REVIEW

CrossMark

Interplay between NRF1, E2F4 and MYC transcription factors regulating common target genes contributes to cancer development and progression

Kaumudi Bhawe[1] · Deodutta Roy[1]

Abstract

Background Nuclear respiratory factor 1 (NRF1), historically perceived as a protein regulating genes controlling mitochondrial biogenesis, is now widely recognized as a multifunctional protein and as a key player in the transcriptional modulation of genes implicated in various cellular functions. Here, we present emerging data supporting novel roles of NRF1 in cancer development and progression through its interplay with the transcription factors E2F4 and MYC. To identify common human NRF1, E2F4 and MYC target genes, we analyzed the Encyclopedia of DNA Elements (ENCODE) NRF1 ChIP-Seq data. By doing so, we identified 9253 common target genes with NRF1, E2F4 and MYC binding motifs. NRF1 binding motifs were found to be present in genes operating in signaling pathways governing all hallmarks of malignant transformation and progression, including proliferation, invasion, self-renewal and apoptosis.

Conclusions In addition to controlling mitochondrial biogenesis NRF1, in conjunction with E2F4 and MYC, may play a critical role in the acquisition of human cancer characteristics. Additionally, NRF1 may orchestrate both MYC and E2F4 to regulate common target genes linked to multiple networks in the development and progression of cancer. A comprehensive understanding of this dynamic interplay will set the stage, not only for the design of novel treatment strategies, but also for the discovery of pan-cellular transcription factor regulatory strategies to predict cancer risk, therapy response and patient prognosis.

Keywords Nuclear respiratory factor 1 (NRF1) · E2F4 · MYC · Cancer

1 Introduction

Cancer is a complex disease that evolves through discrete stages involving multiple genetic and epigenetic changes. Aberrations in distinct pathways at each stage appear to be required for the ultimate development of a malignant metastatic phenotype. Dysfunctional regulation of transcription factors (TFs), with gain or loss of functions controlling cell fate decisions, is important for the etiology of human cancers [1]. Currently, there are 1500 to 3000 known human TFs [2]. The interplay between multiple TFs affecting biological pathways and networks has been found to contribute to the differential susceptibility, progression and treatment response seen in patients. Recently,

Falco et al. [3] reported increased activity of TFs in eleven different human cancers. Nuclear respiratory factor 1 (NRF1), E2F4 and MYC were among the top five TFs that showed an increased activity across all eleven human cancers. The role of both MYC and E2Fs in human cancer development has amply been documented [4], but evidence supporting a role of NRF1 in cancer development is just emerging. NRF1 has e.g. been found to be highly expressed in head and neck cancer, skin cancer, testicular cancer and glioma, and at lower levels in stomach cancer and liver cancer (www.proteinatlas.org). In addition, we recently uncovered a novel oncogenic function of NRF1 in breast cancer development and progression [5–7]. Many MYC binding motif-enriched genes have been found to be associated with E2F or NRF1 binding motifs, suggesting that MYC target genes require additional transcription factors for their expression [4]. The pluripotency transcription factors SOX2, OCT4 and KLF4, and several cancer stem cell (CSC) marker genes have, for example, been found to be regulated by multiple TFs, including MYC and E2Fs [4], implying that a single TF may not be sufficient to activate CSC acquiring target genes.

✉ Deodutta Roy
droy@fiu.edu

[1] Department of Environmental Health Sciences, Florida International University, Miami, FL 33199, USA

NRF1, MYC and E2Fs have been found to regulate many common genes in mammalian cells, and these genes have also been implicated in various human diseases including cancer [3]. Therefore, it is of critical importance to assess whether these TFs actively co-operate or compete with each other during early cancer development, progression and/or metastasis. In this review, we discuss emerging new roles of NRF1 and elaborate on its role in the pathogenesis of cancer by highlighting evidence for overlap, cooperation and exclusivity of its activity in conjunction with MYC and E2Fs.

2 NRF1, MYC and E2F4 - an overview

The literature is rich in information on MYC and E2Fs. Here, we focus on the underlying orchestration of their combined regulatory effects, as well as on that of NRF1.

NRF1 (synonym: alpha palindromic-binding protein, α-PAL): Human NRF1 is homologous to P3A2 in sea urchin and erect wing (ewg) in Drosophila [8]. The chromosomal location of its gene is 7q32.2, and it codes for a 68 kDa nuclear protein (503 amino acids) [7–9]. As per Uniprot, there are 4 known isoforms that can be generated through alternative splicing (http://www.uniprot.org/uniprot/Q16656). Several 5′-untranslated exons spanning a region of 47 kb contribute to transcript heterogeneity, and mutations within UTR1 have been shown to alter NRF1 expression through mRNA translational efficiency interference [9]. The continued use of the NRF1 (Nrf1) gene symbol also for the nuclear factor erythroid-derived 2-like 1 (official symbol NFE2L1) gene, has created confusion in the scientific community. Chan et al. [10] identified NFE2L1, a distinct human bZIP transcription factor, which they called Nrf1 (NFE2-related factor-1). Subsequently, Tiranti et al. [11] mapped the gene to 7q32 and referred to it as NFE2L1. Many researchers working on NFE2L1- or NFE2L1-regulatable proteins continue to use Nrf1 instead of NFE2L1, which has led to erroneous interpretations of the original findings. Here, we use NRF1 as symbol for the human, and Nrf1 for the rodent nuclear respiratory factor 1 in accordance with current HGNC recommendations [9].

The various NRF1 protein isoforms can form homo-dimers and bind to unique DNA recognition sequences to regulate the transcription of target genes [9, 12]. The initial discovery of NRF1 target genes suggested that its main role was to control the transcription of genes involved in mitochondrial respiratory sub-complexes [9]. It was soon recognized, however, that the target genes controlled by NRF1 extend beyond the respiratory subunits to genes controlling the assembly of the respiratory apparatus, constituents of the mtDNA transcription and replication machinery, mitochondrial and cytosolic enzymes of the heme biosynthetic pathway, and components of the mitochondrial protein import pathway. Despite these advances, the role of NRF1 initially remained confined to the transcriptional regulation of genes involved in mitochondrial function and biogenesis. Non-mammalian NRF1 homologues showed, however, more diverse functions. P3A2, for example, has been found to direct the transcription of muscle genes in sea urchin embryos, and ewg (nrf1) to control the transcription of flight muscle and neuronal genes in Drosophila embryos [9, 12]. Based on the varied roles of these non-mammalian NRF1 homologs, it was reasoned that NRF1 may also control the transcription of similar genes during human embryogenesis [13]. Indeed, NRF1 binding elements have been identified in genes involved in cellular growth, metabolic energy production, protein translation and DNA replication/repair [13]. ChIP-on-chip analysis of human T98G glioblastoma-derived cells showed that NRF1 binds to ~691 genes encoding proteins regulating cellular growth, DNA replication, DNA repair, chromosome organization and mRNA processing [14]. Recent analysis of NRF1 ChIP-Seq data from the Encyclopedia of DNA Elements (ENCODE) revealed that NRF1 binds to promoter sequences of thousands of genes involved in regulating RNA metabolism, DNA damage repair, protein translation, cell cycle progression and ubiquitin-mediated protein degradation in SK-N-SH human neuroblastoma-derived cells [15]. Hence. it is now widely recognized that NRF1 is a multifunctional protein with critical roles in diverse cellular functions.

MYC The human *MYC* gene is located at chromosome 8q24.21 [4, 19]. MYC is the prototype of a family of related proteins that are not only conserved across metazoans, but can also be found in similar forms and functions in pre-metazoan organisms such as choanoflagellates [20]. In mammalian cells, MYC proteins are encoded by three distinct gene family members - CMYC, NMYC and LMYC - which function in a similar manner, but display notable differences in potency and patterns of expression [20]. Rodents also express a b-Myc variant that shares homology with the amino-terminus of the MYC proteins [20].

MYC has a carboxyl terminal DNA binding domain containing a ~100 amino acid basic helix-loop-helix-leucine zipper (BR-HLH-LZ) region. BR-HLH-LZ containing proteins bind DNA as obligate dimers and recognize a consensus sequence "CACGTG", which is termed the "Enhancer box" (E-box). At physiological concentrations MYC does not homodimerize, but instead interacts with the small BR-HLH-LZ protein MAX to form a heterodimer that constitutes a core DNA-binding module. Dimerization of MYC with MAX is driven by the leucine zipper which forms an extended coiled coil between the two proteins that, following a crisp turn at the loop, presents two basic helices that insert into the major groove of the DNA in a scissor-like fashion. Interaction of MYC with MAX, which occurs at all MYC bound genes across the

genome, is crucial for the oncogenic potential of MYC and is important for *trans*-gene regulation by MYC, since MAX is known to dimerize with additional BR-HLH-LZ proteins that antagonize the MYC-MAX interaction [20]. In contrast to the two ends of the MYC protein, the central portion is poorly defined. MYC regulates a multitude of diverse biological functions [16–18]. MYC target genes include several genes that code for proteins involved in ribosome biogenesis, metabolism, chromatin structure/function, mitochondrial biogenesis, nuclear metabolism, DNA replication and cell cycle progression, as well as genes that code for tRNAs, rRNAs and miRNAs [19]. MYC is often deregulated in cancer [4].

E2F4 E2F4 belongs to the E2F family of transcription factors, which includes seven "classical" E2Fs (E2F1, E2F2, E2F3a, E2F3b, E2F4, E2F5, E2F6) that bind DNA with an essential dimerization partner protein (DP1–4), and two "atypical" E2Fs (E2F7 and E2F8) that function in a DP-independent manner. The classical E2Fs, with the exception of E2F6, interact physically with the retinoblastoma (RB) family of proteins (RB, p130 and p107) through their transactivation domains. In some cases E2Fs make contact with the C-terminus of RB and p107 at the DP dimerization domain. E2F4 associates with all three RB protein family members under physiological conditions. Most studies to date have indicated that E2Fs 1, 2 and 3a act as transcriptional activators, E2F3b, 4 and 5 as passive repressors, and E2F6, 7a, 7b and 8 as active repressors [21]. Although such classification is an oversimplification, all E2Fs play critical roles in cell cycle regulation [22, 23]. The E2F genes are scattered across different chromosomal locations, with the *E2F4* gene being located at 16q22.1. This chromosomal region has frequently been associated with allelic imbalances in several different cancers including breast cancer, prostate cancer and hepatocellular carcinoma [24].

The *E2F4* gene has a unique structural property in that it contains a polymorphic trinucleotide repeat which codes for a poly-serine stretch [22]. The number of serine residues in this stretch has been shown to vary from 8 to 17 [25]. The DNA binding domain is located at the N-terminal end of the protein, whereas the C-terminal end contains a tumor protein-associated or p107/p130 binding domain [22]. Although E2F4 can bind to three tumor suppressors (i.e., pRb, p107 and p130), it binds to the latter two with a higher affinity.

3 Co-occurrence of NRF1, MYC and E2F4 binding motifs in human gene promoters

The canonical DNA binding sites for the three TFs are as follows: 5′ – YGCGCAYGCGCR– 3′ for NRF1, 5′ – CACGTG– 3′ (canonical E-box) for MYC, and 5′ – TTTC[CG]CGC – 3′ for E2F4. The canonical NRF1 binding site contains a non-canonical E-box sequence nested within it.

Full-length MYC alone cannot bind DNA under physiological conditions: it needs to partner with MAX. On the other hand, MAX can homodimerize, heterodimerize with MYC, or heterodimerize with NRF1 (Fig. 1). E2F4 is known to bind to DNA as a homodimer, but exhibits a higher DNA binding affinity when heterodimerized with one of the TFDP proteins. Such E2F4-DP1/2 heterodimers also have the capacity to bind to E-boxes [26]. These data suggest that NRF1, MYC and E2F4 may bind to adjacent regions on the DNA (Fig. 1). There are gene promoters such as those of *PARK2*, *E2F6* and *eIF2-α*, which are regulated by NRF1, E2F and MYC individually, and these promoter regions contain NRF1 binding sites in relatively close proximity [27, 28]. Concordantly, over-expression of MYC or NRF1 has been found to repress *PARK2* gene expression [29, 30]. This observation suggests that NRF1 may compete with MYC to regulate common target genes (Fig. 1).

Within human gene promoters, MYC, E2F1, E2F4 and NRF1 recognition sequences belong to the most conserved motifs [31]. Significant enrichment in MYC, E2F and NRF1 binding motifs is found in promoters of key human cell cycle regulating genes [14, 32, 33]. Co-occurrence of NRF1, MYC and E2F binding motifs on the same human gene promoters suggests that these TFs may act together to regulate target genes [32].

4 NRF1 regulates both MYC and E2F

There are numerous reports indicating that these three TFs are involved in common biological and cellular processes, and may share binding sites, binding partners and downstream targets [27–33]. In mouse embryonic stem cells, the Nrf1 DNA binding motif has been found to be indicative of a strong Nrf1 pioneer activity along with 8 other motifs (Klf/Sp, NFY, ETS/GABP/NRF2, CREB/MYC, YY1, GFY, Clus1 and TBP) [34]. Impairing Nrf1 binding impacts adjacent binding of the settler TF Myc at several genomic loci, which is consistent with the concept that Nrf1 contributes in the opening of chromatin in order to allow other TFs, such as Myc/Max, to bind [35]. Recently, Lavigne et al. [36] found that NRF1 can bind to the variant histone protein macroH2A (mH2A) and that mH2A/NRF1 nucleosomes are strategically placed within key gene promoters, thereby leading to stable chromatin landscapes that provide and/or limit access to subsets of TFs [37]. The possibility of NRF1 acting upstream of MYC has been underscored. Experiments specifically aimed at investigating regulatory relationships between the two proteins have been focused on MYC performing NRF1 functions by binding to non-canonical E-box sequences within the NRF1 response element. Previously, MYC has been suggested to act as an upstream regulator of NRF1 in the context of mitochondrial biogenesis and diverse other mitochondrial functions [33].
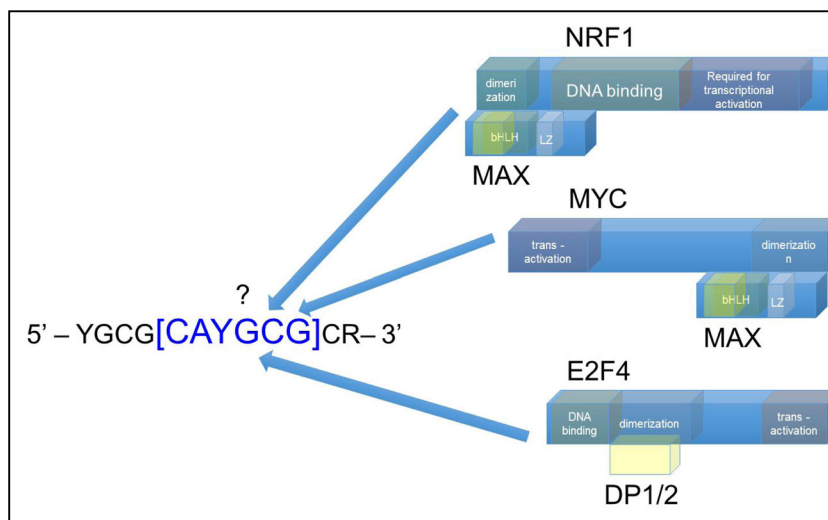
Contrary to this, many MYC binding motif-enriched genes have been found to be associated with E2F or NRF1 binding motifs, which suggests that MYC target genes may require additional transcription factors for their expression [4]. There is some evidence pointing at the possibility of NRF1 regulating MYC. In rat fibroblasts it has, for example, been found that dominant negative Nrf1 inhibits Myc-induced apoptosis, but has no effect on the proliferation-inducing function of Myc [38]. The *PARK2* gene (see above) is a target of NRF1, MYC and p53 [29, 39, 40]. Since NRF1 is one of the pioneer transcriptions factors, it has been suggested that it may help MYC to gain access to target sites where MYC as a settler possibly could not do so on its own [41].

