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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.

Contents

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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; Barry et al., 2008; Piper et al., 2014). 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).

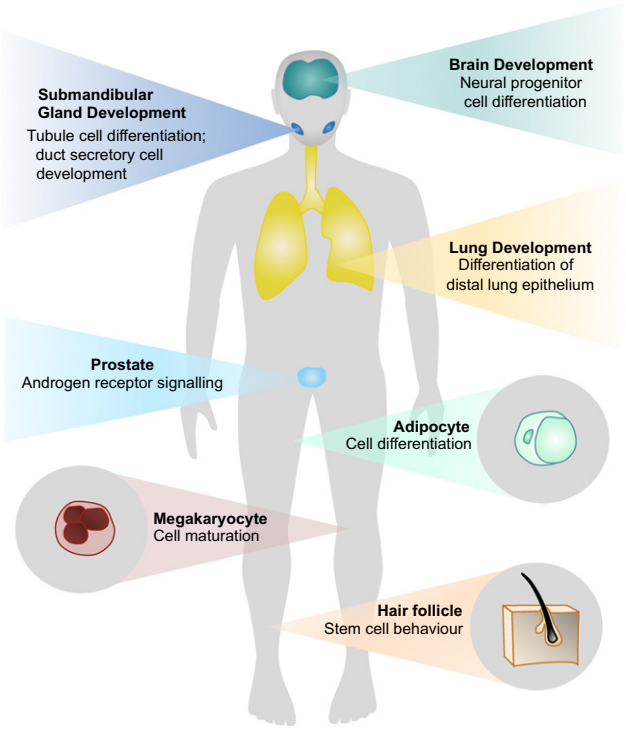

Fig. 2. NFIB functions in development and physiology. NFIB is required for the development of the lung, brain and submandibular glands. It is also required for the maintenance of a range of physiological processes in several tissues, including adipocyte differentiation, megakaryocyte maturation, regulation 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.

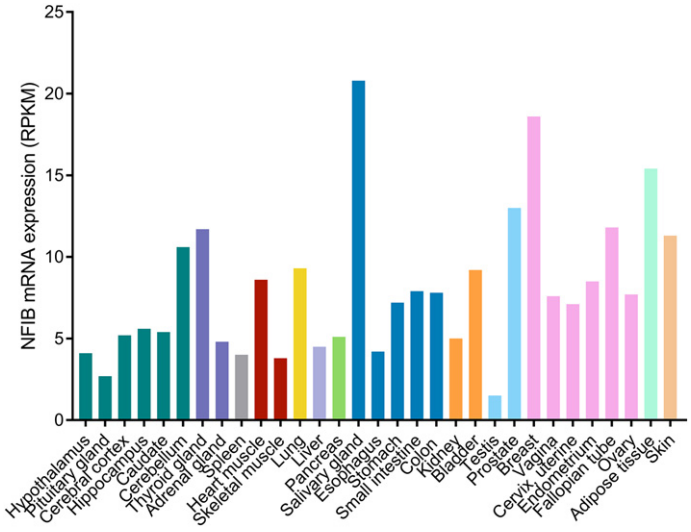

Fig. 1. NFIB expression overview in human tissues. NFIB is expressed in a range of tissues. RNA-sequencing data from 31 tissues generated by the Genotype-Tissue Expression Project (GTEx; https://www.gtexportal.org/) are reported as median RPKM (Reads Per Kilobase of transcript per Million mapped reads). 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).

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 (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 open chromatin sites, maintained the hyper-accessible chromatin state in these regions, and was also proposed to alter a variety 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

Table 1
Summary of alterations in NFIB reported in cancer.

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 **Oncogenic behaviour in some subtypes of glioblastoma*	Stringer et al., 2016; Suzuki et al., 2015
Germline 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-AIG1*, *NFIB-MAN1A1*, *NFIB-NKAIN2*, *NFIB-PTPRD*, *NFIB-XRCC4*)	Salivary, lacrimal & ceruminal 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 Mitani et al., 2016
Gene fusions (*HMGA2-NFIB*)	Head & neck	Pleomorphic adenoma	Unknown	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

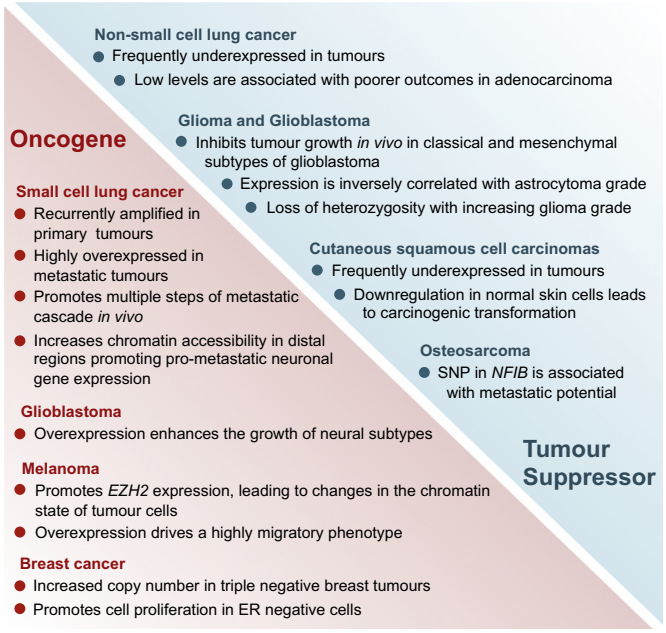

Fig. 3. Paradoxical roles of NFIB in cancer. NFIB has shown both oncogenic and tumour suppressive functions in different cancer types and subtypes.

