Review

Nuclear Factor I/B: A Master Regulator of Cell Differentiation with Paradoxical Roles in Cancer

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Abstract

Emerging evidence indicates that nuclear factor I/B (NFIB), a transcription factor required for proper development and regulation of cellular differentiation in several tissues, also plays critical roles in cancer. Despite being a metastatic driver in small cell lung cancer and melanoma, it has become apparent that NFIB also exhibits tumour suppressive functions in many malignancies. The contradictory contributions of NFIB to both the inhibition and promotion of tumour development and progression, corroborates its diverse and context-dependent roles in many tissues and cell types. Considering the frequent involvement of NFIB in cancer, a better understanding of its multifaceted nature may ultimately benefit the development of novel strategies for the management of a broad spectrum of malignancies. Here we discuss recent findings which bring to light NFIB as a crucial and paradoxical player in cancer.

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2352-3964/© 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. NFIB in Development and Cell Physiology

The Nuclear Factor I (NFI) family of site-specific DNA binding proteins functions in adenoviral DNA replication and in the regulation of transcription of a large variety of cellular and viral genes (Gronostajski, 2000). This family is comprised of four genes in vertebrates (NFIA, NFIB, NFIC and NFIX), whose encoded proteins interact with DNA as homo- or hetero-dimers. They bind to the palindromic sequence TTGGC(N5)GCCAA with high affinity, resulting in transcriptional activation or repression, depending on the cellular context and regulatory region (Gronostajski, 2000). Binding sites for these factors have been identified in promoter, enhancer and silencer regions of a plethora of genes expressed in almost every organ and tissue (Kruse and Sippel, 1994; Gronostajski, 2000). Reflecting their important roles, NFIs are essential for the development of a number of organ systems and show non-redundant functions during murine development (Chaudhry et al., 1997; das Neves et al., 1999; Steele-Perkins et al., 2005; Barry et al., 2008).

Transcriptome and proteome analyses reveal that NFIB is commonly expressed throughout the human body (Fig. 1; GTEx Consortium, 2015, Uhlen et al., 2015). Consistent with this ubiquitous expression pattern and the apparent abundance of target genes, data supports that NFIB plays a fundamental role in a range of biological processes (Fig. 2). Mice lacking this gene present with a very severe phenotype, marked by the death of all animals shortly after birth due to lung dysfunction (Steele-Perkins et al., 2005). Loss of Nfib results in an undifferentiated primordial respiratory system in addition to major neuroanatomic defects, including corpus callosum dysgenesis and delayed glial and neuronal differentiation (Steele-Perkins et al., 2005). Notably, some Nfib heterozygous animals show related phenotypes, suggesting haploinsufficiency at the Nfib locus (Steele-Perkins et al., 2005). Besides being essential to lung and brain development, Nfib has also been shown to be required for tubule cell differentiation during development of mouse submandibular glands (Mellas et al., 2015).

In addition to these roles in development, NFIB has been implicated in a range of physiological processes, such as, adipocyte differentiation (Waki et al., 2011), megakaryocyte maturation (Chen et al., 2014), and in the regulation of androgen receptor signaling in the prostate (Grabowska et al., 2014). Furthermore, NFIB functions as a gatekeeper, governing activity within the quiescent stem cell niche of hair follicles, where its loss enhances melanocyte stem-cell self-renewal, disturbing epithelial-melanocyte stem cell synchrony (Chang et al., 2013). Recently, NFIB has also been shown to regulate hippocampal neural stem cell fate (Rolando et al., 2016).

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**Fig. 1.** NFIB expression overview in human tissues. NFIB is expressed in a range of tissues. RNA-sequencing data from 31 tissues generated by the Genotype-Tissue Expression Project (GTEx; https://www.gtexportal.org/) are reported as median RPKM (Reads Per Kilobase of transcript per Million mapped reads). Colour-coding is based on 13 tissue groups, each consisting of tissues with common functional features (adapted from the Human Protein Atlas: http://www.proteinatlas.org/ENSG00000147862-NFIB/tissue, available from v16.1.proteinatlas.org).