NRF1 has also been shown to regulate human E2F1 and E2F6 promoter activity [27]. The observed binding of NRF1 and E2F4 to common target genes suggests a potential functional crosstalk between these factors [42]. NRF1 binding sites have also been identified and confirmed to be present in several E2F target gene promoters using motif-finding algorithms and genome-wide factor binding assays, respectively [14, 43].

E2Fs and MYC have been shown to function together to control cell cycle progression in normal and Rb-deficient cells within the mouse intestine. Specifically, MYC and E2F1–3 have been found to be required for progression through the S/G2 phase, but not the G1/S phase. In Rb-deficient cells, however, MYC and E2F3 are recycled for G1/S cell cycle phase progression [44]. E2F4/5, along with p107, has been found to acts as a co-factor of Smad3 and, thus, to repress MYC at the transcriptional level [45]. E2F6 is together with MAX part of a multimeric protein complex that can bind, not only to E2F binding sites, but also to MYC binding sites. The multimeric protein complex containing E2F6 and MAX preferentially occupies target gene promoters in cells in the G0 rather than in the G1 phase of the cell cycle, and it also contains a novel histone methyltransferase that can modify lysine 9 of histone H3, HP1γ and Polycomb group (PcG) proteins

[46]. Even more intriguingly, it has been found that NRF1-MAX heterodimers can bind to both tandem palindromic repeat sites present in the eIF2-α gene promoter [28].

NRF1 may also regulate E2F4 in cells based on their cell cycle status, since NRF1 has been shown to bind promoters of E2F4 target genes in states of transcriptional repression, and to be implicated in the activation of these genes in a cell-cycle dependent manner [43]. It has also been reported that E2F activities may affect the potential of MYC-induced oncogenesis [47]. In summary, these findings suggest that that NRF1 may regulate MYC and E2F in a cell context-dependent manner. NRF1 may regulate MYC functions through three distinct mechanisms: (i) by acting as a "pioneer" TF and facilitating or repressing the ability of "settler" MYC protein to bind to the DNA, (ii) through the formation of NRF1-MAX heterodimers that may compete with MYC-MAX heterodimers in a fashion similar to that of the well-known MAD-MAX heterodimers and/or (iii) by regulating E2F1/E2F6 expression, which may result in MYC modulation by forming multimeric complexes with MAX (Fig. 2).

5 Impact of NRF1, MYC and E2Fs on cancer stem cell transcriptomes

A gradual loss of epithelial cell identity and gain of properties of cancer precursor/progenitor cells are considered to be early
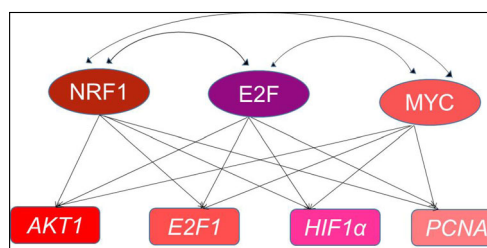

Fig. 2 NRF1 regulates E2F and MYC and many of their target genes

steps in carcinogenesis [48–50]. NRF1 has been found to reg- ulate mitochondrial activity and the proliferation of mitochon- dria in adult hematopoietic stem cells [51]. The NRF1 binding motif exhibits one of the strongest pioneer activities (the pio- neer index indicates the increase in chromatin opening activity during developmental processes) in mouse embryonic stem cells. We have recently shown that NRF1 plays an important role in estrogen-driven breast cancer [30, 52] and that NRF1 controls estrogen-induced malignant transformation of breast epithelial cells to breast cancer stem cells (BCSCs) through transcriptional regulation of chemokine receptor 4 (CXCR4) [30]. We have also shown that exogenous expression of NRF1 can reprogram MCF10A mammary epithelial cells to become induced pluripotent stem cells [53]. As recent work has impli- cated pioneer TFs in cellular reprogramming [38], also NRF1 may participate in cell fate decision making [53, 54]. We have also shown that NRF1 can reprogram adult human brain cells into neural stem/progenitor cells (NSPCs) [53]. Both 17β- estradiol and NRF1 over-expression have been found to in- crease the percentage of cells co-expressing SOX2 and Nestin. Nestin is an intermediate filament protein important for guaranteeing NSPC self-renewal, while SOX2 is expressed at the earliest developmental stages of the brain and functions as a marker of neural development. SOX2 also plays a key role in the maintenance of neural stem cell (NSC) properties, including proliferation, survival, self-renewal and neurogenesis. NRF1-induced SOX2$^+$/Nestin$^+$ NSPCs have been found to express the neuronal marker β-III-tubulin, and to exhibit a neural phenotype and a capacity to form neurospheres [53]. Bayesian network (BN) analysis on RNA-Seq data of 154 glioblastoma patient samples obtained from TCGA showed that NRF1 gene networks are associated with the development of these tumors. Some of the NRF1 network genes associated with glioblastoma are known to be involved in the acquisition of cancer stem cell (CSC) charac- teristics. NRF1-based gene association networks have been found to significantly differ between short-term and long- term glioblastoma survivors. In conclusion, these data provide evidence in support of a role of NRF1 in the acquisition of breast cancer and glioblastoma stem cell characteristics [54].

The role of MYC in the acquisition of CSCs is well accepted and widely reviewed and, therefore, only briefly described here. In order to maintain glioma CSCs in culture, MYC ex- pression has been found to be required [55]. It has been sug- gested that MYC may link glycolysis to stemness [56]. In glio- blastoma, oncomyc, a MYC-derived polypeptide interfering with MYC activity, has been found to affect proper MYC lo- calization. In the presence of oncomyc, OLIG2, POU3F2 and SOX2 have been found to be downregulated, while ID4, MIAT and PTEN have been found to be upregulated [57]. Mouse embryonic stem cells (mESCs) that are maintained in a naive ground state of pluripotency in the presence of MEK and GSK3 inhibitors express low Myc levels. Deletion of both c-

Myc and N-Myc in double knockout mice or pharmacological inhibition of Myc activity in rodents strongly decreases gene transcription, mRNA splicing and protein synthesis, leading to proliferation arrest in a reversible manner without affecting pluripotency, suggesting that Myc-depleted stem cells enter a state of dormancy similar to embryonic diapause [58].

E2Fs also play a significant role in influencing the self- renewal capacities of human pluripotent stem cells (hPSCs). E2Fs directly target broad classes of genes regulating metab- olism in hPSCs [59]. E2Fs, in conjunction with their partner pocket proteins, have been found to regulate stem cell homeo- stasis in a highly evolutionarily conserved manner [60]. Pauklin et al. [61] have shown that initiation of stem cell differentiation involves a cell cycle-dependent regulation of developmental genes by Cyclin D, and that E2F1 is involved in a transcriptionally repressive interaction with Cyclin D1, specifically in the late G1 phase.

The concept that E2F, MYC and NRF1 co-regulate genes in hPSCs is underscored by the finding that a number of NRF1 target genes involved in mitochondrial biogenesis, mitosis, DNA replication and cytokinesis are transcriptionally regulat- ed by E2F4 and/or MYC [47, 62]. Similarly, it has been found that expression of the embryonic pluripotency transcription factors SOX2, OCT4 and KLF4, as well as several CSC mark- er genes, are regulated by multiple TFs, including MYC, E2F and NRF1 [4, 52, 54]. These observations imply that a single TF may not be sufficient to activate CSC phenotype acquiring target genes, unless they are bound by multiple TFs. Some of the phenotypic characteristics associated with tumor initiation and progression, including the acquisition of CSC pheno- types, may be affected by joint activities of NRF1, MYC and E2Fs.

6 Role of NRF1, MYC and E2Fs in evading senescence and developing resistance to apoptosis

Cellular senescence and apoptosis are major barriers to cellu- lar reprogramming, and removal of these barriers facilitates the acquisition of CSC characteristics. NRF1/MYC/E2F4 tar- get genes are critical for the regulation of cellular senescence and apoptosis. Recently, we have shown that NRF1 overex- pression enhances the acquisition of induced adult pluripotent cells as well as the growth, survival and maintenance of stem cells [30, 52]. NRF1 has also been found to regulate human telomere transcription [62], and pharmacological activation of AMPK has been found to upregulate telomeric repeat- containing RNA (TERRA), sequences that are important for telomere integrity, thereby linking metabolism to telomere fitness. Notably, it was also found that endurance exercise, which is associated with AMPK activation, increases TERRA levels in skeletal muscle cells [62]. Interaction

between NRF1 and sirtuin 7 (SIRT7) suppresses the mitochondrial translational machinery and leads to depletion of mitochondrial activity. Consistent with the ability of sirtuins to perform metabolic sensing, SIRT7 levels have been found to increase with nutrient deprivation, which in cooperation with NRF1 hampers mitochondrial function, yet promotes cell survival by promoting nutritional stress resistance. While loss of mitochondrial proteostasis triggers the unfolded protein response (UPR^{mt}), SIRT7 and NRF1 have been found to interact and, thereby, to reduce mitochondrial protein folding stress [63]. NRF1 protects neural stem cells from neurotoxin-induced apoptosis and senescence by enhancing their self-renewing ability via upregulating SOX2/nestin expression [53]. Overexpression of NRF1 suppresses cellular senescence and increases resistance to anoikis pathways and to anchorage-independent growth during estrogen-induced malignant transformation [30, 52]. Since the role of E2F and MYC in the regulation barriers of senescence is widely recognized and documented [63–68], we do not elude further on their role in senescence here. Together, these finding suggest that NRF1, E2F4 and MYC may play pivotal roles in removing senescent and apoptosis barriers and in enhancing cancer stem cell self-renewing capacities.

7 Impact of NRF1, MYC and E2Fs on malignant transformation, tumor progression and metastasis

NRF1 has been found to exhibit a strong association with epithelial ovarian cancer risk [69] and to act in conjunction with estrogen in the development of breast cancer [5, 52–54]. It has also been found that interactions of KISS1 with NRF1 may contribute to metastasis [70] and that NRF1 overexpression may inhibit 4-OHT-induced apoptosis and increase cell survival, suggesting that NRF1 may act as an anti-apoptotic modulator [71]. The expression of the *HIF1A* gene in immature hematopoietic cells has been found to be inhibited by hyper-methylation of its promoter. NRF1 acts as a transcriptional repressor of *HIF1A* [72] and, in addition, has been found to regulate the transcription of the CpG island-associated insulin-degrading enzyme (IDE) gene [73]. It has amply been reported that through fine-tuning the accessibility of DNA, CpG island gene promoter methylation contributes to the regulation of normal developmental processes as well as tumorigenesis [74–76]. CPG-rich promoter regions predispose genes to hyper-methylation by directly or indirectly interacting with DNA methyltransferases [77]. These regions seem to be deprived of some TF binding sites, such as those for Sp1, Yin Yang 1 (YY1) and NRF1, which are regarded as methylation inhibitors in cancer cells [78]. Therefore, it is possible the NRF1 maintains mitochondrial activity in

hypoxic CSCs independent of HIF1/2 through some other proteins, such as the prolyl hydroxylase EglN2/PHD1.

By promoting cell proliferation, survival, differentiation blockade, genetic instability and angiogenesis in cancer, the MYC protein has the ability to directly contribute to tumor progression and metastasis [79]. Paradoxically, however, MYC has also been shown to suppress the metastatic capacity of xenografted lung and liver tumors through direct transcriptional silencing of α_v and β_3 integrin subunits [80]. Jung et al. [81] identified an 18-gene MYC activity signature that is highly predictive for a poor prognosis in MYC-associated malignancies. When MYC is overexpressed in high expressing/gain-of-function mutated c-RAF, K-RAS or LKB1 lung cancer cells, MYC itself is sufficient to induce tumor progression and/or metastasis [82]. MYC has been found to drive a self-reinforcing regulatory network that maintains stem cell identity [83]. TLR4-dependent NFκB and CREB activation has been found to result in co-regulation of the *NRF1* gene promoter with NFκB intronic enhancement and redox-regulated nuclear translocation in mouse liver cells [84]. The induction of glutaminolysis in mitochondria is a key factor explaining how tumors become "addicted" to MYC [85]. Interaction of MYC with the zinc finger protein MIZ1 mediates resistance to anti-mitogenic signals [86]. Enforced expression of miRNAs that have been repressed as a result of MYC signaling has been found to diminish the tumorigenic potential of lymphoma cells, thus providing evidence that extensive reprogramming of the miRNA transcriptome by MYC contributes to tumorigenesis [87].

