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The Multi Regulatory Role of Signal Transducer and Activator of Transcription Factor Brn-3a

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Abstract

In molecular biology and genetics, the transcription factor is a protein that binds to specific DNA sequences, thereby controlling the rate of transcription of genetic information from DNA to messenger RNA. Brn-3a is a POU-domain transcription factor that involve in the neurite outgrowth, induction of synaptic proteins, activation of the neurofilaments genes promoter, neuronal development, protects neuronal cells from apoptosis and plays a vital role in regulating different kinds of cancers. Brn-3a is an antiapoptotic transcription factor and the up-regulation of Brn-3a protects neuronal cells from undergoing apoptosis. Brn-3a specifically triggers the expression of Bcl-2 and Bcl-XL gene in neuronal cells. On the other hand, Brn-3a inhibits the pro-apoptotic factor like Bax. Brn-3a not only expresses in the neuronal cells but also its activity is detected in the cancer cells of non-neuronal nature. Brn-3a also modulates the activity of various others transcription factors, enzymes, receptors, ion channels, antiapoptotic proteins, adhesion molecules and cyclins. In this Review, we describe all the above factors in detail which are regulated by Brn-3a signaling in the neurology and the possible mechanisms underlying the many different functions of the Brn-3a complexes in neurological diseases. It also highlights the potential of Brn-3a as a novel target in heart development and cancer therapy.

Keywords: Brn-3a; Transcription factor; Development; Cancer therapy; Apoptosis

Introduction

Transcription factors are the key regulators of gene expression by working as the recruitment of transcription initiation factors or conformational changes in DNA, working alone or as part of the protein complexes. Brn-3 is a family of related transcription factors, namely, Brn-3a, Brn-3b and Brn-3c. Alternatively, it is also known as Brn-3.0, Brn-3.2, and Brn-3.1 respectively. These member proteins are encoded by POU4F1, POU4F2, and POU4F3 genes respectively. Brn-3a is an anti-apoptotic transcription factor having an important role in regulation of various biological processes [1]. Most importantly, Brn-3a is linked with survival and differentiation of cells. In contrast Brn-3b is expresses in actively proliferating cells. The cells with cease proliferation but with differentiation of neurite outgrowth have high Brn-3a expression while low Brn-3b expression [2].

Interestingly the Brn-3a deficient mice have defective apoptosis and various abnormalities in sensory axon growth. That's, because Brn-3a regulates the expression of certain genes that decide the phenotypic fate of developing trigeminal neurons. These Brn-3a regulated genes include the expression of genes responsible for neurotransmitters, neuron receptors, and ion channels proteins along with other mediators of axon growth [3]. It is well known that general somatic feelings are transferred to the central nervous system by the trigeminal ganglion (TG) at cerebral levels and by the dorsal root ganglia (DRG) at spinal levels. Most interestingly the microarray analysis of E13.5 embryos explored that Brn-3a target genes have over expression in the TG but not in the DRG [4]. The Brn-3a knockout mice revealed a defective differentiation, migration or survival along with proper axon growth of TG and DRG neurons [1-6]. Furthermore, Brn-3a also have an important role in heart development especially important for proper valve development, myocardial remodeling and maturation [7].

A number of approaches have been followed for investigating the mechanism of Brn-3a regulation. For this purpose, the mRNA and protein expression of Brn-3a were examined in rat retinal ganglion cells after axotomy-induced conditions, which verify that the regulation of Brn-3a occurred at the transcriptional level and Brn-3a activates the transcription of anti-apoptotic genes [8]. Moreover, it is important to mention that the expression of Brn-3a is regulated by neurotrophin-3 especially in trigeminal sensory neurons [9]. The extracellular signal-regulated kinase (ERK) pathway is reported to have antiapoptotic role in retinal ganglion cell death induced by glutamate [10] and ERK1/2 activate the Brn-3a during retinoic acid-mediated neuronal differentiation [11]. Another important revelation was that

homeodomain interacting protein kinase 2 (HIPK2), which is a pro-apoptotic transcriptional cofactor and regulates the Brn-3a and hence this cofactor have the ability to control the entire downstream Brn-3a targets. The deletion of HIPK2 leads to increased expression of Brn-3a, TrkA, and Bcl-xL. The over expression of these anti-apoptotic proteins lowered the apoptosis and increases the number of neurons in the trigeminal ganglion. While the loss of Brn-3a promoted the downregulation of TrkA expression, resulted in a remarkable increase in apoptotic cell death [12].

