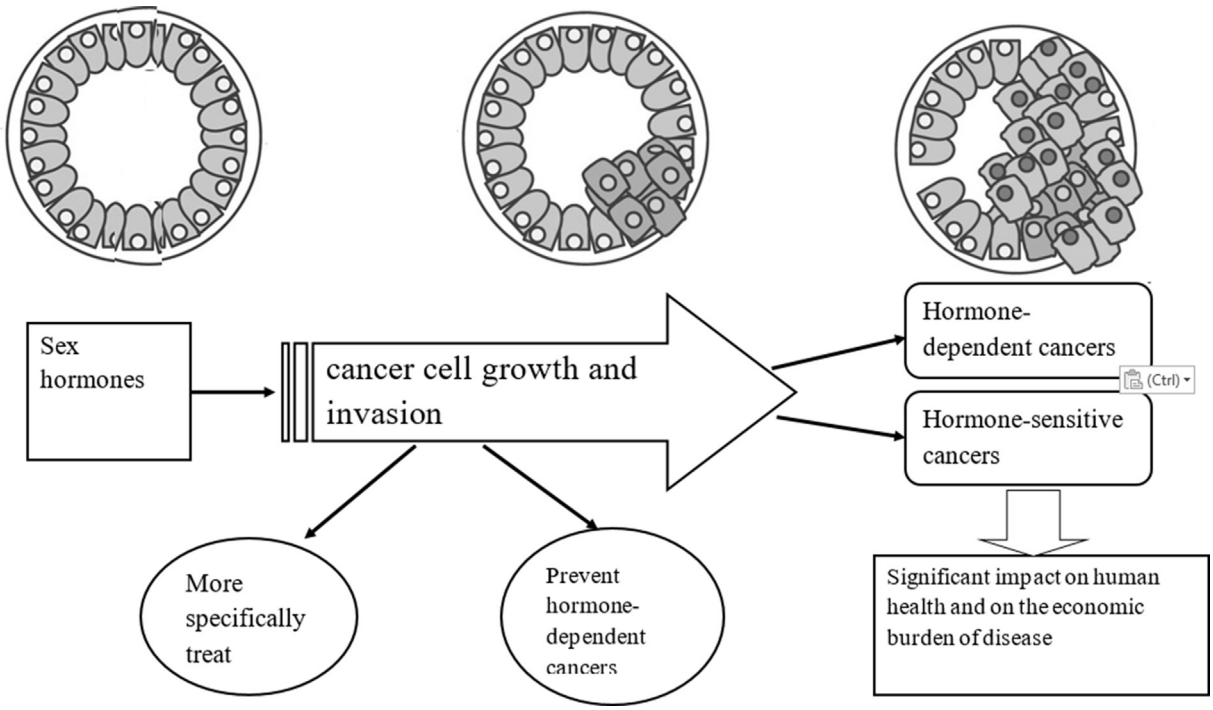

Fig. 1. Sex hormone and cancer cell growth. Note: Hormones influence not only breast and prostate cancer, but also have a major impact on less common hormone-sensitive malignancies (e.g. ovary, testes, endometrium). Developing a means to more specifically treat and ideally prevent hormone-dependent cancers is of critical importance given the significant impact these malignancies have on human health and the economic burden of disease.

by interferons and have a wide spectrum of action affecting various processes of cell vital activity [7]. The high protein content is observed at embryonic stages of development in comparison with adult tissues, in the tissues of the male and female sex glands, the small and large intestine, the placenta, the heart, the mammary glands [8]. TRIM16 can reduce the content of estrogen receptors and has an "anti-estrogenic" effect [9]. The molecular mechanisms of TRIM16 action have not been studied.