Mutations of components regulating the CDK-RB-E2F pathway have been identified in almost every human malignancy, and several studies have shown that the CDK-RB-E2F pathway is critical for the control of cell proliferation [88–92]. More recently, additional roles of E2Fs in tumor progression, angiogenesis and metastasis have been reported. Specific E2Fs may also be used as prognostic markers for human breast cancer [93] and in a mouse metastatic breast cancer model E2Fs have been found to regulate tumor development and metastasis [94]. It has also been found that HER2-positive human breast cancers exhibiting altered E2F activities may show differences in relapse-free survival rates [95]. Additionally, E2F4 expression has been found to be associated with lymph node metastasis in triple-negative breast cancer patients [96]. Nuclear E2F4 expression has been reported to induce cell death via multiple pathways in normal human intestinal epithelial crypt cells, but not in colon cancer cells [97]. Finally, genetic and biochemical data indicate an essential negative function of E2F4 in cardiac myocyte apoptosis [98].

In summary, these studies point at an emerging role of NRF1 in human cancer. A gradual loss of epithelial cell identity and a gain of precursor/progenitor cell properties are considered early steps in tumorigenesis. Some of the

characteristics of malignant transformation and progression may be affected by combined effects of NRF1, MYC and E2Fs. Notably, E2F4 seems to be a transcriptional regulator associated with both MYC and NRF1. Like MYC and E2F4, NRF1 also controls cell cycle progression, DNA replication and apoptosis [30]. Thus, NRF1 deregulation coupled to E2F4 and MYC may lead to uncontrolled cellular growth. Like MYC, NRF1-regulated E2F4 activity contributes to cell cycle control. The cooperative binding of NRF1, MYC and E2F4 to key downstream targets, followed by transcriptional activation and/or repression, may play a pivotal role in tumorigenesis through promoting cell proliferation and invasion, removing senescent and apoptosis barriers, and enhancing self-renewing abilities.

8 Role of NRF1, MYC and E2Fs in therapy resistance

Radiotherapy resistance of nasopharyngeal carcinoma cells has been directly linked to miR504-mediated downregulation of NRF1 [99]. NRF1 and its target mitochondrial transcription factor A (TFAM) have been reported to exhibit higher expression levels in tamoxifen-resistant LCC2 and LCC9 than in tamoxifen-sensitive MCF-7 breast cancer cells [100]. We have shown that redox sensitive transcription factors, including NRF1, may act in concert to activate the expression of genes that contribute to the resistance of breast cancer cells to endocrine therapeutic agents [100]. NRF1, in conjunction with 17 other genes (collectively defined as a MitoBiogenesis signature), serves as a biomarker for inherent MAPKi resistance in BRAF-mutated melanoma cells [101]. MAPKi has been found to block the expression of NRF1 and other MitoBiogenesis genes in A375 melanoma cells (with a high inherent expression of the MitoBiogenesis genes), but to up-regulate the mitochondrial biogenesis genes, including NRF1, in WM793 and WM9 melanoma cells (with a low inherent expression of the MitoBiogenesis genes). This dual response towards MAPKi by cells exhibiting a high expression of mitochondrial regulatory genes, such as NRF1, versus those with low expression levels, may explain the mechanism underlying the resistance to MAPKi treatment observed in mitochondrial biogenesis low expressors [101]. Recently, NRF1 has been suggested as a target of choice for combatting mitochondrial biogenesis-associated chemoresistance in a multicenter case-control study of Caucasian patients with epithelial ovarian cancer [102].

When MET-addicted EBC1 human lung cancer cells that have acquired resistance to anti-MET therapy were subjected to MYC blockade by RNA interference or pharmacologic inhibition, they could circumvent the acquired resistance to MET inhibition. Using MET-amplified patient-derived xenograft mouse models, it was subsequently found that combining MYC blockade with MET inhibition increased the therapeutic efficacy of the MET inhibitors [103]. It has also been reported that drug resistant acute myeloid leukemia cells may undergo differentiation and switch to a drug sensitive phenotype when MYC is inhibited [104, 105].

It has additionally been found that downregulation of endogenous E2F1 mRNA and protein expression by E2F1 shRNA in cisplatin-resistant SGC7901/DDP gastric cancer cells may significantly promote the sensitivity of these cells to cisplatin, doxorubicin and 5-fluorouracil [106]. The major multidrug transporter ABCG2 (BCRP/MXR) is directly and specifically activated by E2F1, which is perturbed in the majority of human cancers. Concordantly, E2F1 has been found to regulate ABCG2 expression in multiple cell systems, and a significant correlation has e.g. been observed between elevated E2F1 and ABCG2 expression in human lung cancers [107].

In summary, these data indicate that NRF1, E2F4 and MYC may act in concert to activate/inhibit the expression of genes that contribute to resistance to both endocrine and chemotherapeutic agents.

9 Compounds affecting NRF1, MYC and E2F4 activity

Using the NIH Toxicology Data Network (TOXNET) and the Comparative Toxicogenomics Database (CTD) we identified 160 compounds that may interact with different combinations of NRF1, MYC and E2F4 (Table 1). Interestingly, no compounds were identified that affect E2F4 and NRF1, but not MYC. Enriched pathway analysis based on the CTD data revealed the top pathways associated with a number of common estrogenic endocrine disrupting compound bisphenol A (BPA)/E2/NRF1 target genes, including (1) Metabolism (85 genes), (2) Disease (84 genes), (3) Gene Expression (71 genes), (4) Signal Transduction (68 genes), (5) Immune System (66 genes), (6) Cell Cycle (61 genes), (7) Metabolic Pathways (58 genes), (8) Metabolism of Proteins (47 genes), (9) Developmental Biology (41 genes) and (10) Cancer Pathways (34 genes) [53]. We observed a significant overlap between the MYC and NRF1 gene networks associated with brain cancer. Brain cancer-associated NRF1 regulatable genes were also found to be regulated by both estrogen and the estrogenic endocrine disrupting compound BPA [54].

It is interesting to note that all compounds affecting NRF1 and E2F4 also affect MYC. Of particular interest are the groups of compounds that seem to affect well-studied cellular signaling pathways or specific organelles such as mitochondria. Close to 90% of the compounds that affect all three TFs, such as aflatoxin B1, curcumin, quercetin, estrogen, arsenic trioxide and selenium, affect hypoxia driven pathways. Arsenic trioxide (ATO), under the tradename Trisenox®, is a

Table 1   Compounds affecting NRF1, MYC and E2F4 activity

NRF1, E2F4 and MYC	NRF1 and MYC	E2F4 and MYC
Bis(4-aminophenyl)methane	Dorsomorphin	2'-Amino-3'-methoxyflavone
Afimoxifene	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine	2-Acetylaminofluorene
Aflatoxin B1	1,3,5-Tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole	PCB 138
Ammonium Chloride	2-(4-Morpholinyl)-8-phenyl-4H-1-benzopyran-4-one	Enterolactone
Arsenic	2,2',4,4'-Tetrabromodiphenyl ether	2,4,4'-Trichlorobiphenyl
Arsenic trioxide	4-Hydroxy-2-nonenal	PCB 153
Atrazine	4-Toluidine	PCB 101
Benzo(a)pyrene	7,8-Dihydro-7,8-dihydroxybenzo(a)pyrene 9,10-oxide	PCB 52
Bisphenol A	Acetylcysteine	4-OH-PeCB1
C646 compound	Acrolein	PCB 126
Carbamazepine	Antirheumatic Agents	Acetaminophen
Cisplatin	Arsenite	Amiodarone
Clofibrate	Ascorbic Acid	Butyraldehyde
Cobaltous chloride	Cadmium	Coumestrol
Copper Sulfate	Caffeine	Cuprizone
Curcumin	Cannabidiol	Cylindrospermopsin
Cyclosporine	Carbon Monoxide	Diazinon
Decitabine	Chlorodiphenyl	Diclofenac
Dietary Fats	Choline	Dieldrin
Estradiol	Cocaine	Diuron
Estrogens	Copper	Emodin
Ethinyl Estradiol	Dexamethasone	Ethyl Methanesulfonate
Formaldehyde	Doxorubicin	Eugenol
Glucose	Dronabinol	Flavonoids
ICG 001	Enzyme Inhibitors	Fluorouracil
Nicotine	Finasteride	Genistein
Oxaliplatin	Folic Acid	Jinfukang
Quercetin	Fulvestrant	JP8 aviation fuel
Rosiglitazone	Gentamicins	Methyl Methanesulfonate
Selenium	Glafenine	Methylselenic acid
Sodium arsenite	Hydrogen Peroxide	Nanotubes, Carbon
Soman	Ionomycin	Paclitaxel
Tetrachlorodibenzodioxin	Ketolides	PCB 180
Tetradecanoylphorbol	Lindane	Phenobarbital
Topotecan	Lipopolysaccharide	Potassium chromate (VI)
Tretinoin	Losartan	Potassium Dichromate
Tunicamycin	MnTE-2-PyP	Silver
Valproic Acid	Metformin	Sirolimus
Vehicle Emissions	Methamphetamine	Smoke
Vinclozolin	Methionine	Sodium bichromate
	Methotrexate	Tamoxifen
	Methoxyacetic acid	Thioacetamide
	Methylmercuric chloride	Tobacco Smoke Pollution
	Monobutyl phthalate	Vanadates
	Methylarsonous acid	
	Midomafetamine	
	Norepinephrine	
	PCI 5002	
	Pentachlorophenol	
	Perfluorooctanoic acid	
	Pirinixic acid	
	Piroxicam	
	Progesterone	
	Raloxifene	
	Resveratrol	
	4-Pentynoic acid	
	Sodium Selenite	
	Sulforafan	
	Sulindac	
	T-2 Toxin	
	Testosterone	
	Thapsigargin	
	Trichostatin A	
	Trimellitic anhydride	
	Troglitazone	
	Uranium	
	Uranyl acetate	
	Vincristine	
	Vitamin E	
	Zidovudine	
	Zinc	

chemotherapeutic agent approved by the US FDA as a second line treatment for acute promyelocytic leukemia. ATO can cross the blood-brain barrier, and it has been shown that ATO induces brain cancer cells to undergo apoptosis [108]. Recently, Bell et al. [109] have reported that ATO may act as a potent inhibitor of proneural glioblastoma and glioma stem cells, while mesenchymal glioma stem cells appear to be less sensitive. However, ATO is readily absorbed by the digestive system and may elicit toxic effects when inhaled or upon skin contact. As a result, it is necessary to thoroughly comprehend the context-dependent effects of ATO. In summary, environmental compounds affecting TFs suggest a functional overlap between NRF1, E2F4 and MYC.

10 NRF1, E2F4 and MYC interplay regulates target genes affecting malignant transformation and progression

Functional links between NRF1 and MYC or E2F are well documeanted [4, 43]. How NRF1 exactly interacts with E2Fs and MYC is, however, not fully clear yet. It is imperative to understand how such interactions bring about changes in both normal and cancer cells. This will allow an assessment of how NRF1, MYC and E2F4 jointly contribute to the establishment of hallmark characteristics of malignant transformation and progression. NRF1, E2Fs and MYC act in concert to regulate common target genes in cancer cells. The advantage of this redundancy, however, remains elusive. These TFs bind to a significant proportion of the GC-rich elements present within the genome. In many gene promoters NRF1 binding motifs share a MYC recognition sequence [104], but how exactly these TF binding motifs contribute to biological function is not clear. MYC-MAX binding, but not NRF1 binding, to these DNA motifs has recently been advocated as a key node of gene regulation control, even though the effects of MYC-MAX binding to these DNA motifs have been found to be inhibited by dominant negative NRF1 [110]. To identify common human NRF1, E2F4 and MYC target genes, we analyzed the NRF1 ChIP-Seq dataset from the Encyclopedia of DNA Elements (ENCODE). NRF1, E2F4 and MYC enriched motifs were found in 9253 common genes (Fig. 3). In order to uncover putative overlapping roles, we further mapped these common target genes to different cancer hallmark features. In Table 2 and Fig. 4 the NRF1, E2F4 and MYC common target genes identified in different signaling pathways are depicted, as well as the associated hallmarks of cancer. We found E2F4-, MYC- and NRF1-enriched motifs in genes operating in signaling pathways governing all hallmark characteristics of malignant transformation and progression. We found that eleven critical signaling pathways are enriched in NRF1 target genes, i.e., the PI3K-Akt, RAS, cadherin, chemokine, cytokine,
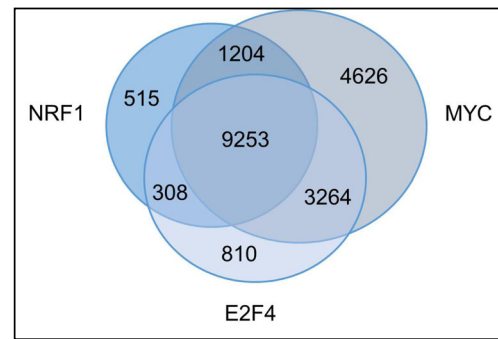

Fig. 3 Venn diagram depicting distribution of NRF1, MYC and E2F4 target genes

NOTCH, apoptosis, TGF-β, VEGF, T-cell receptor and B-cell receptor signaling pathways.

Using a couple of common downstream targets and assessing the experimental evidence for TF crosstalk, we here explore this concept in further detail. One example of a common downstream target gene of NRF1, MYC and E2Fs is EZH2. EZH2 (Enhancer of Zeste Homolog 2) is a key epigenetic regulator and epithelial-mesenchymal transition (EMT) inducer that participates in a variety of cancer metastasis pathways [111]. MYC upregulates EZH2 expression by downregulating miRNA 101 (miR-101), miR-26a and miR-26b. MYC expression is also positively regulated by EZH2 in glioblastoma. Meanwhile, it has been found that E2Fs positively control EZH2 transcription, and that EZH2 is critical for regulation of the pRB-E2F pathway. EZH2 is considered to suppress miR-31 [112], which has recently been shown to have the ability to downregulate NRF1 expression at both the mRNA and protein levels in a dose-dependent manner [113]. Another target gene that is co-regulated by NRF1, MYC and E2Fs (specifically E2F4) is *CDC2*. CDC2 is co-expressed with MYC, TFAM and NRF1 [114], and it has been reported that p130/E2F4 binds to and represses the *CDC2* gene promoter in response to p53 [115]. MYC cooperates with activated RAS to induce the *CDC2* gene promoter [116]. The *CDC2* gene promoter also contains a functional NRF1 consensus binding site [116, 117]. Activation of NRF1-regulated target cell cycle genes, including *CDC2*, has been shown to be involved in estrogen-induced malignant transformation [118].