The Brn-3a also plays a key role in various types of cancer such as cervical neoplasia, and identified as one of the most recent potential targets in curing of prostate cancer [13,14]. The Brn-3a may be therapeutically targeted by transcription and growth factors, UV, natural products and synthetic compounds for the treatment of cancer.

In this Review, we summarize the recent advances in our understanding of the role of Brn-3a in normal neuronal, retina, and heart development as well as in cancer regulation. Understanding the mechanisms by which Brn-3a contributes to neurodevelopment, heart development and different cancers disorders will be fundamental for the development of new treatments for these disorders. We also discuss the possible mechanisms underlying the diverse functions of Brn-3a.

Interaction of Brn-3a with other factors

Incorrect regulation of Brn-3a may cause developmental defects, apoptosis, immune diseases, and cancer. The regulatory expression of Brn-3a is vital for normal development and for the survival of a variety of cell types. **Figure 1** shows the known interaction of Brn-3a with different types of factors. It is revealed that the Brn-3a expression was lowered by ultraviolet-B (UVB) irradiation in HaCaT cells [15]. Interestingly, the ginsenoside F1 treatment reinstate the UVB-induced down-regulation of Brn-3a expression in HaCaT cells [15]. Ginsenoside F1 may exert its antiapoptotic effect through the Brn-3a-mediated transcriptional regulation of Bcl-2 [15]. Similarly the steroid receptor coactivator 1 (SRC1) has a functional role in enhancing Brn-3a mediated transactivation [16]. Thus, Src-1 could be used to enhance the anti-apoptotic role of Brn-3a. Homeodomain interacting protein kinase 2 (HIPK2) is a pro-apoptotic transcriptional cofactor that has the ability to negatively regulate the Brn-3a-mediated gene expression. The HIPK2 altered the Brn-3a dependent transcriptions of trkA, and Bcl-xL [17]. The exact mechanism of the suppression function of HIPK2 for the Brn-3a is not known however, this study suggested that HIPK2 interacted with Brn-3a, enhanced Brn-3a binding to DNA, but it is interesting to mention that it represses the Brn-3a-dependent transcription of the aforementioned genes [17]. Moreover, the up-regulation of HIPK2 promoted apoptosis in cultured sensory neurons [17]. On the other hand, the deletion of HIPK2 leads to over-expression of the Brn-3a, TrkA, and Bcl-xL. Thus, HIPK2 is one of the critical regulators of Brn-3a transcriptional activity in neuronal cells. [17].

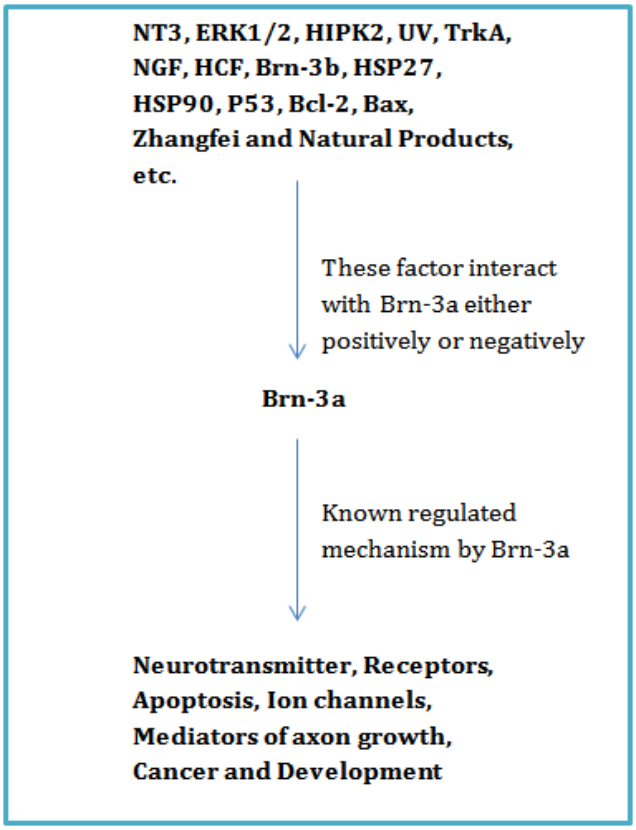

Figure 1 The schematic representation for possible interaction of Brn-3a with other factors and known modulating effect of Brn-3a.