1.1. The role of transcription factor POU (Brn-3a) in the regulation of intracellular processes

Brn-3α is overexpressed in differentiating primary neurons and neuronal cell lines that are protected from stimuli that would generally induce apoptosis. This happens through activation and increased expression of anti-apoptosis genes, including Bcl-2 [3,10]. On the other hand, the ability to activate the promoters of differentiation-associated neurofilaments and neuronal outgrowth is dependent upon the C-terminal POU domain of Brn-3a and on both long (l) and short (s) forms of the molecule.

Thus, Brn-3 α has distinct functions in neuronal cells, Brn-3a(l) induces Bcl-2 expression and protects neurons from apoptosis, whereas, Brn-3a(s) induces the expression of differentiation-associated genes and induces neuronal differentiation [11]. Moreover, Brn-3 targets many other genes, particularly those with oncogenic (such as ras and src) and apoptotic/anti-apoptotic roles (such as p53, Bcl-2, Bcl-x, Bax, p21, Hsp27) [12, 13, 14].

It is found an oncogenic role of Brn-3α by linking it with Bcl-2/VEGF induction involved in tumor angiogenesis [15], further implicating the role of this neuronal transcription factor in tumor progression. Diss J.K. with co-authors (2006) has reported the transcription factor Brn-3α plays an important role in various processes in the cell [16]. It is known that an increase in its expression reduces the rate of cell proliferation, as well as transformed ones. It is believed that this fact is a due influence of a Brn-3 on the expression of significant oncosuppressor, the regulator of the cell cycle. It was found that Brn-3α decreases the expression of p53-dependent proteins Bax, Noxa, and p21, the inducer of proliferation [10, 11, 17].

The experimental data have been obtained showing that the blockage of Brn-3α results in double-strand breaks of DNA in cells [5]. At the same time activation of the nuclear factor is combined with the active proliferation of both melanocytes and melanoma tumor cells. The role of Brn-3α in the regulation of BRAF protein and MAPK signaling cascade has also been revealed. Their combined effect is expressed in a decrease in the level and rate of melanocytes senescence.

The development of tumors is associated with impaired apoptosis. There is evidence that Brn-3α is able to regulate the expression of Bcl-2 proteins [2]. There is an assumption that the anti-apoptotic effect of Brn-3α is associated with the activation of these proteins.

At present, the importance of the nuclear factor in regulating the proliferation of cells, as well as the processes of growth and formation of blood vessels, has been identified, which can also affect the development of cancer. Bcl-2 and VEGF dependent induction of angiogenesis are shown to be under the action of this nuclear factor [18].

In addition, associations of this indicator with sex hormone receptors have been identified both ER and AR [19]. Berwick D.C. and co-authors (2010) demonstrate that these transcription factors form complexes within the nucleus of ND7 neuroblastoma cells, while in vitro pull-down assays show a direct association. As a functional consequence of the Brn-3a-AR interaction, the factors bind cooperatively to multiple elements within the promoter of the voltage-gated sodium channel, Nav1.7, leading to a synergistic increase in its expression [2]. By pull-down assays and the yeast two-hybrid system, the POU domain of Brn-3a was shown to interact with the DNA-binding domain of the ER. Brn-3–ER interactions also affect the transcriptional activity of an ERE-containing promoter, such that in estradiol-stimulated cells, Brn-3b strongly activated the promoter via the ERE, while Brn-3α had a mild inhibitory effect [10].

Consequently, the transcription factor Brn-3α has many functions; its effect on the processes of oncogenesis is associated with a change in the processes of cell proliferation, apoptosis. From this point of view, the study of the nuclear factor Brn-3 in the development of malignant neoplasms is pivotal.

1.2. The role of transcription factor TRIM16 in the regulation of intracellular processes

The significance of TRIM16 in the development of tumors is associated with inhibition of cell proliferation due to this action it is often called as a tumor suppressor. This protein inhibits the expression of cell cycle markers E2F1 and pRb [8], which affects the mitotic activity of the tumor cell. The differentiation of keratinocytes is also dependent on TRIM16 expression [20].