A subset of mitochondrial genes acts as targets of NRF1, MYC and E2F4, and some of the TF binding sites are co-shared by NRF1 and MYC in the ERE set of ERβ prevalent sites [119] and in leukemia cell-associated transcriptional networks [120]. A degree of redundancy in the system has also become apparent from a recent study showing that gene motifs bound by E2F and NRF1 positively correlate with breast tumor progression, angiogenesis and metastasis [93]. Promoter analysis of breast cancer subtype-specific gene signatures showed that NRF1 represents one of the top 15 significantly enriched transcription factor binding site (TFBS) matrices in breast cancer subtypes. Principal component analysis

Table 2 NRF1, E2F4 and MYC common target genes linked to signaling pathways associated with hallmarks of cancer

| Hallmarks of cancer	Signaling pathway associated with a hallmark feature		Common target genes of MYC, E2F4 and NRF1 linked to a hallmark-specific pathway
Sustaining proliferation	Cell cycle		ANAPC2, CCNB1, CCND2, CCND3, CCNE1, CCNE2, CCNK, CDK2, CINP, E2F3, PSMD11, PSMD12, PSMD13, PSMD3, PSMD4, PSMD7, PSME2, RPA3
	DNA replication		BLM, PCNA, XRN1, POLD2, PRIM2, RTCB, TOP2A, H3F3B/H3F3A, PRIM1, RCF5, HIST1H3A, RPA2, TOP1, RCF3, RCF2, CENPA, RNASEH1/RNH1, RNASEH2A, DNA2
Evading growth suppressors	TGFβ signaling pathway		RRAS, ATF2, DCP1A, BMPR1A, GDF9, JUNB, JUND, TLL2, FKBP1B/FKBP9, TGFB1, ACVRV2B, TGFBR2, SNIP1, FKBP1A, SMAD2, DCP1B, SKIL, SKI, SMURF1, BAMBI, EP300, MAPK14, MAPK1, CITED4, FKBP2, TAB1, SMAD5, FOSL1, HRAS, MAPK7, MAPK11, NRAS, ZFYVE16, BMPR2, BMPR1B, SMAD7, CREBBP, MAPK12, CITED2, JUN, PDF
	Cadherin signaling pathway		ACTA2, ACTB, ACTG1, ACTR2, CDH1, CDH15, CDH2, CDHR2, CELSR3, CSNK2A1, CTNNA1, CTNNB1, EGFR, ERBB2, FER,FRK, FYN, FZD1, FZD2, FZD3, FZD3/FZD9, FZD4, FZD5, FZD7, FZD8, GSK3B, LEF1, LYN, PCDH1, PCDH9, PCDHAC2, PCDHGC3, PTPN1, TCF7L1, TCF7L2, WNT1, WNT2B, WNT5A, WNT7A, WNT7B, WNT9A, YES1
Resisting cell death	Apoptotic pathway members		AIFM1, AKT1, AKT2, APAF1, ATF1, ATF2, ATF4, ATF6, ATF6B, ATF7, BAG1, BAG3, BAK1, BCL2, BCL2A1, BCL2L1, BCL2L11, BIRC2, BIRC3, CASP3, CASP7, CASP9, CFLAR, CHUK, CREM, CYCS, DIABLO, EIF2S1/EIF2A, ENDOG, FADD, FAS, HSPA1L, HSPA2, HSPA5, HSPA6, HSPA8, IKBKB, JUN, KLHL20, M6PR/IGF2R, MADD, MAP2K3, MAP2K4, MAP2K7, MAP3K1, MAP3K14, MAP3K5, MAP4K1, MAP4K5, MAPK1, MAPK7, MCL1, NFKB1, NFKB2, NFKBIA, PIK3CA, PIK3CD, PRKCA/PRKCACA, PRKCH, PRKRA, REL, RELA, RELB, TMBIM6, TNFRSF10A, TNFRSF10D, TNFRSF1A, TNFRSF1B, TNFSF10, TRADD, TRAF2, XIAP
		BCL-2 Family regulated pathway	BCL2, BAG1, BAG3, BAK1, BCL2, BCL2A1, BCL2L1, BCL2L11,
		TNF receptor pathway	TNFRSF10A, TNFRSF10D, TNFRSF1A, TNFRSF1B, TRADD, TRAF2
		TNF Superfamily	TNFSF10
		Fas signaling pathway (CD95)	FAS
		Caspase family	CASP3, CASP7, CASP9, CFLAR
		NF-KB signaling pathway	NFKB1, NFKB2, NFKBIA
		IAP family	DIABLO
		CARD family	APAF1
		Kinases	CHUK
		Other	SOCS6/SOCS4
	TP53 pathway	TP53 activators	ADGRB2, ADGRB3, AIFM2, AKT1, AKT2, APAF1, ATR, CCNB1, CCNE1, CCNG1, CD82, CDC25C, CDK1, CDK2, CDK5, CDKN2A, CDKN2D, CHEK2, CREBBP, E2F3, EP300, FAS, GADD45B, GTSE1, HDAC1, HDAC2, HMGB1, IGFBP3, KAT6B, MDM2, PDK1, PIK3C3, PIK3CA, PIK3CD, PIK3R1, PIK3R2, PIK3R3, PM1D, PMAIP1, PML, PP2CA, PP2CB, PTEN, RRM2, SFN, SIN3A, SIRT1, SUMO2, SUMO3, THBS1, TNFRSF10A, TNFRSF10D, TP73, TRAF2, WRN, ZMAT3
	Oxidative stress response		ATF2, MYC, MKNK2, ELK1, STYX, MAX, MAP2K4, EEF2K, DUSP16, MEF2A, DUSP12, TXN, MAPK14, DUSP5, STYXL1, NGLY1, DUSP10, STAT1, MAPK11, DUSP14, DUSP19, DUSP6, DDIT3, DUSP7, MAP2K3, TXNL1, BCL2, MAPK12, MAP3K4, JUN, DUS2/DUSP2, MKNK1, DUSP22
Enabling replicative immortality	PI3K pathway		PTEN, PIK3R2, SOS2, PIK3CA, INPP5A, FOXO4, GSK3B, GNAI2, RPS6KB1, GRB2, SOS1, CCND2, GNAI1, GNA13, PDK1, CASP9, PIK3R1, FOXO3, AKT2, INPPL1, HRAS, PIK3R3, AKT1, NRAS, RPS6KB2, YWHAZ, GNB4, GNAI1
	Telomere maintenance	Regulation of telomere length	ACD, BLM, DCLRE1C, DKC1, ERCC1, HSPA1L, MRE11A, MYC, NBN, PIF1, POT1, PRKDC, PTGES3, RAD50, RTEL1, SMG6, TEP1, TERF1, TERF2IP, TNKS
		Telomerase complex	NHP2, TERT, ACD, TERF1, TINF2, SLX4, ERCC1, MSH2, MSH3, DKC1, GAR1, POT1, RAP1A

Table 2 (continued)

Hallmarks of cancer	Signaling pathway associated with a hallmark feature		Common target genes of MYC, E2F4 and NRF1 linked to a hallmark-specific pathway
	Telomerase regulation		ATP5C1, BCL2, EGF, IGF1, MYC, PAX8, PINX1, PPARG, PPP2R1A, PPPSR1B, PRKCA, PRKCB, RB1, SART1, SP1, TGFB1, TP53, MAD1L1, BL1, AKT1, KRAS, MEN1
	Senescence pathways (Intracellular)		CCND1, CCNE1, CDK2, CDK4, CDK6, CDKN1A, CDKN2A, CDKN2D, CHEK2, ETS2, MDM2, RB1, RBL2, TP53, ATM, BMI1, E2F1, E2F3,
	Senescence pathways (secretome)	Soluble factors	IL7, IL15
		Chemokines	CXCL12
		Inflammatory factors	RELA
		Growth factors	IGFBP3
		Protease, regulators	TIMP1, TIMP2
		Soluble or shed receptors or ligands	ICAM1, EGFR
	RAS pathway		ATF2, SOS2, PIK3CA, PIK3CD, CDC42, MAPKAPK3, GSK3B, ELK1, RAC1, RALB, GRB2, MAP2K4, SOS1, MAP2K2, RHOB, RPS6KA3, PDK1, RALGDS, MAP2K7, TIAM1, MAPK14, MAPK1, MAP3K1, PAK1, HRAS, STAT1, ARAF, MAPK11, SHC1, AKT1, NRAS, RPS6KA1, PAK2, RGL2, RAC3, SRF, MAP2K1, PLD1, MAP2K3, RAC2, RHOA, PIK3C3, MAPK12, MAP3K4, RGL1, GSK3A, JUN, RAF1, RLA, MAPKAPK2, EXOC2
Inducing angiogenesis	VEGF signaling pathway		AKT1, ARAF, ARHGAP1, CASP9, HIF1A, HRAS, HSPB1, LPXN, MAP2K2, MAPK1, MAPK14, MAPK6, MAPKAPK2, MAPKAPK3, NRAS, PIK3CA, PIK3C3, PIK3CD, PIK3R1, PIK3R2, PIK3R3, PKD1, PLCG1, PLCG2, PRKCA, PRKCH, PRKCI, PRKCZ, PRKD2, PRR5-ARHGAP8, PTK2, PXN, RAC2, RAC3, RAF1, RAK1, SH2D2A, SPHK2, VEGFA
	Growth factors and receptors		FGF2, TGFB1, VEGFA
	Proteases, inhibitors and other matrix proteins		ANGPTL5
	Adhesion molecules		COL4A3, IL8
	cytokines and chemokines		CXCL12, IL10
	Other		AKT1, AKT2, APC, ARAF, ARHGAP1, AXIN1, AXIN2, BIRC3, CASP9, CRK, CRKL, CTNNB1, DLL1, DLL4, DOK1, DVL1, DVL2, EFNB2, EPHB1, F2R, FGF1, FGF2, FGFR1, FRS3, FZD1, FZD2, FZD3, FZD5, FZD8, GRB2, GSK3B, HIF1A, HRAS, HSPB1, JAG1, JAK1, JUN, LPXN, MAP2K1, MAP2K2, MAP3K1, MAPK1, MAPK14, MAPK6, MAPKAPK2, MAPKAPK3, NCK1, NCK2, NOTCH1/HN1, NRAS, PAK1, PAK2, PDGFA, PIK3C3, PIK3CA, PIK3CD, PIK3R1, PIK3R2, PIK3R3, PKD1, PLA2G4C, PLCG1, PLCG2, PLD1, PRKC1, PRKCA/PRKCACA, PRKCH, PRKCZ, PRKD2, PRR5-ARHGAP8, PTK2, PXN, RAF1, RASA1, RBPJ, RHOA, RHOB, SFRP1, SH2D2A/SCAP, SHC1, SOS1, SOS2, SPHK2, STAT1, TCF7, TCF7L2, VEGFA, WNT1, WNT2B, WNT5A, WNT7A, WNT7B
Activating invasion and metastasis	RAS pathway		ATF2, SOS2, PIK3CA, PIK3CD, CDC42, MAPKAPK3, GSK3B, ELK1, RAC1, RALB, GRB2, MAP2K4, SOS1, MAP2K2, RHOB, RPS6KA3, PDK1, RALGDS, MAP2K7, TIAM1, MAPK14, MAPK1, MAP3K1, PAK1, HRAS, STAT1, ARAF, MAPK11, SHC1, AKT1, NRAS, RPS6KA1, PAK2, RGL2, RAC3, SRF, MAP2K1, PLD1, MAP2K3, RAC2, RHOA, PIK3C3, MAPK12, MAP3K4, RGL1, GSK3A, JUN, RAF1, RLA, MAPKAPK2, EXOC2
	EMT transcription factors		HIF1A, TGFB1
	Cell motility	Chemotaxis	FGF2, MAPK1, MYH10, MYH9, PRKCA, RAC2, TGFB1, VEGFA, WASF2
		Receptors	EGFR, IGF1R, ITGA4, ITGB1, RHOA, RHOB
		Growth factors	FGF2, TGFB1, VEGFA
		Cell-cell adhesion	EGFR, EXR, ITGA4, ITGB1, ITGB2, MYH9, ROCK1, TGFB1

Table 2 (continued)