In vitro experiments had revealed that the expression of Brn-3a mRNA is regulated by NT-3 (Neurotrophic factor-3) during differentiation in trigeminal neurons [9]. However, *in vivo* studies showed no reduction of Brn-3a mRNA expression in NT-3 knockout embryos during developing sensory neurons from E-10 to E-14 in mice model [9]. The extracellular-signal-regulated kinase (ERK) pathway is reported to have an important role in the anti-apoptotic mechanism of retinal ganglion cells against glutamate induced cell death [10]. Moreover the ERK is also essential for nerve growth factor (NGF) dependent neurite outgrowth or NGF non-dependent neuritogenesis [18]. Most importantly, the ERK1/2 activates the Brn-3a during retinoic acid-mediated neuronal differentiation [11]. The aforementioned studies suggest that Brn-3a may interact with other factor and hence play an important role in neuronal cell differentiation and survival.

Brn-3a Role in neural development

Although, the biology of vertebrate nervous system development are very complex but the current research era has revealed a large numbers of transcription factors that are necessary for the proper developmental regulation of vertebrate nervous system. The more studied portion of the nervous system development includes sensory and motor pathways of the peripheral sensory ganglia, spinal cord and

brainstem [5]. Among these, several transcription factors have been determined including the Brn-3a which was shown to have important regulatory role in the development of nervous system [5]. Brn-3a transcription factor is necessary for proper axon growth as well as target innervations and survival of TG and DRG neurons. Most importantly the loss of Brn-3a in the developing DRG may cause changes in the expression of target genes. These target genes may include various neurotransmitters, receptors, developmental regulators, mediators of signal transduction, and transcription factors [4]. Another study concluded that Brn-3a may control the expression of CGRP (Calcitonin gene related peptide) but not parvalbumin in DRG neurons [19].

Interestingly the inhibition of Brn-3a leads to the death of sensory neurons in cell culture conditions even in the presence of neurotrophic factors and the mice lacking the Brn-3a gene showed extreme losses of somato-sensory neurons. While the animals have deleted Brn-3a gene is not able to survive after birth [20]. The Brn-3a is needed to halt the expression of early neurogenic transcription factors (Neurod1 and Neurod4) in the developing TG [21]. The regulatory role of Brn-3a was studied on the Runx3 expression and was found that Brn-3a directly regulates Runx3 expression. This statement was supported by the experimental results that Brn-3a-/- TG showed almost complete loss of Runx3. These results suggested the direct regulatory role of Brn-3a on Runx3 regulation. It also indicated that Brn-3a work as a transcriptional regulator in initial stages of TG development [22]. In another side the Brn-3a also plays a role in sensory subtype specification through up-regulation of Runx1 and Runx3 expression in E11.5 to E13.5 ganglia [22]. The regulatory mechanism suggests that Brn-3a may directly bind to conserved upstream regulatory elements hence leads to the activation of Runx3 gene [22]. There are several scientific evidences from different organisms that Brn-3a dependent Runx3 regulate various aspect of embryonic development and its miss-regulation may leads to several developmental defects [23]. It is evident from the aforementioned studies that Brn-3a has an important direct or in-direct role in neuronal development.

Tropomyosin receptor kinase A/Nerve growth factor (TrkA/NGF) receptors are important for the differentiation as well as survival of sensory neurons. The main cellular pathways for regulation of tissue and stage-specific expression of TrkA are poorly understood. However, the Brn-3a transcription factor was considered to have an important role in the development of the peripheral nervous system (PNS) and most importantly as a transcription regulator for TrkA [24]. The main molecular mechanisms for the Brn-3a mediated regulation of TrkA are still unknown. However, the genetic, transgenic and biochemical results suggested that Brn-3a mediated regulation of TrkA in embryonic sensory neurons occurs through specific binding to enhancer region of TrkA promoter [24]. It has been recently discovered through establishing a culture system based of embryonic stem cells that TrkA itself promote the killing of specific nerve cells in the absence of NGF [25]. These finding suggested that nerve cells in the developing brain are much less dependent on growth factors for their survival, compared with those of the peripheral nervous system [25].

The Kruppel-like factor 7 (Klf7) and Brn-3a also regulate and activate the TrkA enhancer *in vitro* and during the development in mice [26]. The detail link between Brn-3a, TrkA, NGF signaling, Zhangfei and herpes simplex virus-1 (HSV-1) latency and reactivation are still to be investigated. However, it was determined that Zhangfei has the ability to repress Brn-3a to activate the expression of TrkA. This important phenomenon would disturb the normal NGF-TrkA signaling; hence have an impact on HSV-1 reactivation from latency [26].

