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Review Article

Expression and function of NF-Y subunits in cancer

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ABSTRACT

NF-Y is a Transcription Factor (TF) targeting the CCAAT box regulatory element. It consists of the NF-YB/NF-YC heterodimer, each containing an Histone Fold Domain (HFD), and the sequence-specific subunit NF-YA. NF-YA expression is associated with cell proliferation and absent in some post-mitotic cells. The review summarizes recent findings impacting on cancer development. The logic of the NF-Y regulome points to pro-growth, oncogenic genes in the *cell-cycle*, *metabolism* and *transcriptional regulation* routes. NF-YA is involved in growth/differentiation decisions upon cell-cycle re-entry after mitosis and it is widely overexpressed in tumors, the HFD subunits in some tumor types or subtypes. Overexpression of NF-Y -mostly NF-YA- is oncogenic and decreases sensitivity to anti-neoplastic drugs. The specific roles of NF-YA and NF-YC isoforms generated by alternative splicing -AS- are discussed, including the prognostic value of their levels, although the specific molecular mechanisms of activity are still to be deciphered.

1. CCAAT in promoters of genes overexpressed in cancer

The CCAAT box is an important regulatory element recognized by NF-Y (CBF), a heterotrimer formed by two histone-like subunits —NF-YB/NF-YC— and by NF-YA, which dictates sequence-specificity [1]. The structural details of the DNA-binding parts are known in several species [2–4]. Following the initial characterization in several promoters, the high information CCAAT/NF-Y logo was formalized [5,6], inserted in the TRANSFAC and JASPAR databases [7,8] and, following validation by ChIP-seq, in FactorBook and HOCOMOCO [9,10]. The DNA matrix is thus immediately recognizable as the NF-Y binding site. Two subunits are subject to alternative splicing (AS): NF-YA has two major isoforms —"short" NF-YAs and "long" NF-YAl— differing in 28 amino acids [11]. NF-YC has two promoters and multiple isoforms arise by AS at the C-terminal [12]. In both subunits, AS events involve the Trans-Activation Domains (TADs), rich in glutamines and hydrophobic residues.

The ubiquitous nature of NF-Y was initially assumed based on the presence of its DNA-binding activity —as measured in EMSAs— in all cell lines, and on apparent widespread mRNA and protein expression of each subunit. The location and evolutionary conservation of CCAAT in promoters of disparate sets of genes consolidated the conclusion that NF-Y is a constitutive —and scarcely regulated— TF. This view started to change as microarray profilings identified genes involved in cancer development, namely Differentially Expressed Genes (DEG) overexpressed —or down-regulated— in specific tumor types, sub-types, or models of transformation. Characterization of mammalian promoters —and later enhancers— systematically identified Transcription Factor Binding Sites (TFBS) organized in databases, such as TRANSFAC and JASPAR. Thereafter, TFBSs were identified as enriched in promoters of "cancer" DEG, hence presumably responsible for their activation/overexpression: the CCAAT matrix was one of them. Following its identification in signature genes of a cellular transformation model [13], CCAAT/NF-Y was reported in many types of cancers analyzed by microarrays [14–34]. Profilings of >60,000 cancer specimens present in the ONCOMINE database generalized NF-Y and E2F as the two most enriched motifs in promoters of "cancer" genes [35]. Note that the

Abbreviations: ACRG, Asian Cancer Research Group; AS, Alternative Splicing; ATC, Anaplastic Thyroid Carcinoma; BLCA, Bladder Carcinoma; BRCA, Breast Carcinoma; CAF, Cancer Associated Fibroblasts; CPC, Choroid Plexus Carcinoma; CRC, Colorectal Cancer; CSC, Cancer Stem Cell; DEG, Differentially Expressed Genes; DFS, Disease Free Survival; DLBCL, Diffuse Lymphoblastic B Cell Lymphoma; EC, Endometrial Cancer; EMT, Epithelial Mesenchymal Transition; ESCA, Esophageal Stomach Carcinoma; HBV, Hepatitis B Virus; HCC, Hepatocellular Carcinoma; HFD, Histone Fold Domain; HNSCC, Head and Neck Squamous Cell Carcinoma; LUAD, Lung Adenocarcinoma; LUSC, Lung Squamous Cell Carcinoma; NB, Neuroblastoma; OS, Overall Survival; PCA, Prostate Cancer; SCC, Squamous Cell Carcinoma; STAD, Stomach Adenocarcinoma; TAD, Transcription Activation Domain; TCGA, The Cancer Genome Atlas; TF, Transcription Factor; TFBS, Transcription Factor Binding Site; UC, Urothelial carcinoma; WGCNA, Weighted Gene Co-Expression Network Analysis.