Hallmarks of cancer	Signaling pathway associated with a hallmark feature		Common target genes of MYC, E2F4 and NRF1 linked to a hallmark-specific pathway
		Cell-matrix adhesion	ACTN3, CSF1, ILK, ITGB1, MMP14, PTEN, PTK2B, PXN, RASA1, RHOA
		focal adhesion	ACTN3, CAV1, EMAH, ILK, ITGB1, MYL9, PTK2, PTK2B, PXN, TLN1, VASP
	RHO family GTPases	RHO signaling	ACTR2, ACTR3, ARHGDIA, LIMK1, MYL9, MYLK-AS1, PLCG1, PLD1, PRKCA, PTEN, PTPN1, RHO, RHOA, RHOB, RND3, ROCK1, VIM
		RAC signaling	Rac1, Rac2, Rac3, PAK1
		CDC42 signaling	CDC42, VAV2,PAK1, PAK2
	Invasion	Matrix metalloproteases	MMP14, MMP15, MMP16, MMP28
		TFs, Regulators, other	CXCR4, MYC, PARK2,FOXO3,PGK1,NOTCH1/HN1
	Integrin signaling pathway		PXN, ARPC3, RRAS, ACTA2, FYN, RAP2B, RAPGEF1, ITGB8, PIK3R2, ARL1, SOS2, ACTN3, PIK3CA, PTK2B, PIK3CD, CDC42, ARHGAP26, RND2, ELMO2, RAP1A, RAP1B, MEGF9, ARF3, ACTG1, RND3, COL14A, COL9A2, ARF6, RAC1, ACTB, PTPN12, ITGA3, GRB2, CRK, MAP2K4, SOS1, ARFGAP1, MAP2K2, FLNB, RHOB, ARHGAP10, ARPC1B, ARPC1A, RND1, CAV1, VASP, MAP3K5, DNAJC27, MAPK1, COL13A1, ELMO1, MAP3K1, PIK3R1, ARPC5L, TLN1, ILK, FRK, MICALL1, MESDC1, COL4A1, ITGAV, LIMS1, CSK, HRAS, ARF1, PIK3R3, ARAF, SHC1, NRAS, RAC3, CRKL, MAP2K1, ITGA4, PTK2, MAP2K3, RAC2, COL4A2, COL27A1, RHOA, ACTN4, RAP2A, PIK3C3, ARPC2, ARPC5, MAP3K4, LAMB1, ITGB1, RAF1, MAPK6, COL4A4
Genome instability and mutation	TP53 activators		ADGRB2, ADGRB3, AIFM2, AKT1, AKT2, APAF1, ATR, CCNB1, CCNE1, CCNG1, CD82, CDC25C, CDK1, CDK2, CDK5, CDKN2A, CDKN2D, CHEK2, CREBBP, E2F3, EP300, FAS, GADD45B, GTSE1, HDAC1, HDAC2, HMGB1, IGFBP3, KAT6B, MDM2, PDK1, PIK3C3, PIK3CA, PIK3CD, PIK3R1, PIK3R2, PIK3R3, PM1D, PMAIP1, PML, PP2CA, PP2CB, PTEN, RRM2, SFN, SIN3A, SIRT1, SUMO2, SUMO3, THBS1, TNFRSF10A, TNFRSF10D, TP73, TRAF2, WRN, ZMAT3
	P53 pathway feedback loops		AKT1, AKT2, ATR, CCNA2, CCNE1, CCNG1, CDK2, CTNNB1, E2F3, HRAS, MAPK11, MAPK14, MDM2, MYC, NRAS, PDK1, PIK3C3, PIK3CA, PIK3CD, PIK3R1, PIK3R2, PIK3R3, PP2CA, PPM1D, PPP2CB, PTEN, RB1, RBL1, STAT1, TP73
	Cell cycle check POINT		BARD1, FANCD2, H2AFX, MDC1, RAD1, RAD17, RNF168, RNF8, SMC1A, TOPBP1, RAD50, RAD9A
	Nucleotide excision repair		, ERCC5, ERCC6, LIG1, MMS19, PNKP, POLL, RAD23A, RAD23B, RPA1, RPA3, XAB2, XPA, XPC
	Base excision repair		NEIL1, NEIL2, NEIL3, NTHL1, OGG1, PARP2, PARP3, POLB, UNG, XRCC1
	Mismatch repair		MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, PMS2, POLD3, TREX1
	Histone acetylation		KAT5, NCOA3
	Histone deacetylation		HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7
	Chromatin modification molecules		PPARGC1B, CBX3, NAP1L1
	P53 pathway by glucose deprivation		AKT1, AKT2, MTOR, PPP2CA, PPP2CB, PRKAA1, PRKAA2, PRKAB1, PRKAB2, PRKAG1, RPS6KB1, RPS6KB2, STK11, TP73, TSC1, TSC2
Deregulating cellular energetics	ATP synthesis		ATP5B, ATP5C1, CYCS, ATP5A1, CYC1
	Glutamine glutamate conversion		GLUD1
	Gluconeogenesis		FBP1, FBP2, PCK1, PCK2
	Regulation		PDK1, PDK2, PDK3, PDK4, PDP2, PDPR
	Pentose phosphate pathway		G6PD, H6PD, PGLS, PRPS1, PRPS1L1, PRPS2, RBKS, RPE, RPIA, TALDO1, TKT
	Glycogen metabolism		GBE1, GYS1, UGP2, AGL, PGM1, PGM2, PGM3, PYGL, GSK3A, GSK3B, PHKA1, PHKB, PHKG2

Table 2 (continued)

Hallmarks of cancer	Signaling pathway associated with a hallmark feature	Common target genes of MYC, E2F4 and NRF1 linked to a hallmark-specific pathway
	Glycolysis	GCK, GPI, PGM1, PGM2, PGM3, NLK, TPI1, PFKL, PKM, PFKM, ALDOC, PGAM1, ENO1, GAPDH, BPGM, HK2, ENO2, ALDOA, PGK1
	Mitochondial: Complex I	NDUFA1, NDUFA2, NDUFA3, NDUFA4, NDUFA6, NDUFA8, NDUFA11, NDUFAB1, NDUFB2, NDUFB3, NDUFB4, NDUFB6, NDUFB7, NDUFB8, NDUFB9, NDUFC1, NDUFS1, NDUFS3, NDUFS5, NDUFS6, NDUFS7, NDUFV1, NDUFV2, NDUFV3
	Mitochondial: Complex II	SDHA, SDHB, SDHC, SDHD
	Mitochondial: Complex III	CYC1, UQCR11, UQCR1, UQCRC2, UQCRFS1, UQCRH, UQCRQ
	Mitochondial: Complex IV	COX4I1, COX5A, COX5B, COX6A1, COX6A2, COX6B1, COX6C, COX7A2, COX7A2L, COX8A
	Mitochondial: Complex V	ATP5A1, ATP5B, ATP5C1, ATP5F1, ATP5G1, ATP5G2, ATP5G3, ATP5H, ATP5I, ATP5J, ATP5J2, ATP5L, ATP5O, PPA1
	Activator genes	ARRDC3, ASB1, CYB561D1, DNAJB1, EDN1, HSPA1B, LRP5L
	TCA cycle	ACO1, CS, DLAT, DLD, DLST, FH, IDH1, IDH2, IDH3A, IDH3B, IDH3G, DHTKD1, FH, OGDH, PDHA1, PDK2, SDHA, SDHB, SDHC, SDHD, SUCLA1, SUCLG1, SUCLG2, MDH1, MDH1B, MDH2, OGDH, PCK2
Tumor promoting inflammation	Chemokine and cytokine signaling pathway	ARPC3, PTEN, RRAS, PLCG1, ACTA2, ARRB2, CISH, NFKB1, JUNB, PLCL2, PLCB4, JUND, PIK3CA, GNG5, GRK6, PTK2B, PIK3CD, LTB4R2, CDC42, BCL3, NFKB2, RHOG, GNAI2, CYTH2, ARRB1, ROCK1, CAMK2D, ACTG1, PLCG2, COL14A1, ITPR3, RAC1, ACTB, ITPR2, PRKACA, PLCL1, GRB2, TYK2,SOS1, GNAI1, SOCS7/SOCS4, ARPC1B, GNAI3, REL, ARPC1A,, ARPC4, PDK1, NFATC3, NFAT5, PRKCZ, GNAO1, ITPR1, IKBKE, IKBKB, MAPK1, CXCR4, RGS17, SOCS6/SOCS7, ARPC5L, CHUK, AKT2, PRKX, RELA, INPPL1, PAK1, MYH10, RELB, MAPK7, STAT1, SOCS6/SOCS4, ARAF, SHC1, AKT1, NRAS, CCR10, MYH7B, GNG3, PAK2, RAC3, IFNAR1, NFKBIA, IL12A, ITGA4, NFATC1, RAC2, RHOA, ARPC2, ARPC5, MAP3K4, MYH9, ITGB1, JUNA, DRBK1, RAF1, ADCY6, GNAI1, IFNGR1, PLCD3, STAT6, IL15
	NOTCH signaling pathway	LNX2, MFNG, MAML1, HES4, NUMB, JAG1, POFUT1, NEURL2, PSEN2, HEY1, ADAM10, RBPJ, FUTB, ADAM17, BPTF, NOTCH1/HN1, DLL1, HES1, DLL4, HEY2, APH1A, NCSTN, NEURL1, NEURL4, KAT2A
Avoiding immune destruction	B cell activation	NFKB1, SOS2, PIK3CA, PIK3CD, VAV2, NFKB2, PLCG2, NFKBIL1, ITPR3, RAC1, ITPR2, GRB2, SOS1, MAP2K2, PPP3CC, NFATC3, ITPR1, IKBKB, MAPK14, MAPK1, CHUK, FRK, LYN, HRAS, ARAF, PPP3CB, MAPK11, NRAS, RAC3, MAP2K1, NFKBIA, NFATC1, RAC2, MAPK12, JUN, RAF1
	T cell activation	PLCG1, NFKB1, PIK3R2, SOS2, PIK3CA, NCK1, PIK3CD, CDC42, NCK2, VAV2, NFKB2, CALM1, RAC1, GRB2, SOS1, MAP2K2, PPP3CC, NFATC3, ITPR1, IKBKB, MAPK1, MAP3K1, PIK3R1, CHUK, AKT2, PAK1, CSK, HRAS, PIK3R3, ARAF, PPP3CB, AKT1, NRAS, PAK2, RAC3, MAP2K1, NFKBIA, NFATC1, RAC2, PIK3C3, JUN, RAF1, B2M, CD74

Fig. 4 Illustration of common target genes of MYC, E2F4 and NRF1 linked to hallmark-specific pathways. 1° = Primary, 2° = Secondary
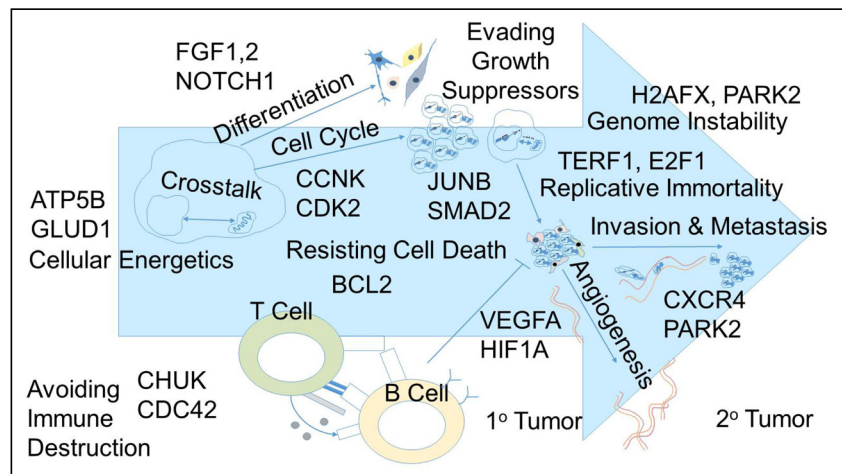

(PCA) of TFBS enrichment, which reduces redundancy and highlights the most effective tumor subtype discriminators, indicated that NRF1 acts as one of the dominating discriminating factors for both the basal-like and luminal B breast cancer subtypes [121]. Either cooperation or competition between NRF1 and MYC may take place at many NRF1 or MYC target sites. The binding motif on TFAM serves, for example, as a target for both NRF1 and MYC [122]. Retrospective brain tumor microarray-based expression analyses led to the identification of a set of genes that significantly correlated with MYC, TFAM and NRF1 in brain tumor tissues [122]. PRIMA analysis revealed that TF signatures enriched in cell cycle-dependent promoters are also enriched in a MYC-MAX target gene set (E2F, NF-Y, Sp1, NRF1, ETF, CREB and AhR/Arnt) [123], and that the MYC-MAX signature is markedly enriched in a NRF1 target gene set [124]. These findings suggest that by activating or repressing genes regulating proliferative signaling and growth suppression, genomic stability, apoptosis/autophagy, senescence, and reprogramming of differentiation and cellular energetics, NRF1 in conjunction with E2F4 and MYC may play an important role in regulating the acquisition of CSC characteristics and human cancer hallmark features (Fig. 5).

Coordination between NRF1 and MYC action may take place at several target gene levels. NRF1 can heterodimerize with MAX, and the NRF1 α palindromic sequence may serve as an alternative MAX binding site as identified in the *eIF2S2* gene promoter [125]. NRF1 may initiate transcription and direct dispersed transcription initiation [126], and can displace MAX from key gene promoters and enhancers in vivo. Although the cellular context is important, actual TF binding to genomic DNA is also critical. A recent study using an attention-based neural network approach strictly relying on analysis of genomic sequence features (EPIANN) has, for example, revealed that the NRF1 protein has a higher propensity to bind to enhancer regions compared to promoter regions [127]. Even more interestingly, E2F4, E2F1 and MAX

proteins bound to promoter regions have been found to interact with NRF1 protein bound to the enhancer region, but not vice versa [127].

CSCs are maintained in a hypoxic microenvironment within a tumor. In addition to reprogramming cancer cell metabolism, hypoxia is considered to play an important role in the survival and maintenance of CSCs, and in resistance to apoptosis. However, the TFs that regulate these properties of CSCs under physiologic hypoxic microenvironmental conditions remain to be fully understood. Here, we set out to define the potential role for NRF1 to orchestrate MYC and E2F4 to regulate PI3K-driven survival mechanisms, as well as apoptotic pathways under hypoxic conditions. All genes depicted in the scheme in Fig. 6 are regulated by NRF1, MYC and E2F4 (Table 2). These three TFs govern the survival and maintenance of CSCs, and have been shown to protect cells from apoptosis. Under hypoxia, however, a heterodimeric hypoxia-inducible factor 1 (HIF1) subunit, i.e., HIF1α, escapes the degradation, dimerizes with ARNT and binds to hypoxia-regulated element (HRE)-containing gene promoters to drive apoptosis-related gene expression. Differential expression of HIF1α and 2α proteins within the hypoxic microenvironment has been implicated in CSC biology, including stemness, reprogramming of metabolism, invasion, EMT and chemoresistance. It is noteworthy that HIF1α, HIF1AN (inhibitor of HIF1α), and HIF1A-AS2 (HIF1α antisense RNA 2) serve as common targets of NRF1, E2F4 and MYC (Table 2). Recently, a non-canonical role of EZH2 (a common target of NRF1, E2F4 and MYC, see above) as a molecular switch with regard to hypoxia has been reported [128]. In case of genes such as *EZH2*, for which there is contention whether they act as a tumor suppressor or an oncogene, it might be helpful to add the biological context. Hypoxia, for example, and its effects on TFs such as NRF1, may affect their capacity to act as master regulators through the choice of TF interactions and the concomitant sets of proteins that are expressed in one condition versus another. There is evidence suggesting that