Brn-3a Role in retina development

Retina is currently the best understood subdivision within the vertebrate central nervous system (CNS). Research in the past few decades have provided detailed insights into the neuronal morphology, synaptic connectivity, and physiology of the retina. Expression and regulation of various genes involved in the development were also studied in detail [27]. However, exact regulatory mechanisms at transcription level for the morphologic and functional diversity of retina neuron are still poorly understood. The developmental, morphological and functional role of Brn-3a and Brn3b transcription factors were evaluated in retinal ganglion cell (RGC) [28]. The handy results highlight that Brn-3a and Brn3b expressing RGCs shows overlapping but different dendritic stratifications and central projections. Moreover, the deletion of Brn-3a resulted in changes of dendritic stratification but little or no alteration in central projections [28]. The Brn-3a is largely expressed in the retina and tectum, in a wild-type embryo. In addition, the habenula and cranial sensory ganglia also have Brn-3a expression [29]. The expression of Brn-3a in retina at embryonic and other developmental stages suggests the important regulatory role in the proper development of retina. However, further research is needed to fully evaluate the role of this important transcriptional factor in retinal development.

Brn-3a Role in heart development

Like in other organs and tissues, the Brn-3a transcription factors have been reported to have an important role in the proper development of heart. Previous study have shown that Brn-3a regulating various genes including small heat shock protein (Hsp27) and P53, which is needed for normal heart tube formationischaemic/hypoxic regulation [30,31]. The above lines show an association of Brn-3a, Brn-3b and Hsp27 expression in the developing rodent heart. The early developmental stages express both Brn-3a and Brn-3b, even though there was more significant increase in later developmental stages. Thus Brn-3a is expressing in relation with Brn-3b and Hsp27 in the rodent heart [30]. Brn-3a is required for the precise valve and myocardial remodelling and maturation. Experimentally it was proved that Brn-3a-/- mice had developed partially penetrant phenotype with thickening of the endocardial cushions and atrio-ventricular valve leaflets along with hypoplastic ventricular myocardium [32]. The reporter assay determined that Brn-3a as well as Brn-3b turns on the hsp27 promoter through Brn-3-binding site. The aforementioned lines suggested that Brn-3 transcription

factors have an essential role in the development as well as maintenance of important cell types and other function in heart through the regulation of myocardial heat shock proteins [33].

Brn-3a as a novel target for cancer and therapies

Brn-3a transcription factor was initially discovered in the nervous system [30], but later it expression was also detected in reproductive tissues including breast, ovary, cervix, prostate and testis [34]. Brn-3a controls the equilibrium between cell proliferation, differentiation and apoptosis by regulating promoters of specific genes. The targeted genes are directly regulated by Brn-3a or it interacts with various other cofactors [35]. The aberrant expression of Brn-3a transcription factors were linked to various types of cancers. The significant over-expression of Brn-3a levels was reported in cervical cancer [36], prostate cancer [14], neuroendocrine tumors [37] and Ewing's sarcoma [38].

Worldwide, cervical cancer is the second most reported cancer type and developing countries are having even more higher incidence. The miss-regulation of various genes and transcription factors were linked with cervical cancer. In recent past, the over-expression of Brn-3a was reported in high-grade ovarian carcinomas. Similarly, the tumor cells from ascites of patients with advanced-stage ovarian cancer also showed higher expression of Brn-3a. Furthermore, cytoplasm and nuclear Brn-3a expression was more prominent in ovarian cancer cell lines as compared to normal ovarian cell lines [39]. It was concluded from this study that Brn-3a expression may inhibits apoptosis and enhance tumorigenesis in ovarian tissues [39]. Therefore, the exact targeting of Brn-3a might be useful approach to regulate the multiple tumor related genes involved in the ovarian carcinomas [39].

In 2005, Diss et al., have reported that over-expression of Brn-3a is associated with prostate cancer and Brn-3c miss-regulation have no linked with prostate cancer [14]. The Brn-3a over-expression increases with cancer progression [14]. Other than prostate cancer high level of Brn3a expression was also found in aggressive neuroendocrine tumors [40]. The main suggested molecular mechanism is that interaction of Ewing's Sarcoma protein (EWS) with the Brn-3a blocks its ability to activate transcription of the targeted genes and might be responsible for Ewing's sarcoma [38].