**Fig. 2.** NFIB functions in development and physiology. NFIB is required for the development of the lung, brain and submandibular glands. It is also required for the maintenance of a range of physiological processes in several tissues, including adipocyte differentiation, megakaryocyte maturation, regulation of androgen receptor signaling in the prostate, and epithelial-melanocyte stem cell behaviour in the hair follicle niche. Note: Experiments assessing the diverse functions of NFIB were performed mainly using mouse models, and in some cases human cell lines.
Corroborating its functions in regulating a variety of developmental and physiological processes, NFIB has become increasingly implicated in a range of malignancies (Table 1), which is the focus of this review article.

2. NFIB as an Oncogene

2.1. Small Cell Lung Cancer

Using genetically engineered mouse model systems of small cell lung cancer (SCLC) in combination with analyses of human SCLC specimens, a number of studies have defined NFIB as an oncogene. In 2011, Dooley et al., identified NFIB amplification/overexpression within murine tumour tissue, showed that NFIB regulated cell viability and proliferation during transformation of murine SCLC, and reported recurrent amplification of NFIB in ~15% of primary human SCLC (Dooley et al., 2011). More recently, a major oncogenic role was assigned to NFIB in this class of lung tumours. In a series of experiments, Denny et al. implicated NFIB in critical molecular events that drive metastasis in SCLC. In a series of experiments, Denny et al. implicated NFIB in critical molecular events that drive metastasis in SCLC, and reported recurrent amplification of NFIB in ~15% of primary human SCLC (Dooley et al., 2011). More recently, a major oncogenic role was assigned to NFIB in this class of lung tumours. In a series of experiments, Denny et al. implicated NFIB in critical molecular events that drive metastasis in SCLC (Denny et al., 2016). They showed that NFIB is both necessary and sufficient to promote multiple steps of the metastatic cascade in vivo, through the reconfiguration of chromatin accessibility in SCLC cells. Chromatin in metastatic lesions displayed a widespread increase in accessibility at gene distal regions that were enriched for NFI motifs, resembling regions found in neural tissue. NFIB was associated with the newly opened chromatin sites, maintained the hyper-accessible chromatin configuration in SCLC cells. This suggests that NFIB is involved in the de novo open chromatin sites, which are associated with the reprogramming of gene expression programs by influencing the combinatorial binding of other transcription factors to these open chromatin regions (Denny et al., 2016). In addition, a different study using another mouse model of SCLC also showed that NFIB promotes metastatic spread, and that it is highly overexpressed in human metastatic high-grade neuroendocrine lung tumours (Semenova et al., 2016). Moreover, an additional report demonstrated oncogenic properties of NFIB in a related model system of SCLC, supporting its role as a metastatic driver, and identifying target gene networks including those related to axon guidance, focal adhesion and extracellular matrix-receptor interactions (Wu et al., 2016).

2.2. Melanoma

Most recently NFIB has been shown to mediate a highly invasive and migratory phenotype in melanoma, where it directly promotes EZH2 expression, also leading to changes in the chromatin state of tumour cells to facilitate this aggressive behaviour (Fane et al., 2017). This study showed that the direct regulation of NFIB expression by BRN2 in melanoma cells, leads to increased cell migration and potentially invasion through the positive and negative regulation of EZH2 and MITF respectively. In melanoma, heterogeneous expression of the MITF and BRN2 transcription factors has been proposed to constitute a key switching mechanism between phenotypic states essential to tumour development and progression (Goodall et al., 2008; Hoek and Goding, 2010). While MITF is a driver of a highly proliferative, less invasive cell state, BRN2 promotes an invasive and less differentiated state crucial to drive tumour progression towards metastasis. NFIB seems to be a key mediator of this phenotype switching.

2.3. Other Cancers

Increased copy number and expression of NFIB have also been reported in triple negative breast cancer (Han et al., 2008) consistent with an oncogenic role in estrogen receptor-negative breast tumours (Moon et al., 2011). Furthermore, NFIB amplifications within squamous cell carcinoma of the esophagus (Yang et al., 2001), large cell neuroendocrine carcinoma of the submandibular gland (Andreasen et al., 2016), and metastatic giant cell tumour of the bone (Quattrini et al., 2015) have