Fig. 5 Putative actions of NRF1 in cooperation or competition with MYC and E2F transcription factors
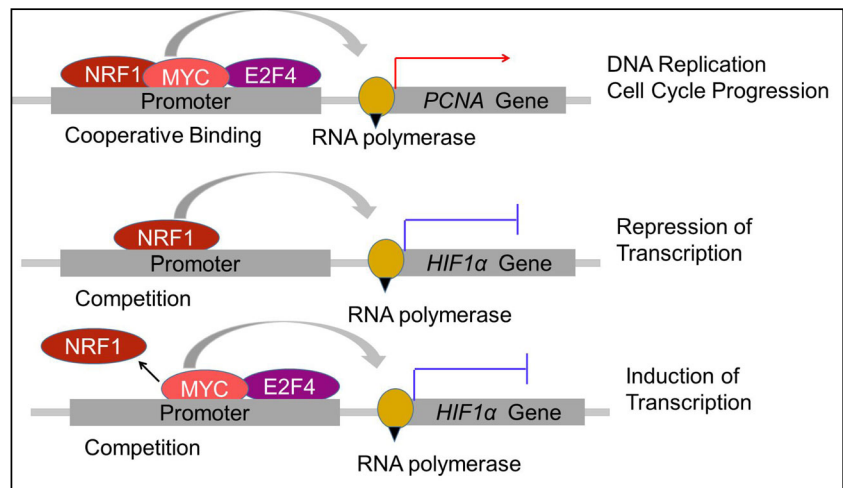
NRF1 and MYC may have opposite effects on HIF1α activity [72, 129]. Although the role of both TFs has not been studied under the same experimental conditions, it appears that over-expression of MYC induces *HIF1α* gene transcription, whereas NRF1 may be able to competitively inhibit this transactivation and further inhibit the transcription of the *MYC* gene (Fig. 5). Silencing of HIF1α results in a decreased induction of one of the EMT-associated TFs, ZEB2, and its related factors VIM and TGFβ1, implying an hypoxia/HIF1α-dependency for their expression [130]. The *HIF2α* gene is directly controlled by E2F1, E2F1 and E2F4 [131, 132]. These findings suggest a joint regulation of hypoxia-induced genes related to EMT and resistance to apoptosis by NRF1, MYC and E2F4 as a novel escape mechanism to hypoxia-driven cytotoxicity. There is further merit added to the above idea considering the fact that NRF1, E2F4 and MYC bind to motifs that are consistently over-represented in bidirectional promoters [31], whereas 73% of the known vertebrate DNA binding motifs are under-represented [31]. Through binding to bidirectional promoter sites, these TFs may simultaneously govern disparate proteins and non-coding RNAs that act in concert to bring about even the simplest change in cellular state. A TF such as NRF1 bound to an enhancer may even be able to control the effect of another TF, such as MYC, by promiscuously binding to its partner MAX, since NRF1-MAX heterodimers have previously been reported in the literature [133]. In terms of biophysical aspects of binding and alteration, NRF1 binding has been reported at least in one case to bend DNA towards the major groove [134], while MYC-MAX and other E-box binding proteins are known to bend DNA towards the minor groove [135]. In summary, evidence supporting the interplay between NRF1, MYC and E2F4 points towards a more focused interrogation with respect to their crosstalk affecting the development and progression of different human cancers.

11 Conclusions and perspectives

The contribution of both MYC and E2Fs in the pathogenesis of human cancers is unequivocally proven, while that of NRF1 is less well understood. Here, we present emerging evidence supporting a role of NRF1 in cancer development and for overlap, cooperation and exclusivity of its activity with MYC and E2Fs. NRF1 is one of the top five TFs that shows increased activity in many human cancers. Recently, we have uncovered a novel oncogenic function of NRF1 in breast cancer development and progression. NRF1, MYC and E2F recognition sequences are present within the promoters of many common target genes and these TFs may compete or co-operate for binding to these promoter sequences. The frequent co-occurrence of NRF1, MYC and E2F binding motifs within human gene promoters suggests that NRF1, in conjunction with MYC and E2Fs, may commonly regulate many genes in mammalian cells. A CTD search of chemical compounds revealed that many of them affecting NRF1 and E2F4, also affect MYC, again suggesting a functional overlap between these TFs. Similar to MYC and E2Fs, NRF1 controls EMT, apoptosis, senescence and chromatin stability/relaxation. By doing so, NRF1 may contribute to the acquisition of
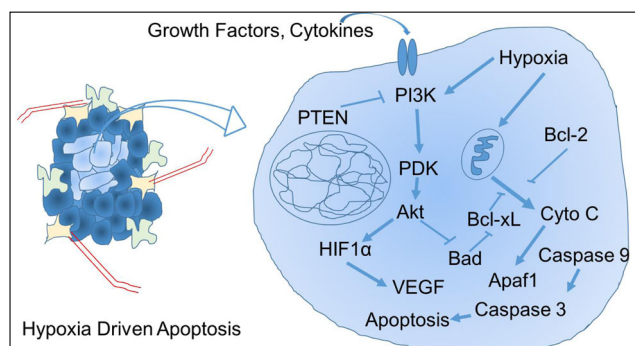

Fig. 6 Potential of NRF1 to orchestrate MYC and E2F4 effects in hypoxia driven apoptosis: All proteins shown are regulated by NRF1, MYC and E2F4

pluripotent stem cell characteristics, since its underlying processes are transcriptionally regulated by E2F4 or MYC. Contrary to this concept, NRF1 may regulate MYC and E2F functions in a cellular context-dependent manner by acting as a "pioneer" TF and facilitating or repressing the ability of "settler" MYC protein to bind DNA through the formation of NRF1-MAX heterodimers, that may compete with MYC-MAX heterodimers, or by regulating E2F1/E2F6, which may modulate MYC activity. The reprogramming of pluripotency TFs, EMT and cancer stem cell marker genes is regulated by MYC, E2F and NRF1, which suggests that a single TF may not be sufficient to reprogram adult cells to CSCs. The cooperative binding of NRF1, MYC and E2F followed by transcriptional activation and/or repression of key downstream target genes, may also play a pivotal role in removing senescent and apoptosis barriers and, thus, enhancing the acquisition of CSC characteristics. Recently, NRF1 has even been suggested as a target for combatting chemoresistance in a multicenter case-control study. NRF1, E2F4 and MYC may also work in concert to activate/inhibit the expression of genes that contribute to resistance to endocrine or chemo-therapeutic agents. A further elucidation of these NRF1/E2F/MYC-driven mechanisms is expected to guide the development of new therapeutic regimens to slow down or prevent the development of human cancers. These efforts should be aimed at understanding how NRF1 exactly interacts with E2Fs and MYC in individual normal and tumor cells. Clinical validation of the role of the interplay between these transcription factors in the evolution of cancer cells will set the stage for the establishment of a pan-cellular TF regulatory strategy to predict cancer risk, therapeutic response and patient prognosis.

Compliance with ethical standards

Conflict of interest None declared.

References

1. J. Wang, Q. Liu, J. Sun, Y. Shyr, Disrupted cooperation between transcription factors across diverse cancer types. BMC Genomics **17**, 560 (2016)
2. S.A. Lambert, A. Jolma, L. Campitelli, P. Das, T. Yin, M. Albu, X. Chen, J. Taipale, T. Hughes, M. Weirauch, The human transcription factors. Cell **172**, 650–665 (2018)
3. M.M. Falco, M. Bleda, J. Carbonell-Caballero, J. Dopazo, The pan-cancer pathological regulatory landscape. Nature Sci Rep **6** (2016)
4. C.V. Dang, MYC on the path to cancer. Cell **149**, 22–35 (2012)
5. V.O. Okoh, Q. Felty, J. Parkash, R. Poppiti, D. Roy, Reactive oxygen species via redox signaling to PI3K/AKT pathway contribute to the malignant growth of 4-hydroxy estradiol-transformed mammary epithelial cells. PLoS One **8**, e54206 (2011)
6. V.O. Okoh, N.A. Garba, R.B. Penney, J. Das, A. Deoraj, K. Singh, S. Sarkar, Q. Felty, C. Yoo, R. Jackson, D. Roy, Redox signaling to nuclear regulatory proteins by reactive oxygen species contributes to estrogen-induced growth of breast cancer cells. British J Cancer **112**, 1687–1702 (2015)
7. D. Roy, R. Tamuli, NRF1 (nuclear respiratory factor 1). Atlas of Genetics and Cytogenetics in Oncology and Haematology **13**, 4 (2008)
8. L. Gopalakrishnan, R.C. Scarpulla, Structure, expression, and chromosomal assignment of the human gene encoding nuclear respiratory factor 1. J Biol Chem **270**, 18019–18025 (1995)
9. R.C. Scarpulla, Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiol Rev **88**, 611–638 (2008)
10. J.Y. Chan, X.L. Han, Y.W. Kan, Cloning of Nrf1, an NF-E2-related transcription factor, by genetic selection in yeast. Proc Natl Acad Sci U S A **90**, 11371–11375 (1993)
11. V. Tiranti, E. Rossi, M. Rocchi, S. DiDonato, O. Zuffardi, M. Zeviani, The gene (NFE2L1) for human NRF-1, an activator involved in nuclear-mitochondrial interactions, maps to 7q32. Genomics **27**, 555–557 (1995)
12. R.C. Scarpulla, Nuclear control of respiratory chain expression by nuclear respiratory factors and PGC-1-related coactivator. Ann N Y Acad Sci **1147**, 321–334 (2008)
13. J.S. Bassey, J.A.C. Efiok, B. Safer, A key transcription factor for eukaryotic initiation factor-2a is strongly homologous to developmental transcription factors and may link metabolic genes to cellular growth and development. J Biol Chem **269**, 18921–18930 (1994)
14. H. Cam, E. Balciunaite, A. Blais, A. Spektor, R.C. Scarpulla, R. Young, Y. Kluger, B.D. Dynlacht, A common set of gene regulatory networks links metabolism and growth inhibition. Mol Cell **16**, 399–411 (2004)
15. J. Satoh, N. Kawana, Y. Yamamoto, Pathway analysis of ChIP-Seq-based NRF1 target genes suggests a logical hypothesis of their involvement in the pathogenesis of neurodegenerative diseases. Gene Reg Syst Biol **7**, 139–152 (2013)
16. C. Amin, A.J. Wagner, N. Hay, Sequence-specific transcriptional activation by Myc and repression by max. Mol Cell Biol **13**, 383–390 (1993)
17. A.L. Gartel, K. Shchors, Mechanisms of c-myc-mediated transcriptional repression of growth arrest genes. Exp Cell Res **283**, 17–21 (2003)
18. B. Lüscher, Function and regulation of the transcription factors of the Myc/max/mad network. Gene **277**, 1–14 (2001)
19. C.V. Dang, S.B. McMahon, Emerging concepts in the analysis of transcriptional targets of the MYC oncoprotein: Are the targets targetable? Genes & Cancer **1**, 560–567 (2010)
20. W. Tansey, P. Mammalian, MYC proteins and cancer. New Journal of Science, Hindawi **757534**, 1–27 (2014)
21. H.Z. Chen, S.Y. Tsai, G. Leone, Emerging roles of E2Fs in cancer: An exit from cell cycle control. Nature Rev Cancer **9**, 785–797 (2009)
22. S. Schwemmle, P. Pfeifer, Genomic structure and mutation screening of the E2F4 gene in human tumors. Int J Cancer **86**, 672–677 (2000)
23. P.J. Iaquinta, J.A. Lees, Life and death decisions by the E2F transcription factors. Curr Opin Cell Biol **19**, 649–657 (2007)
24. S. Skirnisdottir, G. Eiriksdottir, T. Baldursson, R.B. Barkardottir, V. Egilsson, S. Ingvarsson, High frequency of allelic imbalance at chromosome region 16q22-23 in human breast cancer: Correlation with high PgR and low S phase. Int J Cancer **64**, 112–116 (1995)

25. X. Zhong, H. Hemmi, J. Koike, K. Tsujita, H. Shimatake, Various AGC repeat numbers in the coding region of the human transcription factor gene E2F-4. Hum Mut **15**, 296–297 (1999)

26. N. Palmer, P. Kaldis, Regulation of the embryonic cell cycle during mammalian preimplantation development. Curr Top Dev Biol **120**, 1–53 (2016)

27. Z. Kherrouche, D.Y. Launoit, D. Monte, The NRF-1/α-PAL transcription factor regulates human E2F6 promoter activity. Biochem J **383**, 529–536 (2004)

28. S.T. Shors, B.J.S. Effiok, S.J. Harkin, B. Safer, Formation of pal/max heterodimers synergistically activates the eif2 promoter. J Biol Chem **273**, 529–536 (1998)

29. A.B. West, G. Kapatos, C. O'Farrell, F. Gonzalez-de-Chavez, K. Chiu, M.J. Farrer, N.T. Maidment, N-myc regulates parkin expression. J Biol Chem **279**, 28896–28902 (2004)

30. J.K. Das, D. Roy, Transcriptional regulation of chemokine receptor 4 (CXCR4) by nuclear respiratory factor 1 (NRF1) controls estrogen-induced malignant transformation of breast epithelial cells to breast cancer stem cells. Cancer Res **76**, 3312 (2016)

31. J.M. Lin, P.J. Collins, N.D. Trinklein, Y. Fu, H. Xi, R.M. Myers, Z. Weng, Transcription factor binding and modified histones in human bidirectional promoters. Genome Res **17**, 818–827 (2007)

32. Y.M. Oh, J.K. Kim, S. Choi, J.Y. Yoo, Identification of co-occurring transcription factor binding sites from DNA sequence using clustered position weight matrices. Nucl Acids Res **40**, e38–e38 (2012)

33. R. Elkon, C. Linhart, R. Sharan, R. Shamir, Y. Shiloh, Genome-wide in silico identification of transcriptional regulators controlling the cell cycle in human cells. Genome Res **13**, 773–780 (2003)

34. C. Benner, S. Konovalov, C. Mackintosh, K.R. Hutt, R. Stunnenberg, I. Garcia-Bassets, Decoding a signature-based model of transcription cofactor recruitment dictated by cardinal cis-regulatory elements in proximal promoter regions. PLoS Genet **9**, e1003906 (2013)

35. R.I. Sherwood, T. Hashimoto, C.W. O'Donnell, S. Lewis, A.A. Barkal, J.P. van Hoff, V. Karun, T. Jaakkola, D.K. Gifford, Discovery of directional and nondirectional pioneer transcription factors by modeling DNase profile magnitude and shape. Nature Biotech **32**, 171–178 (2014)

36. M.D. Lavigne, G. Vatsellas, A. Polyzos, E. Mantouvalou, G. Sianidis, I. Maraziotis, M. Agelopoulos, D. Thanos, Composite macroH2A/NRF-1 nucleosomes suppress noise and generate robustness in gene expression. Cell Rep **11**, 1090–1101 (2015)

37. A. Ferraro, Altered primary chromatin structures and their implications in cancer development. Cell Oncol **39**, 195–210 (2016)

38. F. Morrish, C. Giedt, & Hockenbery D. C-MYC apoptotic function is mediated by NRF-1 target genes. Genes Dev **17**, 240–255 (2003)

39. H.B. Suliman, J.E. Keenan, C.A. Piantadosi, Mitochondrial quality-control dysregulation in conditional HO-1−/− mice. JCI Insight **2**, e89676 (2017)