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-PTPRD*, *NFIB-XRCC4*) (Mitani et al., 2011; Mitani et al., 2016). Further supporting a tumour suppressor role in adenoid cystic carcinomas, truncating mutations and homozygous deletions affecting *NFIB* have also been reported 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 upregulation of *HMGA2* and truncation of *NFIB* (as in the *MYB-NFIB* rearrangement, 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 adenoid 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 expression 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 extending 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 repressed 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 remain 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 (Borromeo et al., 2016; Mollaoglu et al., 2016), PAX6 in neural progenitor cells (Ninkovic et al., 2013), and BRN2 in melanoma (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 specificities, it is possible that there are common downstream targets for all NFI 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 between isoforms, and therefore might promote interactions with different 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 summarizes 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 chromosomal breakpoints in cancer cells (Arlt et al., 2006). This location could explain the high frequency of chromosomal rearrangements involving *NFIB* described in several cancers (Table 1), although this hypothesis needs to be further explored.

6. Conclusions and Perspectives

A number of transcription factors that induce lineage-specific differentiation 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 adenovirus 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 development of a number of organs (Chaudhry et al., 1997). Thus, as is the case with other transcription factors involved in developmental processes, it is not surprising that NFIB has become increasingly appreciated 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 similar 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, tumour suppressive functions have been demonstrated or strongly suggested 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 conceivably 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 cancer aggressiveness and ultimately poorer patient survival. The concept

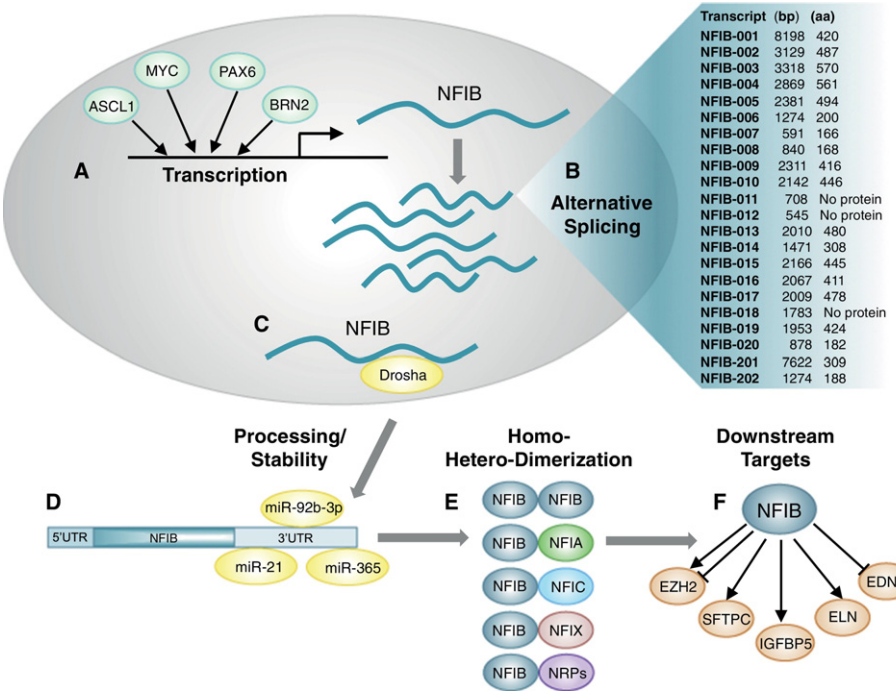

Fig. 4. NFIB activity is regulated at multiple levels. A) Cell-type and context-specific transcription of *NFIB* in various tissues is regulated by multiple transcription factors including ASCL1, MYC, PAX6 and BRN2. B) At least 20 alternatively-spliced isoforms of *NFIB* have been identified. C & D) Drosha has been shown to destabilize *NFIB* nuclear transcripts (C) and miRNAs, such as, miR-92b-3p, miR-21 and miR-365 have been shown to affect cytosolic *NFIB* transcript stability (D). E) NFIB protein products of alternatively-spliced transcripts can form homo- and hetero-dimers with other NFI gene products. In addition, NFIB activity can also be influenced by its binding to other nuclear regulatory proteins (NRPs), and by post-translational modifications (not shown). F) NFIB regulates the expression levels of multiple downstream targets in various tissues, including *EZH2*, *SFTPC*, *IGFBP5*, *ELN* and *EDN2*.

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 co-operative, 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

included. The majority of the articles reported were published in the last 5 years.

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