| Type of aberration | Organ/site | Tumour type | Function/potential role | Reference(s) |
|--------------------|------------|-------------|------------------------|--------------|
| Amplification/overexpression | Lung | Small cell lung cancer | Oncogene | Denny et al., 2016; Dooley et al., 2011; Semenova et al., 2016; Wu et al., 2016 |
| Overexpression | Skin | Melanoma | Oncogene | Fane et al., 2017 |
| Amplification/overexpression | Breast | Triple negative; ER negative | Oncogene | Han et al., 2008 |
| Amplification | Esophagus | Squamous cell carcinoma | Unknown | Yang et al., 2001 |
| Amplification | Submandibular gland | Large cell neuroendocrine carcinoma | Unknown | Andreasen et al., 2016 |
| Amplification | Bone | Metastatic giant cell tumour | Unknown | Quattrini et al., 2015 |
| Underexpression | Lung | Non-small cell lung cancer | Tumour suppressor | Becker-Santos et al., 2016 |
| Loss of heterozygosity/underexpression | Brain | Glioma, Glioblastoma | Tumour suppressor | Stringer et al., 2016; Suzuki et al., 2015 |
| Germine mutation | Bone | Osteosarcoma | Tumour suppressor | Mirabello et al., 2015 |
| Underexpression | Skin | Cutaneous squamous cell carcinoma | Tumour suppressor | Zhou et al., 2014 |
| Gene fusions (MYB-NFIB, MYBL-NFIB, NFIB-AK1, NFIB-MAN1A1, NFIB-NKAIN2, NFIB-PTPRD, NFIB-XRCC4) | Salivary, lacrimal & ceruminous glands; breast; vulva | Adenoid cystic carcinomas | Unknown | Marchio et al., 2010; Xing et al., 2016; Persson et al., 2009; Mitani et al., 2010; Brayer et al., 2016; Mitani et al., 2011; Geurts et al., 1998 |
| Gene fusions (HMGA2-NFIB) | Head & neck | Pleomorphic adenoma | Unknown | Mitani et al., 2016; Geurts et al., 1998 |
| Gene fusions (HMGA2-NFIB) | Colon & retroperitoneal space; intramuscular | Lipoma | Unknown | Italiano et al., 2008; Pierron et al., 2009 |
also been reported, although, the role of NFIB in these cancers is unknown.

3. NFIB and Tumour Suppressive Characteristics

Despite NFIB’s established role as an oncogene in SCLC, and most recently in melanoma (and potentially in other malignancies as well), several lines of evidence suggest a tumour suppressor function in other cancer types (Fig. 3).

3.1. Non-small Cell Lung Cancer

We have shown that NFIB is underexpressed in 40–70% of non-small cell lung cancers (NSCLC), and that higher NFIB expression is associated with favourable prognosis in lung adenocarcinoma, but not in squamous cell carcinoma patients (Becker-Santos et al., 2016). This lineage-specific phenotype, likely reflects the role of NFIB in regulating the differentiation of cell types comprising the terminal respiratory units of the lung (Steele-Perkins et al., 2005) where lung adenocarcinomas, but not squamous cell carcinomas, typically develop. Accordingly, we observed that tumours presenting low levels of NFIB, displayed less differentiated phenotypes, accompanied by the repression of lung differentiation markers involved in the development of type II pneumocytes, which are thought to be the progenitor cells for lung adenocarcinomas (Becker-Santos et al., 2016).

3.2. Glioma and Glioblastoma

NFIB has shown tumour suppressor activity in glioblastoma, where its expression is inversely correlated with astrocytoma grade, and ectopic expression significantly inhibits tumour growth in vivo. Similar to the findings in NSCLC versus SCLC, NFIB appears to exert a context-dependent role in glioblastoma, whereby its expression induced differentiation and inhibited proliferation and self-renewal of classical and mesenchymal glioblastoma subtypes, while enhancing the growth of neural subtypes (Stringer et al., 2016). Furthermore, a tumour suppressive function for NFIB in brain is also supported by a genome-wide study of genetic alterations associated with gliomas, which revealed NFIB loss of heterozygosity with increasing glioma grade (Suzuki et al., 2015).

3.3. Cutaneous Squamous Cell Carcinoma

Contrary to the findings in melanoma, expression of NFIB has been proposed as a barrier for the development of cutaneous squamous cell carcinoma. Underexpression of NFIB has been reported as a general feature in tumours from patients with this type of skin cancer, and its downregulation in keratinocytes led to carcinogenic transformation. While suppression of NFIB led to upregulation of CDK6 and Bcl-2, it also decreased p53 levels, suggesting that NFIB may mediate G1 arrest and consequently apoptosis in cutaneous squamous cell carcinoma (Zhou et al., 2014).