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Authors used unbiased bioinformatic tools to find enriched "words", rather than pre-established lists of matrices. This conclusion was confirmed in a further study [36].

Following NGS, RNA-seq experiments provided better quantification of transcripts, possibly including individual mRNA isoforms: the abundance of CCAAT in "cancer" genes was confirmed [37–44]. Table I lists these studies collectively. Further unbiased bioinformatic analyses of large RNA-seq datasets concur that CCAAT is common in promoters of genes overexpressed in cancer [45–47]. An important point is that CCAAT is not simply an abundant, neutral element, enriched in promoters at large, as it has not been found so far in promoters of genes down-regulated in cancer specimens, whenever these signatures were analyzed for TFBSs. It is therefore fair to conclude that growth-promoting genes, typically enriched in "cancer" signatures, often have CCAAT in their promoters. Given the high information content of the matrix and the adherence to the binding specificities of a single TF, the assumption is that CCAAT promoters of "cancer" genes are regulated by NF-Y.

2. Genetic alterations

The most common genetic alterations driving cells to acquire uncontrolled growth capacity are gene amplifications, rearrangements or single nucleotide mutations. In general, the current —large— body of genetic data suggests that NF-Y subunits are neither recurrently amplified (*a-la* NMYC in neuroblastoma), nor rearranged (*a-la* RAR in promyelocytic leukemias), nor mutated (*a-la* TP53 in carcinomas). Yet, some evidence pointing at NF-Y subunits as direct drivers of transformation are reported, mostly concerning the HFD subunits. Choroid plexus carcinoma (CPC) is a rare aggressive brain disease of young children, targeting post-mitotic cells of the cuboidal epithelium. The genetic basis involves both gain of oncogenes and loss of tumor suppressors. Various chromosomal alterations were reported: in a systematic search for the early events of CPC pathogenesis, the Gilbertson's lab found that a region of human Chromosome 1 (1p31.3-ter) harbors oncogenes driving the disease; they went on to prove that NF-YC, TAF12 and RAD54L in this region (i) promote proliferation of CPC cells and (ii) are individually required for the early pathogenesis and maintenance of CPC [48]. These genetic experiments suggest a direct role of NF-YC as a driving oncogene, although the role of the other subunits, specifically the NF-YB partner, was not investigated.

In search for aberrant mRNA fusions in T-cell lymphoblastic lymphomas, Lopez-Nieva et al. found a transcript resulting from juxtaposition of the 5'UTR and exon-1 of NF-YC to exon-3 of TAL1, a b-HLH TF known to play a role in the development of T-cell acute lymphoblastic leukemia [49]. The functional consequences of the fusion transcript were not further assessed. Following treatment with the DNA alkylating drug Temozolomide (TMZ), glioma cells develop resistance, which is often determined by fusions between the MGMT gene, involved in DNA-repair, and a handful of partners, among which NF-YC: Oldrini et al. have shown that the NF-YC-MGMT fusion protects glioma cells from DNA-damage *in vitro*, conferring resistance to TMZ [50]; in the case of

Table I
Studies with prevalence of CCAAT in cancer genes.