40. C. Zhang, M. Lin, R. Wu, X. Wang, B. Yang, A.J. Levine, W. Hu, Z. Feng, Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect. Proc Natl Acad Sci U S A **108**, 16259–16264 (2011)

41. A. Soufi, G. Donahue, K.S. Zaret, Facilitators and impediments of the pluripotency reprogramming factors' initial engagement with the genome. Cell **151**, 994–1004 (2012)

42. J.D. Lin, Minireview: The PGC-1 coactivator networks: Chromatin-remodeling and mitochondrial energy metabolism. Mol Endocrin **23**, 2–10 (2009)

43. W.-S. Tzou, Identification of potential E2F target genes through cis-regulatory modules derived from chromatin immunoprecipitation microarray data. Fooyin J Health Sci **2**, 66–70 (2010)

44. H. Liu, X. Tang, A. Srivastava, T. Pecot, P. Daniel, B. Hemmelgarn, S. Reyes, N. Fackler, A. Bajwa, R. Kladney, C. Koivisto, Z. Chen, Q. Wang, K. Huang, R. Machiraju, M.T. Saenz-Robles, P. Cantalupo, J.M. Pipas, G. Leone, Redeployment of Myc and E2f1-3 drives Rb-deficient cell cycles. Nature Cell Biol **17**, 1036–1048 (2015)

45. C.R. Chen, Y. Kang, P.M. Siegel, J. Massagué, E2F4/5 and p107 as Smad cofactors linking the TGFβ receptor to c-myc repression. Cell **110**, 19–32 (2002)

46. H. Ogawa, K.I. Ishiguro, S. Gaubatz, D.M. Livingston, Y. Nakatani, A complex with chromatin modifiers that occupies E2F and Myc responsive genes in G0 cells. Science **296**, 1132–1136 (2002)

47. R.E. Rempel, S. Mori, M. Gasparetto, M.A. Glozak, E.R. Andrechek, S.B. Adler, N.M. Laakso, A.S. Lagoo, R. Storms, C. Smith, J.R. Nevins, A role for E2F activities in determining the fate of Myc-induced lymphomagenesis. PLoS Genet **5**, e1000640 (2009)

48. A. Fortunato, The role of hERG1 ion channels in epithelial-mesenchymal transition and the capacity of riluzole to reduce cisplatin resistance in colorectal cancer cells. Cell Oncol **40**, 367–378 (2017)

49. A. Sathyanarayanan, K.S. Chandrasekaran, D. Karunagaran, microRNA-145 modulates epithelial-mesenchymal transition and suppresses proliferation, migration and invasion by targeting SIP1 in human cervical cancer cells. Cell Oncol **40**, 119–131 (2017)

50. S. Bugide, V.K. Gonugunta, V. Penugurti, V.L. Malisetty, R.K. Vadlamudi, B. Manavathi, HPIP promotes epithelial-mesenchymal transition and cisplatin resistance in ovarian cancer cells through PI3K/AKT pathway activation. Cell Oncol **40**, 133–144 (2017)

51. M. Mohrin, J. Shin, Y. Liu, K. Brown, H. Luo, Y. Xi, C.M. Haynes, D. Chen, Stem cell aging. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. Science **347**, 1374–1377 (2015)

52. J. Vazquez, J. Das, D. Roy, Estrogen and nuclear respiratory factor 1 act as joint mediators of redox modulation and stem cell aging that contribute in the pathogenesis of breast cancer. Cancer Res **76**, 3322 (2016)

53. K. Bhawe, J. Das, C. Yoo, and D. Roy, NRF1 regulated gene-network characterizing chemical toxicity through TF effects in brain cancer. In: The Toxicologist: Supplement to Toxicological Sciences, 150, Abstract No. 1961, Pp 234, (2018)

54. M. Preciados, C. Yoo, D. Roy, Estrogenic endocrine disrupting chemicals influencing NRF1 regulated gene networks in the development of complex human brain diseases. Int J Mol Sci **17**, E2086 (2016)

55. J. Wang, H. Wang, Z. Li, Q. Wu, J.D. Lathia, R.E. McLendon, A.B. Hjelmeland, J.N. Rich, C-Myc is required for maintenance of glioma cancer stem cells. PLoS One **3**, e3769 (2008)

56. P. Sancho, D. Barneda, C. Heeschen, Hallmarks of cancer stem cell metabolism. Br J Cancer **114**, 1305–1312 (2016)

57. S. Galardi, M. Savino, F. Scagnoli, S. Pellegatta, F. Pisati, F. Zambelli, B. Illi, D. Annibali, S. Beji, E. Orecchini, M.A. Alberelli, C. Apicella, R.A. Fontanella, A. Michienzi, G. Finocchiaro, M.G. Farace, G. Pavesi, S.A. Ciafrè, S. Nasi, Resetting cancer stem cell regulatory nodes upon MYC inhibition. EMBO Rep **17**, 1872–1889 (2016)

58. R. Scognamiglio, N. Cabezas-Wallscheid, M.C. Thier, S. Altamura, A. Reyes, A.M. Prendergast, D. Baumgartner, L.S. Carnevalli, A. Atzberger, S. Haas, L. von Paleske, T. Boroviak, P. Worsdorfer, M.A. Essers, U. Kloz, R.N. Eisenman, F. Edenhofer, P. Bertone, W. Huber, F. van der Hoeven, A. Smith, A. Trumpp, Myc depletion induces a pluripotent dormant state mimicking diapause. Cell **164**, 668–680 (2016)

59. H.C. Yeo, T.T. Beh, J.J. Quek, G. Koh, K.K. Chan, D.Y. Lee, Integrated transcriptome and binding sites analysis implicates E2F in the regulation of self-renewal in human pluripotent stem cells. PLoS One **6**, e27231 (2011)

60. L.M. Julian, A. Blais, Transcriptional control of stem cell fate by E2Fs and pocket proteins. Front Genet **6**, 161 (2015)

61. S. Pauklin, P. Madrigal, A. Bertero, L. Vallier, Initiation of stem cell differentiation involves cell cycle-dependent regulation of developmental genes by cyclin D. Genes Dev **30**, 421–433 (2016)

62. A. Diman, F. Poulain, J. Rodriguez, M. Purnelle, H. Episkopou, L. Bertrand, M. Francaux, L. Deldicque, A. Decottignies, Nuclear respiratory factor 1 and endurance exercise promote human telomere transcription. Science Adv **2**, e1600031 (2016)

63. A. Ocampo, J.C.I. Belmonte, Holding your breath for longevity. Science **347**, 1319–1320 (2015)

64. J.W. Hofmann, X. Zhao, M. De Cecco, A.L. Peterson, L. Pagliaroli, J. Manivannan, G.B. Hubbard, Y. Ikeno, Y. Zhang, B. Feng, X. Li, T. Serre, W. Qi, H. Van Remmen, R.A. Miller, K.G. Bath, R. de Cabo, H. Xu, N. Neretti, J.M. Sedivy, Reduced expression of MYC increases longevity and enhances healthspan. Cell **160**, 477–488 (2015)

65. P. Hydbring, L.G. Larsson, Cdk2: A key regulator of the senescence control function of Myc. Aging **2**, 244–250 (2010)

66. C. Park, I. Lee, W.K. Kang, E2F-1 is a critical modulator of cellular senescence in human cancer. Int J Mol Med **17**, 715–720 (2006)

67. P. Iakova, S.S. Awad, N.A. Timchenko, Aging reduces proliferative capacities of liver by switching pathways of C/EBP growth arrest. Cell **113**, 495–506 (2003)

68. M. Vernier, V. Bourdeau, M.F. Gaumont-Leclerc, O. Moiseeva, V. Begin, F. Saad, A.M. Mes-Masson, G. Ferbeyre, Regulation of E2Fs and senescence by PML nuclear bodies. Genes Dev **25**, 41–50 (2011)

69. J. Permuth-Wey, Y.A. Chen, Y.Y. Tsai, Z. Chen, X. Qu, J.M. Lancaster, H. Stockwell, G. Dagne, E. Iversen, H. Risch, J. Barnholtz-Sloan, J.M. Cunningham, R.A. Vierkant, B.L. Fridley, R. Sutphen, J. McLaughlin, S.A. Narod, E.L. Goode, J.M. Schildkraut, D. Fenstermacher, C.M. Phelan, T.A. Sellers, Inherited variants in mitochondrial biogenesis genes may influence epithelial ovarian cancer risk. Cancer Epidemiol Biomark Prev **20**, 1131–114567 (2011)

70. W. Liu, B.H. Beck, K.S. Vaidya, K.T. Nash, K.P. Feeley, S.W. Ballinger, K.M. Pounds, W.L. Denning, A.R. Diers, A. Landar, A. Dhar, T. Iwakuma, D.R. Welch, Metastasis suppressor KISS1 seems to reverse the Warburg effect by enhancing mitochondrial biogenesis. Cancer Res **74**, 954–963 (2014)

71. M.M. Ivanova, K.H. Luken, A.S. Zimmer, F.L. Lenzo, R.J. Smith, M.W. Arteel, T.J. Kollenberg, K.A. Mattingly, C.M. Klinge, Tamoxifen increases nuclear respiratory factor 1 transcription by activating estrogen receptor β and AP-1 recruitment to adjacent promoter binding sites. FASEB J **25**, 1402–1416 (2011)

72. D. Wang, J. Zhang, Y. Lu, Q. Luo, L. Zhu, Nuclear respiratory factor (NRF1) regulated hypoxia inducible factor 1alpha (HIF1a) under hypoxia in HEK293T. IUBMB Life **68**, 748–755 (2016)

73. L. Zhang, Q. Ding, Z. Wang, Nuclear respiratory factor 1 mediates the transcription initiation of insulin-degrading enzyme in a TATA box-binding protein-independent manner. PLoS One **7**, e42035 (2012)

74. A.G. Vaiopoulos, K. Athanasoula, A.G. Papavassiliou, Epigenetic modifications in colorectal cancer: Molecular insights and therapeutic challenges. Biochim Biophys Acta **1842**, 971–980 (2014)

75. S. Sharma Saha, R. Roy Chowdhury, N.R. Mondal, B. Chakravarty, T. Chatterjee, S. Roy, S. Sengupta, Identification of genetic variation in the lncRNA HOTAIR associated with HPV16-related cervical cancer pathogenesis. Cell Oncol **39**, 583–589 (2016)

76. M. Xu, C.E. Cross, J.T. Speidel, S.Z. Abdel-Rahman, MGMT DNA repair gene promoter/enhancer haplotypes alter transcription factor binding and gene expression. Cell Oncol **39**, 435–447 (2016)

77. C. Gebhard, C. Benner, M. Ehrich, L. Schwarzfischer, E. Schilling, M. Klug, W. Dietmaier, C. Thiede, E. Holler, R. Andreesen, M. Rehli, General transcription factor binding at CpG islands in normal cells correlates with resistance to de novo DNA methylation in cancer cells. Cancer Res **70**, 1398–1407 (2010)

78. S.S. Hammoud, B.R. Cairns, D.A. Jones, Epigenetic regulation of colon cancer and intestinal stem cells. Curr Opin Cell Biol **25**, 177–183 (2013)

79. A. Wolfer, S. Ramaswamy, MYC and metastasis. Cancer Res **71**, 2034–2037 (2011)

80. H. Liu, D.C. Radisky, D. Yang, R. Xu, E.S. Radisky, M.J. Bissell, J.M. Bishop, MYC suppresses cancer metastasis by direct transcriptional silencing of [alpha]v and [beta]3 integrin subunits. Nature Cell Biol **14**, 567–574 (2012)

81. M. Jung, A.J. Russell, B. Liu, J. George, P.Y. Liu, T. Liu, A. DeFazio, D.D. Bowtell, A. Oberthuer, W.B. London, J.I. Fletcher, M. Haber, M.D. Norris, M.J. Henderson, A Myc activity signature predicts poor clinical outcomes in Myc-associated cancers. Cancer Res **15**, 971–981 (2017)

82. U.R. Rapp, C. Korn, F. Ceteci, C. Karreman, K. Luetkenhaus, V. Serafin, E. Zanucco, I. Castro, T. Potapenko, MYC is a metastasis gene for non-small-cell lung cancer. PLoS One **4**, e6029 (2009)

83. L. Fagnocchi, A. Cherubini, H. Hatsuda, A. Fasciani, S. Mazzoleni, V. Poli, V. Berno, R. Rossi, R. Reinbold, M. Endele, T. Schroeder, M. Rocchigiani, Z. Szkarlat, S. Oliviero, S. Dalton, A. Zippo, A Myc-driven self-reinforcing regulatory network maintains mouse embryonic stem cell identity. Nat Commun **7**, 11903 (2016)

84. H.B. Suliman, T.E. Sweeney, C.M. Withers, C.A. Piantadosi, Co-regulation of nuclear respiratory factor-1 by NFkappaB and CREB links LPS-induced inflammation to mitochondrial biogenesis. J Cell Science **123**, 2565–2575 (2010)

85. M.L. Boland, A.H. Chourasia, K.F. Macleod, Mitochondrial dysfunction in cancer. Front Oncol **3**, 292 (2013)

86. K.E. Wiese, S. Walz, B. von Eyss, E. Wolf, D. Athineos, O. Sansom, M. Eilers, Cold Spring Harbor Perspectives in Medicine **3**, a014290 (2013)

87. T.C. Chang, D. Yu, Y.S. Lee, E.A. Wentzel, D.E. Arking, K.M. West, C.V. Dang, A. Thomas-Tikhonenko, J.T. Mendell, Widespread microRNA repression by Myc contributes to tumorigenesis. Nature Genet **40**, 43–50 (2008)

88. C. Bertoli, J.M. Skotheim, R.A. de Bruin, Control of cell cycle transcription during G1 and S phases. Nature Rev Mol Cell Biol **14**, 518–528 (2013)

89. G. Yao, Modelling mammalian cellular quiescence. Interface Focus **4**, 3 (2014)

90. S. Zheng, J. Moehlenbrink, Y.C. Lu, L.P. Zalmas, C.A. Sagum, S. Carr, J.F. McGouran, L. Alexander, O. Fedorov, S. Munro, B. Kessler, M.T. Bedford, Q. Yu, N.B.L. Thangue, Arginine methylation-dependent reader-writer interplay governs growth control by E2F-1. Mol Cell **52**, 37–51 (2013)