TRIM16 interacts with a complex of molecular markers that determine the spread of the tumor in the body. TRIM16 overexpression inhibits the action of the Shh, Smo, Ptc, Gli-1, MMP2, and MMP9 proteins, which play an important role in tumor invasion [21]. The decrease in TRIM16 expression occurs in the progression of prostate cancer by inhibiting the transcription factor Snail [21, 22].

The change in the vimentin content [22], the protein of intermediate filaments, forming the motility of the cells and the development of the epithelial-mesenchymal transition, is recently determined as a key event in the oncogenesis. TRIM16 protein participates in this process. Thus, Huo et al. (2015) have showed decreased motility ability in cells accompanied by increased expression of TRIM16 in the non-small cell lung cancers. But the TRIM16 mRNA level and its protein content are reduced in cancers of patients with metastases compared to non-metastatic ones [23]. The same results are obtained in the study of patients with hepatocellular carcinoma [24].

In addition, the involvement of TRIM16 in the activation of apoptosis in breast cancer and neuroblastoma has been shown, but no similar effect has been demonstrated in the clear-cell renal cell carcinoma [8]. The participation of the protein in the apoptosis activation is mediated by an increase in the procaspase-2 expression, the inactive precursor of caspase, which modifies the activity of cellular proteins (polymerases, endonucleases, nuclear membrane components) responsible for DNA fragmentation in apoptotic cells [25].

Currently, the regulation of the autophagy process due to the action of TRIM16 is being studied. It is one of the ways to rid cells of unnecessary organelles, as well as the body from modified cells [26] and is called as caspase-independent apoptosis. Modification in apoptosis and autophagy processes are the cause of pathology development as well as malignant tumors [25].

The effect of TRIM16 on the activity of the ubiquitin-proteasome system is considered to be the most significant. It is found the activation of the proteasome system in most of the cancers [27]. The effect of TRIM16 on the life span of proteins is mediated by the fact that it can act as an E3 ubiquitin ligase and trigger the process of proteasomal cleavage of proteins [6]. Thus, the role of TRIM16 in the cleavage of TPD43, Gli-1, the main regulator of the Hedgehog pathway (this signaling cascade is named after the main signaling molecule Hedgehog (Hh)) is revealed in the mammary tumor tissue [28]. In addition, TRIM16 is known as EBBP protein, responsible for the regulation of estrogen receptor expression [9]. In previous studies, the association of proteasome activity with the content of estrogen receptors has been revealed [29], which is of particular importance in the development of hormone-dependent human tumors (Fig. 2).

1.3. Transcription factor Brn-3α in cancers

Brn-3α controls the balance between cell proliferation, differentiation, and apoptosis by targeting specific gene promoters either directly or through interactions with other cofactors [2, 3]. Hohenauer T and co-authors (2013) have found the Pit-Oct-Unc (POU) domain transcription factor Brn3a, normally involved in neuronal development, to be frequently expressed in melanoma, but not in melanocytes and pigmented nevi [30]. Methylated POU4F3m could be new methylation biomarkers for detection of CIN3+ and endometrial complex hyperplasia in atypical glandular cells [31]. The detection of Brn-3α is of important clinic value in early diagnosis of the cervical process [32].

Expression of these transcription factors is altered in a number of different cancers. Brn-3α levels are significantly enhanced in cervical cancer [33, 34], prostate cancer [16], neuroendocrine tumors [35], ovarian cancers [36] and Ewing's sarcoma [37].