Cancer	Enriched TFBS	Source	Data	Ref.
Cancer cell lines	NRF1, FOS, NF-Y	study	M	[15]
Cancer cell lines	E74, CHOP-CEBP, CREL- NFKB, NF-Y, P65, NRF2	study	M	[14]
Cancer cell lines	NF-Y, ELK1, CETS, E2F	GSE18232, GSE18337	M	[21]
Cancer cell lines	NF-Y, E2F	study		[19]
Cancers	NF-Y	GEO Database, Oncomine database	M	[36]
Cancers	E2F, NF-Y, P53, AND LET-7	Table S1	M	[35]
Cancers	NF-Y, CHR, E2F	TCGA	R	[41]
Cancers	NF-Y, SP1, FOXO4, MYC	TCGA	R	[46]
Cancers	NF-Y, E2F, SIN3A, TFDP1, MYBL2, FOXM1	TCGA	R	[47]
Cancers	NF-Y, YY1 H3K20me1	GSE30611	R	[45]
Breast cancer	E2F, NF-Y, ELF5	study	M	[23]
Breast cancer	RLK1, E2F, NRF1, NF-Y	GSE3494	M	[16]
Breast cancer	E2F1, YY1, NF-Y	Table1	M	[17]
Breast cancer	NF-YB, E2F1, NRF1, ELK1	GSE2990, GSE2109	M	[22]
Breast cancer	NF-Y, E2F4, FOXM1, E2F1, BRCA1, TP53, MYBL2, MASTL, E2F6, CDC5L	GSE6532, GSE2990, GSE7390, GSE11121	M	[24]
Breast Cancer	NF-Y, ETF, KROX, AP2, E2F1, SP1, EGR, ZF5, ABI4	TCGA	R	[37]
Breast Cancer	NF-Y, EVI1, E2F, MEF2, MEIS1, COMP1	TCGA, GSE3971, EGAS00000000083	R	[39]
Breast Cancer	NF-Y, E2F1, E2F4, FOXO4, STAT5A	TCGA, Metabric EGAS00000000083, Ur-Rehman GSE47561, Vijver (The Netherlands Cancer Institute)	R	[40]
Leukemia	EVI1, ATF4, IRF1, NF1, IK2, CMYC/MAX, NF-Y, MAZ	study	M	[20]
Ewing's Sarcoma	E2F, NF-Y, NRF1	GSE14543	M	[18]
Anaplastic tyroid carcinoma	NF-Y, E2F, FOXM1, CREB3L	GSE65144, GSE33630, GSE29265	M	[29]
Gynecological cancer	E2F, NF-Y	study	M	[25]
Ovarian Cancer	NF-Y	GSE4407, GSE29220	M	[28]
Cervical cancer (HPV16positive)	NF-Y, E2F, AHR:ARNT, KROX	study	R	[43]
Rectal Adenocarcinoma	NF-Y, MYC, TBP, ATF, CDC5, CHX10, RSRFC4, STAT5A	TCGA	R	[38]
Colon cancer	NF-Y, HSFY2, E2F1	GSE25192	M	[27]
Prostate cancer	NF-Y, CETS1P54, OLF1, SRF, COMP1, RP58, HMX1, NF1, PPARA, GFI1	GSE46602, GSE38241, GSE69223, GSE32571, GSE55945, GSE26126	M	[34]
Pancreatic cancer	NF-Y, TFDP3	GSE32676, GSE15471, GSE1989	M	[30]
Pancreatic ductal adenocarcinoma	GATA6, NFYB, IRF1, TRIM22, SREBF1	GSE14426	M	[31]
Hepatocellular carcinoma	NF-Y, NKX6–1, POU2F1, JUN, IRF1, E2F1	E-MTAB-8887	M	[32]
Urothelial Carcinoma	NF-Y, PRC2	study	R	[42]
Medulloblastoma	NF-YA, GATA2, NFIC, YY1, FOXL1, HINFP, FOXC1, CREB1, IRF2, JUN, NFIC, NFKB1, SRF, PPARG	GSE22139, GSE37418, GSE86574	M	[33]
Neuroblastoma	NF-Y, E2F, PAX2, SP1, NKX22, ROAZ, NMYC, EGR2, ZIC3, HOX13, PAX4	https://ocg.cancer.gov/, GSE16476, GSE85047, E-MTAB-1781	R	[44]

M = Microarray, R = RNA-seq.

the related BTRC-MGMT fusion, this was also observed *in vivo*. In the two examples —NF-YC-TAL1 and NF-YC-MGMT— the fusions involve the N-term of NF-YC devoid of the HFD, hence the mechanism of activity is independent from interactions with NF-YB and formation of a trimer with NF-YA, likely following the protein logic of the TAL1 and MGMT parts. For expression, the NF-YC locus provides control of transcriptional regulation, which includes the promoter P1, constitutive and active at relatively high levels, and P2, inducible upon DNA-damage [12], possibly helping mediate the increased resistance to TMZ in the case of the MGMT fusion.