3.4. Osteosarcoma

NFIB underexpression has been associated with aggressive osteosarcoma phenotypes. A multistage genome wide association study assessing the connection between germline genetic variation and osteosarcoma metastasis, identified a common SNP in NFIB (9p24.1), which is associated with a decrease in NFIB expression and metastasis at diagnosis (Mirabello et al., 2015). Decreased NFIB levels led to increased osteosarcoma cell line proliferation, migration and colony formation, supporting its contribution to susceptibility to metastasis.

4. Gene Fusions Involving NFIB

4.1. Adenoid Cystic Carcinomas

NFIB has been linked to other malignancies through gene fusions, which is frequently the case in adenoid cystic carcinomas (tumours that most commonly arise from salivary and lachrymal glands, although they can also occur in other tissues containing secretory glands such as breast, cervix and vulva) (Persson et al., 2009; Mitani et al., 2010; Brayer et al., 2016; Marchio et al., 2010; Xing et al., 2016). These cancers are often characterized by a recurrent translocation t(6;9)(q22–23;p23–24) involving MYB and NFIB, which leads to high expression of a functional MYB and truncation of NFIB – in the majority of cases only exon 9 of NFIB (encoding the last 5 amino acids) is present in the chimeric mRNA transcripts. The MYB-NFIB gene fusion was reported in 23–86% of adenoid cystic carcinomas arising from different anatomical sites (Wysocki et al., 2016). NFIB may have a tumour suppressive role in

Fig. 3. Paradoxical roles of NFIB in cancer. NFIB has shown both oncogenic and tumour suppressive functions in different cancer types and subtypes.
these tumours independent of MYB, as rearrangements leading to
truncation of NFIB, and presumably loss of its function also occur with other partners (e.g.: NFIB-AIG1, NFIB-MAN1A1, NFIB-NKAIN2, NFIB-PTPDR, NFIB-XRCC4) (Mitani et al., 2011; Mitani et al., 2016). Further supporting a tumour suppressor role in adenoid cystic carcinomas, truncating muta-
tions and homozygous deletions affecting NFIB have also been report-
ed in these tumours (Ho et al., 2013).

4.2. Lipomas and Pleomorphic Adenomas

Other chromosomal translocations involving NFIB include HMGA2-
NFIB fusions in lipomas and pleomorphic adenomas, which lead to up-
regulation of HMGA2 and truncation of NFIB (as in the MYB-NFIB rear-
rangements, in many cases only five amino acid residues encoded by
NFIB were shown to replace the carboxyterminal portion of HMGA2)
(Geurts et al., 1998; Italiano et al., 2008; Pierron et al., 2009). Similar
to adenoid cystic carcinomas, NFIB most likely plays a role independently
of HMGA2, as it is also present in rearrangements with other partners
in these malignancies.

Despite the high frequency of rearrangements involving NFIB in ad-
enoid cystic carcinomas, lipomas and pleomorphic adenomas, apart
from the fact that the relocation of NFIB regulatory elements has been
proposed to contribute to high expression of its fusion partners
(Wysocki et al., 2016), little attention has been focused on a potential
direct role for NFIB in these cancers – this highlights the need for studies
assessing the direct contribution of NFIB to these malignancies, where
disruption resulting in its loss of function might play a key role.

5. NFIB Gene Regulation and Downstream Targets

An understanding of the seemingly paradoxical nature of NFIB to
display both oncogenic properties and tumour suppressor activity, is
hampered by the paucity of information regarding regulation of its ex-
pression in various cancer types/subtypes, and the identification of
downstream effectors. Moreover, the NFIB locus (9p23–9p22.3) is very
complex, where at least 20 spliced variants have been identified
(Ensembl version 88; Yates et al., 2016), although their possible distinct
functions remain to be explored. The presence of a large 3′UTR extend-
ing up to 7.8 kb, suggests that NFIB levels may be commonly regulated
by miRNAs. Indeed, we and others have reported that miRNAs such as
miR-92b-3p, miR-21 and miR-365, which are frequently deregulated in
cancers where NFIB is altered, can bind to the 3′UTR of NFIB, leading
to its downregulation (Becker-Santos et al., 2016; Fujita et al., 2008;
Zhou et al., 2014). Recently, NFIB has also been shown to be directly re-
duced by Drosha, independent of miRNAs, representing a novel cell-
intrinsic mechanism that regulates the fate of adult hippocampal stem
cells (Rolando et al., 2016). Nevertheless, the context-dependent and
cell type-specific mechanisms by which NFIB levels are regulated re-
main largely unknown, and only a few transcription factors have been
shown to directly regulate its expression. These include ASCL1 and
MYC in a SCLC context (Borrowe et al., 2016; Mollaoglu et al., 2016),
PAX6 in neural progenitor cells (Ninkovic et al., 2013), and BRN2 in mel-
anoma (Fane et al., 2017).