It is found that RNAi-mediated silencing of Brn3α strongly reduced the viability of melanoma cell lines and decreased tumor growth in vivo

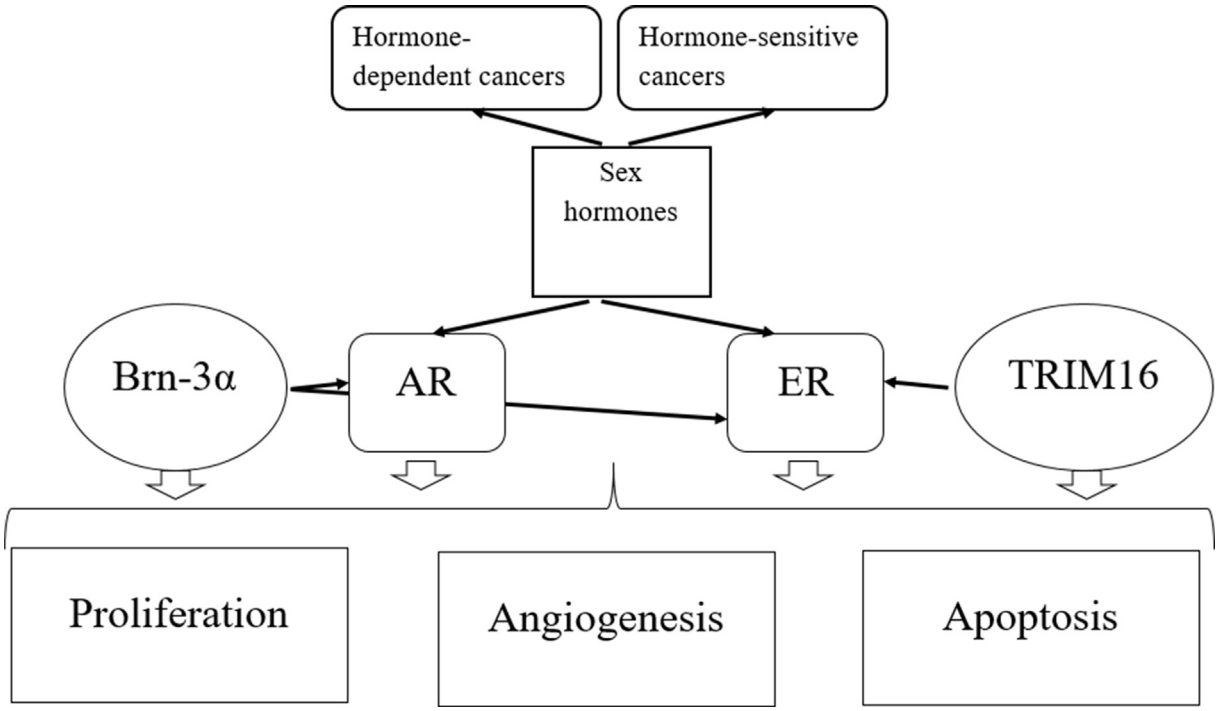

Fig. 2. Nuclear factors Brn-3α, TRIM16, and oncogenesis. Notes: Nuclear factors Brn-3α and TRIM16 are associated with cancer development and progression. They are involved in the key intracellular processes, such as proliferation, cell differentiation, and programmed death - apoptosis. By understanding the action of these factors we can clarify the association between classical hormone-dependent tumors and less sensitive ones with the modification in hormone receptors expression.

[30]. In melanoma cell lines, inhibition of Brn3α caused DNA double-strand breaks as evidenced by Mre11/Rad50-containing nuclear foci. Activated DNA damage signaling caused stabilization of the tumor suppressor p53, which resulted in cell cycle arrest and apoptosis. Furthermore, Brn3 α cooperated with proliferation pathways such as oncogenic BRAF, by reducing oncogene-induced senescence in non-malignant melanocytes.

Recently, the Brn-3α POU family transcription factor is overexpressed in human cervical carcinoma biopsies and is able to activate expression of the human papillomavirus type 16 (HPV-16) upstream regulatory region (URR), which drives the expression of the E6 and E7 oncoproteins [38].

It is shown that Brn3α plays an important role in the regulation of cell proliferation, due to the effect on the p53 protein [30]. Melanocyte culture showed that blockage of this protein leads to DNA damage, p53 protein stabilization. It results in cell cycle arrest and activation of apoptosis [16]. This factor can also regulate the proliferative signaling cascades, for example, BRAF, contributing to a reduction in the oncogene-induced senescence of non-transformed melanocytes.