In a clinical study it was found that approximately 43% of systemic lupus erythematosus (SLE) patients had serum levels of antibodies to Brn-3a. In this study, the serum and peripheral blood mononuclear cells samples were collected from 87 SLE patients and 30 normal individuals. This over-expression of Brn-3a was associated with active SLE disease. It was reported that Hsp90 is the target and regulated by Brn-3a. The over expression of Hsp90 has an important role in SLE disease [40]. In the above mentioned clinical study it was concluded that the increased level of auto-antibodies against Brn-3a proteins may leads to the over-expression of Hsp90 and hence cause SLE [40]. Recently, a study reported the important role of Brn-3a in regulating human papilloma virus (HPV)-16 variants. The infected patients were with risks of progression to cervical carcinoma. The women smokers have elevated levels of Brn-3a expression and infected with low- or high-risk HPV-16 variants and also have higher level E6 HPV-16 antibodies. These types of women were often reported with higher grades of cervical intraepithelial neoplasia (CIN) and cancer. On the other hand women that have never smoked but having same HPV-16 variants infection with same levels of Brn-3a were less reported with CIN and cancer [41].

The aforementioned studies have shown that Brn-3a have an important role in the onset and progression of various cancer types. The targeting of Brn-3a can be a novel strategy in cancer therapy. Therefore, an organized research is needed for the mechanistic regulation of Brn-3a and to find new and novel drugs and other strategies that can specifically target Brn-3a expression. The mechanistic regulation of Brn-3a might be a step forward in the treatment of cervical, prostate cancer, neuroendocrine tumors, Ewing's sarcoma and SLE disease.

The interaction of Brn-3a modulating p53 functional activity

p53 is a tumor suppresser gene and have an important role in maintaining proper cell cycle and growth. p53 is a transcription factor which has the ability to detect and respond to various cellular stress conditions; it can activate or silence different cellular pathways which lead to cell cycle arrest, DNA repair, apoptosis, or senescence. The miss-regulation or deletion of p53 is associated with more than half of all human cancers. The p53 activation and proper function involve a complex repertoire of posttranslational modifications and protein interactions, so the identification of genes and proteins regulated by p53 or which regulates p53 are essential for curing of cancers [42]. Among these, BAX (a member of Bcl-2 (B cell lymphoma-2) gene family) is an apoptotic regulator gene that encodes for a potent pro-apoptotic Bcl-2-like protein 4. The BAX promotes apoptosis through binding to and antagonizes Bcl-2. It has been reported that BAX is involved in p53-mediated apoptosis and its expression is regulated by p53. The p53-mediated apoptotic pathway involves the BAX transactivation, BAX translocation to mitochondria that leads to loss of membrane potential and promotes the cytochrome c release. Moreover, other cellular and molecular events are also involves in the whole process of p53-mediated apoptosis [43].

The Bcl-2 anti-apoptotic function is dependent on its expression level that can be regulated at various stages like at transcription and posttranslational or its degradation after synthesis. Various molecular mechanisms are involved in these regulation processes [44]. In addition to p53, it has also been shown that Brn3a regulate the expression of Bax or Bcl-2 *in vitro* [17,45]. Brn-3a promotes the activation of the Bcl-2 promoter and cell survival. On the other hand, p53 inhibit the activation of Bcl-2 and promotes apoptosis. The Brn-3a and p53 functionally antagonize each other [46]. It has also been reported that p53 can directly interact with Brn-3a. This interaction makes p53 unable to activate pro-cell-death genes

such as Bax, and rather increased affinity for the pro-differentiation gene p21. Previously, it was shown that the interaction of p53 with Brn-3a cause a change in p53 transcriptional activity from cell death to neuronal differentiation [47]. This interaction of Brn-3a with p53 in neuronal cells may be critical for the cell fate [48]. These above mentioned studies suggest that interaction of Brn-3a with p53 modulates the functional activity of this important tumor suppresser gene. More work is needed in this field in order to unleash the importance of this complex transcription factor interaction with tumor suppresser gene [49,50-56].

Conclusion and Future Prospects

The *available* data indicates that Brn-3a plays a critical role in neural organogenesis, apoptosis, cancer and mis-regulation of Brn-3a can lead to a variety of developmental complications. Thus, Brn-3a appears to offer a promising strategy in controlling the neurogenesis, apoptosis and cancer. To understand the mechanism of action of Brn-3a is a challenge for the researcher in the future. The function of Brn-3a is acutely dependent on its interacting partners so the identification of additional Brn-3a target genes should help to understand the complex role of Brn-3a in a variety of tissues' developmental and pathological conditions. The future study need to explore the interaction of Brn-3a with Janus kinase/ signal transducer and activator of transcription (JAK/STAT) signaling, which has been shown to support the survival of various retinal cells against cell death. The detail interactions between Brn-3a, TrkA, NGF signaling, Zhangfei and herpes simplex virus-1 (HSV-1) latency and reactivation are still to be investigated. Finally, improving our understanding of the precise mechanisms by which Brn-3a affects neurodevelopmental and/or cancer regulation will be fundamental for the development of targeted and more effective treatments.

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