Similarly, for most tissue and cell types where NFIB is expressed,
only a few direct downstream targets have been identified. Examples
include EZH2, which is repressed by NFIB during cortical development
(Piper et al., 2014) but activated by NFIB in melanoma (Fane et al., 2017),
IGFBP5 which is activated by NFIB in osteoblasts (Perez-Casellas et al., 2009), and SFTPC (Bachurski et al., 2003) and ELN (Hsu et al., 2011)
both of which are activated by NFIB in lung development. NFIB also
regulates EDN2 in a context related to epithelial-melanocyte stem
cell proliferation and differentiation in hair follicles, where it was also
linked to the regulation of expression of 1449 target genes by ChiP
(Chang et al., 2013). Since NFI members encode proteins with highly
homologous DNA-binding domains with similar DNA-binding specific-
itics, it is possible that there are common downstream targets for all
NF1 genes. In contrast to the highly conserved N-terminal DNA binding
domain, the C-terminal region of NFIB, which encodes a transactivation
domain, diverges extensively between other NFI members as well as be-
etween isoforms, and therefore might promote interactions with differ-
cent nuclear regulatory proteins depending on the cellular context
(Gronostajski, 2000). Adding to this complexity, post-translational
modifications (phosphorylation, O- or N-glycosylation) can significantly
influence the activity of NFI proteins (Sabova et al., 2013). Fig. 4 summa-
rizes the regulation of NFIB activity at multiple levels.

It is also noteworthy that NFIB is located in close proximity to the
fragile site FRA9G at 9p22.2, which is present in a large fraction of the
population (Sawinska et al., 2007), and coincides with recurrent chro-
mosomal breakpoints in cancer cells (Arlt et al., 2006). This location
could explain the high frequency of chromosomal rearrangements in-
volving NFIB described in several cancers (Table 1), although this hy-
pothesis needs to be further explored.

6. Conclusions and Perspectives

A number of transcription factors that induce lineage-specific differ-
entiation during embryonic and fetal development, play crucial, and
sometimes paradoxical roles in the malignant transformation of adult
cells. Although the roles of some of these transcription factors have
been well studied in cancer, which is the case for NKX2-1 and SOX
members (Yamaguchi et al., 2013; Thu et al., 2014), much remains to
be deciphered in terms of understanding the oncogenic and tumour
suppressive functions of the vast majority of such important players.
The first NFI transcription factor was identified over thirty years ago as
a protein required for efficient initiation of adenosine virus replication
(Nagata et al., 1982). Since then, this family of transcription factors
has been implicated in the transcriptional regulation of a variety of
viral and cellular genes, and is critically important for the proper devel-
opment of a number of organs (Chaudhry et al., 1997). Thus, as is the
case with other transcription factors involved in developmental pro-
cesses, it is not surprising that NFIB has become increasingly appreciat-
ed as an important player in tumour development and progression.

Recent studies have ascertained a potent oncogenic role for NFIB in
SCLC. By increasing chromatin accessibility similar to open regions
found in neural tissue, NFIB has emerged as a driver of metastasis in
these highly aggressive neuroendocrine lung tumours (Denny et al.,
2016). These findings suggest that this mechanism may be relevant
to other cancers, especially to other neuroendocrine tumours, which sim-
ilar to SCLC, also rely on the activation of neuron-like programs, and
therefore, might depend on NFIB to drive their metastatic behaviour.
In addition to SCLC, a vital role for NFIB in triggering invasive behaviours
that drive metastatic spread in melanoma was recently shown (Fane et
al., 2017). In this type of skin cancer, NFIB is capable of propagating the
acquisition of a more invasive phenotype through broad changes in
chromatin status, in large part by increasing expression and function
of the histone methyl-transferase enzyme EZH2. Taken together, both
studies reveal that NFIB has the ability to promote dynamic changes in
the chromatin state of tumour cells to facilitate migration, invasion, and
ultimately, metastasis. While in melanoma a key conduct of these
effects is the regulation of EZH2 by NFIB, it remains to be determined if
a similar epigenetic mechanism could be involved in other tumour
types to drive metastatic progression.