In addition, it was found that Brn-3α is able to activate the expression of anti-apoptotic proteins Bcl-2 and Bcl-x, which promotes the protection of neuronal cells from apoptosis [14]. This fact is probably of great importance in the regulation of oncogenesis. Existing experimental work does not allow evaluating the value of this factor in the prognosis of the course and efficacy of therapy of malignant tumors.

1.4. Transcription factor TRIM16 in cancers

The influence of TRIM16 on the basic cellular processes determines its significance in oncogenesis. A lot of facts have been accumulated that attest to its involvement in the pathogenesis of human tumors. The level of protein is significantly lower in tumor tissue of the prostate gland than in normal [39]. The relationship of TRIM16 to the development and progression of ovarian cancer [21], squamous cell carcinomas of the head and neck region [40], lung cancer [23], hepatocellular carcinoma has been shown [24]. These facts allow us to consider the high expression of this protein as a marker of a favorable outcome of the disease [6, 28].

Qi L. et al. have shown that high TRIM16 gene expression is an indicator of the favorable overall survival of prostate cancer patients [39] and patients with squamous cell carcinomas [40]. Its decreased protein content is associated with progression of melanoma with regional lymph node affection and poor disease prognosis [41]. But a low expression of TRIM16 is a favorable prognostic sign in ovarian cancers [21]. It is also noted that the progression of prostate cancer is associated with overexpression of ERs, which is also revealed in our studies [42, 43]. This is consistent with the fact that the protein encoded by the TRIM16 gene has anti-estrogenic activity, reducing the expression of ERs in the cell.

The indirect action of TRIM16 protein on the development of tumors is mediated through various molecular factors that should be identified. The protein DNA-binding protein 43 (TDP43), Gli-1 is known to be one of them [8, 28]. Its significance is shown on the cell lines of neuroblastoma G and breast cancer [22]. In melanoma tissue, a decrease in TRIM16 is mediated by interferon beta-1 [44], followed by a decrease in the locomotor properties of tumor cells. The use of the BRAF inhibitor (tyrosine kinase associated with the MAPK signaling cascade) promotes an increase in the expression of TRIM16 accompanied by a decrease of the melanoma size [45].

Raif A. and coauthors [9] have previously identified the TRIM16, as a novel RARbeta2 transcriptional regulator in the retinoid signal [46]. Overexpression of EBBP alone markedly increased histone acetylation resulted in inhibited cell growth by effects on cyclin D1 and Phospho-Rb, and, reduced cell viability in retinoid-resistant cancer cells [9]. The development of drug-resistant tumors is a consequence of the use of antitumor therapy. Therefore, the study of the molecular mechanisms of its development, as well as the search for predictors is an actual problem in oncology. Thus, these data make a significant contribution to the development of ideas about the potential use of TRIM16 as a prognostic factor and predictor of the efficacy of cancer therapy.

2. Conclusion

The role of transcription factors in the development of hormone-dependent cancers is not a fully clear issue. Nuclear factors are found in both classical hormone-sensitive tumors and less sensitive ones. The regulation of hormonal reception by a change in the expression of Brn-3α and TRIM16 is not the single function of these proteins. The role of Brn-3α and TRIM16 proteins in the development of tumors is linked with their participation in key intracellular processes, such as proliferation, cell differentiation, and also their programmed death - apoptosis.

Developing a means to more specifically treat and ideally prevent hormone-dependent cancers is of critical importance given the significant impact these malignancies have on human health and the economic burden of disease. An in-depth understanding of hormone action in regulating diverse cellular processes, cancer phenotypes, and drug responsiveness is essential for the development of effective and well-tolerated treatment strategies.

Declarations

Author contribution statement

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Additional information

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