91. B.P. Coe, K.L. Thu, S.A. Ronen, E.A. Vucic, A.F. Gazdar, S. Lam, M.S. Tsao, W.L. Lam, Genomic deregulation of the E2F/Rb pathway leads to activation of the oncogene EZH2 in small cell lung cancer. PLoS One **8**, e71670 (2013)

92. H.Z. Chen, M.M. Ouseph, J. Li, T. Pécot, V. Chokshi, L. Kent, S. Bae, M. Byrne, C. Duran, G. Comstock, P. Trikha, M. Mair, S. Senapati, C.K. Martin, S. Gandhi, N. Wilson, B. Liu, Y.W. Huang, J.C. Thompson, S. Raman, S. Singh, M. Leone, R. Machiraju, K. Huang, X. Mo, S. Fernandez, I. Kalaszczynska, D.J. Wolgemuth, P. Sicinski, T. Huang, V. Jin, G. Leone, Canonical and atypical

E2Fs regulate the mammalian endocycle. Nature Cell Biol **14**, 1192–1202 (2012)

93. J. Johnson, B. Thijssen, U. McDermott, M. Garnett, L.F.A. Wessels, R. Bernards, Targeting the RB-E2F pathway in breast cancer. Oncogene **35**, 4829–4835 (2016)

94. D.P. Hollern, J. Honeysett, R.D. Cardiff, E.R. Andrechek, The E2F transcription factors regulate tumor development and metastasis in a mouse model of metastatic breast cancer. Mol Cell Biol **34**, 3229–3240 (2014)

95. E.R. Andrechek, HER2/Neu tumorigenesis and metastasis is regulated by E2F activator trancription factors. Oncogene **34**, 217–225 (2015)

96. A. Mathe, M.W. Brown, B. Morten, J.F. Forbes, S.G. Braye, K.A. Avery-Kiejda, R.J. Scott, Novel genes associated with lymph node metastasis in triple negative breast cancer. Nature Sci Rep **5**, 15832 (2015)

97. H. Garneau, L. Alvarez, M.C. Paquin, C. Lussier, C. Rancourt, E. Tremblay, J.F. Beaulieu, N. Rivard, Nuclear expression of E2F4 induces cell death via multiple pathways in normal human intestinal epithelial crypt cells but not in colon cancer cells. Am J Physiol Gastrointest Liver Physiol **293**, G758–G772 (2007)

98. D. Dingar, F. Konecny, J. Zou, X. Sun, R. von Harsdorf, Anti-apoptotic function of the E2F transcription factor 4 (E2F4)/p130, a member of retinoblastoma gene family in cardiac myocytes. J Mol Cell Cardiol **53**, 820–828 (2007)

99. L. Zhao, M. Tang, Z. Hu, B. Yan, W. Pi, Z. Li, J. Zhang, L. Zhang, W. Jiang, G. Li, Y. Qiu, F. Hu, F. Liu, J. Lu, X. Chen, L. Xiao, Z. Xu, Y. Tao, L. Yang, A.M. Bode, Z. Dong, J. Zhou, J. Fan, L. Sun, & Cao Y. miR-504 mediated down-regulation of nuclear respiratory factor 1 leads to radio-resistance in nasopharyngeal carcinoma. Oncotarget **6**, 15995–16018 (2015)

100. R.B. Penney, D. Roy, Thioredoxin-mediated redox regulation of resistance to endocrine therapy in breast cancer. Biochim Biophys Acta **1836**, 60–79 (2013)

101. B.N. Radde, M.M. Ivanova, H.X. Mai, N. Alizadeh-Rad, K. Piell, P. Van Hoose, M.P. Cole, P. Muluhngwi, T.S. Kalbfleisch, E.C. Rouchka, B.G. Hill, C.M. Klinge, Nuclear respiratory factor-1 and bioenergetics in tamoxifen-resistant breast cancer cells. Exp Cell Res **347**, 222–231 (2016)

102. G. Zhang, D.T. Frederick, L. Wu, Z. Wei, C. Krepler, S. Srinivasan, Y.C. Chae, X. Xu, H. Choi, E. Dimwamwa, O. Ope, B. Shannan, D. Basu, D. Zhang, M. Guha, M. Xiao, S. Randell, K. Sproesser, W. Xu, J. Liu, G.C. Karakousis, L.M. Schuchter, T.C. Gangadhar, R.K. Amaravadi, M. Gu, C. Xu, A. Ghosh, W. Xu, T. Tian, J. Zhang, S. Zha, Q. Liu, P. Brafford, A. Weeraratna, M.A. Davies, J.A. Wargo, N.G. Avadhani, Y. Lu, G.B. Mills, D.C. Altieri, K.T. Flaherty, M. Herlyn, Targeting mitochondrial biogenesis to overcome drug resistance to MAPK inhibitors. J Clin Invest **126**, 1834–1856 (2016)

103. M.H. Uddin, B. Kim, D.H. Suh, Y.S. Song, Anticancer strategy targeting mitochondrial biogenesis in ovarian Cancer. J Cancer Sci Therapy **6**, 422–428 (2014)

104. A. Shen, L. Wang, M. Huang, J. Sun, Y. Chen, Y.Y. Shen, X. Yang, X. Wang, J. Ding, M. Geng, C-Myc alterations confer therapeutic response and acquired resistance to c-met inhibitors in MET-addicted cancers. Cancer Res **75**, 4548–4559 (2015)

105. X.N. Pan, J.J. Chen, L.X. Wang, R.Z. Xiao, L.L. Liu, Z.G. Fang, Q. Liu, Z.J. Long, D.J. Lin, Inhibition of c-Myc overcomes cytotoxic drug resistance in acute myeloid leukemia cells by promoting differentiation. PLoS One **9**, e105381 (2014)

106. L.H. Yan, X.T. Wang, J. Yang, F.B. Kong, C. Lian, W.Y. Wei, W. Luo, Y.B. Xie, Q. Xiao, Reversal of multidrug resistance in gastric cancer cells by E2F-1 downregulation in vitro and in vivo. J Cell Biochem **115**, 34–41 (2014)

107. M.T. Rosenfeldt, L.A. Bell, J.S. Long, J. O'Prey, C. Nixon, F. Roberts, C. Dufès, K.M. Ryan, E2F1 drives chemotherapeutic drug resistance via ABCG2. Oncogene **33**, 4164–4172 (2014)

108. J.J. Stevens, B. Graham, E. Dugo, B. Berhaneselassie-Sumner, K. Ndebele, P.B. Tchounwou, Arsenic trioxide induces apoptosis via specific signaling pathways in HT-29 colon cancer cells. J Cancer Sci Therapy **9**, 298–306 (2017)

109. J.B. Bell, F. Eckerdt, H.D. Dhruv, D. Finlay, S. Peng, S. Kim, B. Kroczynska, E.M. Beauchamp, K. Alley, J. Clymer, S. Goldman, S.Y. Cheng, C.D. James, I. Nakano, C. Horbinski, A.P. Mazar, K. Vuori, P. Kumthekar, J. Raizer, M.E. Berens, L.C. Platanias, Differential response of glioma stem cells to arsenic trioxide therapy is regulated by MNK1 and mRNA translation. Mol Cancer Res **16**, 32–46 (2018)

110. F. Morrish, C. Giedt, D. Hockenbery, c-MYC apoptotic function is mediated by target genes. Genes Dev **17**, 240–255 (2003)

111. Z. Li et al., The degradation of EZH2 mediated by lncRNA ANCR attenuated the invasion and metastasis of breast cancer. Cell Death Diff **24**, 59–71 (2017)

112. H. Kurihara, R. Maruyama, K. Ishiguro, S. Kanno, I. Yamamoto, K. Ishigami, K. Mitsuhashi, H. Igarashi, M. Ito, T. Tanuma, Y. Sukawa, K. Okita, T. Hasegawa, K. Imai, H. Yamamoto, Y. Shinomura, K. Nosho, The relationship between EZH2 expression and microRNA-31 in colorectal cancer and the role in evolution of the serrated pathway. Oncotarget **7**, 12704–12717 (2016)

113. A.P. Russell, S. Lamon, H. Boon, S. Wada, I. Güller, E.L. Brown, A.V. Chibalin, J.R. Zierath, R.J. Snow, N. Stepto, G.D. Wadley, T. Akimoto, Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short-term endurance training. J Physiol **591**, 4637–4653 (2013)

114. B. Kunkle, Q. Felty, F. Narasimhan, F. Trevino, D. Roy. Meta-analysis of brain tumor microarray data using Oncomine identifies NRF1, TFAM and MYC co-expressed genes: Its implications in the development of childhood brain tumors. *18th World IMACS / MODSIM Congress, Cairns,* Australia 720–726 (2009)

115. W.R. Taylor, A.H. Schonthal, J. Galante, G.R. Stark, p130/E2F4 binds to and represses the cdc2 promoter in response to p53. J Biol Chem **276**, 1998–2006 (2001)

116. T.L. Born, J.A. Frost, A. Schönthal, G.C. Prendergast, J.R. Feramisco, C-Myc cooperates with activated Ras to induce the cdc2 promoter. Mol Cell Biol **14**, 5710–5718 (1994)

117. I.B. Rosenwald, D.B. Rhoads, L.D. Callanan, K.J. Isselbacher, E.V. Schmidt, Increased expression of eukaryotic translation initiation factors eIF-4E and eIF-2a in response to growth induction by c-myc. Proc Natl Acad Sci U S A **90**, 6175–6178 (1993)

118. V.O. Okoh, Q. Felty, J. Parkash, R. Poppiti, D. Roy, Reactive oxygen species via redox signaling to PI3K/AKT pathway contribute to the malignant growth of 4-hydroxy estradiol-transformed mammary epithelial cells. PLoS One **8**, e54206 (2013)

119. M.V. Oli, M.M. Grober, G. Giurato, M. Ravo, L. Cicatiello, M.R.D. Filippo, L. Ferraro, G. Nassa, M.F. Papa, O. Paris, R. Tarallo, S. Luo, G.P. Schroth, V.B.A. Weisz, Global analysis of estrogen receptor beta binding to breast cancer cell genome reveals an extensive interplay with estrogen receptor alpha for target gene regulation. BMC Genomics **12**, 1471–2164 (2011)

120. I. Riz, R.G. Hawley, G1/S transcriptional networks modulated by the HOX11/TLX1 oncogene of T-cell acute lymphoblastic leukemia. Oncogene **24**, 5561–5575 (2005)

121. R. Tongbai, G. Idelman, S.H. Nordgard, W. Cui, J.L. Jacobs, C.M. Haggerty, S.J. Chanock, A.L. Borrensen-Dale, G. Livingston, P. Shaunessy, C.H. Chiang, V.N. Kristensen, S. Bilke, K. Gardner, Transcriptional networks inferred from molecular signatures of breast cancer. Am J Pathol **172**, 495–509 (2008)

122. F. Li, Y. Wang, K.I. Zeller, J.J. Potter, D.R. Wonsey, K.A. O'Donnell, J.W. Kim, J.T. Yustein, L.A. Lee, C.V. Dang, Myc

stimulates nuclearly encoded mitochondrial genes and mitochondrial biogenesis. Mol Cell Biol **25**, 6225–6234 (2005)

123. R. Elkon, K.I. Zeller, C. Linhart, C.V. Dang, R. Shamir, Y. Shiloh, In silico identification of transcriptional regulators associated with c-Myc. Nucleic Acids Res **32**, 4955–4961 (2004)

124. M. Collu-Marchese, M. Shuen, M. Pauly, A. Saleem, D.A. Hood, The regulation of mitochondrial transcription factor a (Tfam) expression during skeletal muscle cell differentiation. Biosci Rep **35**, e00221 (2015)

125. M. Lynch, L. Chen, M.J. Ravitz, S. Mehtani, K. Korenblat, M.J. Pazin, E.V. Schmidt, hnRNP K binds a core polypyrimidine element in the eukaryotic translation initiation factor 4E (eIF4) promoter, and its regulation of eIF4E contributes to neoplastic transformation. Mol Cell Biol **25**, 6436–6453 (2005)

126. L. Zhang, H. Yu, P. Wang, Q. Ding, Z. Wang, Screening of transcription factors with transcriptional initiation activity. Gene **531**, 64–70 (2013)

127. W. Mao, D. Kostka, M. Chikina, Modeling enhancer-promoter interactions with attention-based neural networks bioRxiv (2017). https://doi.org/10.1101/219667

128. S. Mahara, W.J. Chng, Q. Yu, Molecular switch of EZH2 in hypoxia. Cell Cycle **15**, 3007–3008 (2016)

129. M.R. Doe, J.M. Ascano, M. Kaur, M.D. Cole, Myc posttranscriptionally induces HIF1 protein and target gene expression in normal and cancer cells. Cancer Res **72**, 949–957 (2012)

130. B.-K. Lee, A.A. Bhinge, V.R. Iyer, Wide-ranging functions of E2F4 in transcriptional activation and repression revealed by genome-wide analysis. Nucleic Acids Res **39**, 3558–3573 (2011)

131. S. Terry, S. Buart, T.Z. Tan, G. Gros, M.Z. Noman, J.B. Lorens, F. Mami-Chouaib, J.P. Thiery, S. Chouaib, Acquisition of tumor cell phenotypic diversity along the EMT spectrum under hypoxic pressure: Consequences on susceptibility to cell-mediated cytotoxicity. OncoImmunology **6**, 2 (2017)

132. S. Moniz, D. Bandarra, J. Biddlestone, K.J. Campbell, D. Komander, A. Bremm, S. Rocha, Cezanne regulates E2F1-dependent HIF2α expression. J Cell Sci **128**, 3082–3093 (2015)

133. S.T. Shors, J.S.E. Bassey, S.J. Harkin, B. Safer, Formation of alpha-pal/max heterodimers synergistically activates the eIF2-alpha promoter. J Biol Chem **273**, 34703–34709 (1998)

134. D. Kumari, A. Gabrielian, D. Wheeler, K. Usdin, The roles of Sp1, Sp3, USF1/USF2 and NRF-1 in the regulation and three-dimensional structure of the fragile X mental retardation gene promoter. Biochem J **386**, 297–303 (2005)

135. D.E. Fisher, L.A. Parent, P.A. Sharp, Myc/max and other helix-loop-helix/leucine zipper proteins bend DNA toward the minor groove. Proc Natl Acad Sci U S A **89**, 11779–11783 (1992)