Despite a clear oncogenic role for NFIB in SCLC and melanoma, tu-
mour suppressive functions have been demonstrated or strongly sug-
gested in other cancers. Although the molecular mechanisms behind
its anti-oncogenic functions are not well understood, the fact that NFIB
is widely expressed in multiple normal tissues and cell types, supports a
potential role in the maintenance of cellular homeostasis, and conceiv-
ablely as a barrier to malignant transformation. Accordingly, we and
others have shown that downregulation of NFIB leads to the activation
of less differentiated tumour phenotypes, culminating in increased can-
cer aggressiveness and ultimately poorer patient survival. The concept
that cells undergo a process of dedifferentiation to a more progenitor like state frequently associated with metastasis, has been documented in various cancer models (Friedmann-Morvinski and Verma, 2014). Moreover, NFIB appears to play a critical role in maintaining stem cell quiescence in some adult tissues (Harris et al., 2015; Chang et al., 2013; Rolando et al., 2016). Further supporting a link between NFIB and the modulation of cellular fate, this NFI member has been shown to be regulated/interact with two key pluripotent transcription factors, MYC and SOX2, respectively (Mollaoglu et al., 2016; Engelen et al., 2011).

Although cancer-related studies have focused mostly on cell-intrinsic changes caused by NFIB, it is worth noting that tumour microenvironment changes might also contribute to drive NFIB-induced cancer aggressiveness. Supporting this hypothesis, NFIB has been shown to regulate endothelins – secreted factors with the ability to mediate intercellular crosstalk – which can promote tumour angiogenesis, migration and invasion (Chang et al., 2013; Rosano et al., 2013). Corroborating a potential role in the tumour microenvironment, NFIB also appears to be expressed in the stroma surrounding tumours (Grabowska et al., 2016; unpublished observations).

Major questions that remain to be answered pertain to the understanding of how NFIB’s diverse functions – which promote cell differentiation during late stages of development in a range of tissues, and regulate the maintenance of populations of stem cells in adult tissues – contribute to its significant and paradoxical roles in tumourigenesis. Some specific questions that need to be addressed are: 1) What are the important upstream regulators of NFIB in different cancer-related contexts? 2) Do the many alternatively-spliced isoforms of NFIB play cooperative, or perhaps antagonist, roles during tumourigenesis? 3) What factors might mediate stabilization or enhanced degradation of NFIB transcripts in tumours? 4) How does the expression of NFIB binding partners, including other NFI family members and other transcription factors, influence its activity in cancer? Lastly, 5) What are the direct downstream targets of NFIB in different tumour types and stages, and are they the same or different from those identified during normal development and maintenance of tissue homeostasis? The development of quantitative pull-down assays with NFIB partner proteins and in vivo FRET measurements of NFI-partner protein interactions, combined with ChIP-seq, ATAC-seq, single cell RNA-seq and the use of conditional knock-out alleles of NFIB and other NFI family members, should allow us to answer these important questions.

In closing, the paradoxical involvement of NFIB in both the inhibition and promotion of tumour development and progression in different malignancies; especially between different tumour subtypes within a single organ system, such as in lung, brain and skin, corroborates its diverse and distinct roles in specific tissues and cell types. This follows from the fact that NFI-mediated transcriptional activation or repression of specific gene promoters, varies depending on cell type and upon details of the cellular context (Chaudhry et al., 1998; Chaudhry et al., 1999), resulting in the modulation of the expression of a plethora of diverse tissue-specific genes (Gronostajski, 2000). Consequently, caution must be exercised in the development of any future therapies aimed to manipulate NFIB levels – which may result in unexpected/undesired effects, with the potential for exacerbation of tumour aggressiveness. Further insights into the fascinating role of this enigmatic transcription factor in cancer will certainly open new doors to clinical translation of these findings.

Conflict of Interest Statement

The authors disclose no potential conflicts of interest.

Search Strategy and Selection Criteria

Data for this review were identified by searches of PubMed, using the following search terms in various combinations: “NFIB”, “cancer”, “development”, “cellular differentiation”, “NFI transcription factors”. Articles resulting from these searches and references cited in those articles were selected based on their relevance to the topic covered in the review. Only articles published in English between 1982 and 2017 were searched.
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