In an unbiased search for drivers of Diffuse Large B-Cell Lymphoma (DLBCL), an aggressive evolution of otherwise relatively indolent follicular lymphomas, the Califano lab identified five important genes, among which NF-YB, whose inactivation inhibits proliferation of DLBCL cells [51]. Individually, the effect of the single factors was modest, but the combination of NF-YB, FOXM1, ATF5 and HMGA1 was synergistic. This finding is consistent with the documented genomic connections of NF-Y with FOXM1 and ATFs [52,53]. The same group had previously identified NF-YB, FOXM1, E2F1/5 and MYB as master regulators of B cell proliferation in normal germinal centers [54]. Thus, NF-YB partakes in a connected module of TFs associated with activation of cell-cycle and DNA replication genes in B cells. Related to this tumor system, an important NF-Y target is Ser/Thr Kinase 33 (STK33), whose high levels correlate with those of NF-YB in tumor cells and whose overexpression mediates resistance to cisplatin [55].

Finally, a genetic and expression screening in the LUDLU-1 cell line (LUSC) found one alteration affecting chromosome 12q, producing duplications and inversions, entailing vast overexpression −25-fold— of an aberrant antisense NF-YB transcript: in turn, this might impact on NF-YB expression, but no functional assay was reported, therefore the implication remains hypothetical [56].

By and large, these examples of genetic alterations of NF-Y subunits genes are to be considered exceptions concerning specific, and relatively rare, tumor types. On the other hand, it has become clear that the main mechanism by which NF-Y impacts on cancer concerns increased expression of the subunits.

3. Increased subunits expression

Based on microarray profilings and RNA-seq, many studies reported on overexpression of NF-YA [39,57–66], NF-YB [55,67–71] or NF-YC [72–74] in cancer, as shown in Table II. NF-Y subunits are also overexpressed in “side populations” of cancer stem cell (CSC) of HCC, PCA and BRCA [26,75,76]. In many cases, these reports were not focused on NF-Y subunits expression *ab initio*, but rather stumbled on them by analyzing the regulatory motifs of DEG with overrepresentation of CCAAT, as mentioned above, or activating elements of smaller signatures of overexpressed genes. Thereafter, NF-Y subunits were specifically analyzed.

Following the initial manuscripts reporting on NF-Y subunits

Table II
NF-Y subunits overexpression in cancers.

NF-Y subunit	Alteration	Method	Tumor	Poor prognosis correlation	Ref.
YA	RNA, amplification	TCGA	BRCA	na	[39]
YA	RNA, Splicing ratio	TCGA, Kaplan-Meier	BRCA	YES	[77]
YA	Splicing ratio RNA	TCGA, Kaplan-Meier	BRCA subtypes	YES	[97]
YA	RNA, protein	GEO, Oncomine, protein expression UA-LCAN, WB	Clear cell RCC	YES	[61]
YA	Splicing ratio RNA	TCGA, Kaplan-Meier	CRC	YES	[84]
YA	Splicing ratio RNA, protein	FFPE WB, qRT-PCR	EC	na	[90]
YA	RNA, Splicing ratio	TCGA, Kaplan-Meier, DeepCC patient clustering	HCC	YES	[80]
YA	RNA	TCGA DEG lipid metabolism	HCC	na	[62]
YA	RNA	TCGA circRNA, TFBS, Kaplan-Meier	HCC	YES	[63]
YA	RNA	PNPT1 gene promoter TFBS; Kaplan-Meier	HCC	YES	[91]
YA	RNA, Splicing ratio	TCGA, Kaplan-Meier	HNSCC subtypes	Negative in HPV$^+$	[81]
YA	RNA, Splicing ratio	TCGA, Kaplan-Meier	LUAD subtypes	YES	[79]
YA	RNA, Splicing ratio	TCGA, Kaplan-Meier	LUSC subtypes	YES	[78]
YA	RNA, Splicing ratio	TCGA, Kaplan-Meier	PCA	YES	[83]
YA	RNA, protein	TCGA, TFBS in AR$^+$ genes	PCA	YES	[64]
YA	RNA	DEG, high risk correlation	Sarcoma	YES*	[66]
YA	RNA, protein	TCGA GEPIA profiling, IHC	SCC	na	[65]
YA	RNA, Pathway activation	PANDA TFBS (GEO microarray), Kaplan-Meier	STAD	YES (Diffuse) NO (Intestinal)	[58]
YA	RNA, protein	TCGA, Kaplan-Meier, WB	STAD	YES	[59]
YA	RNA, Splicing ratio	TCGA, DeepCC-TCGA-ACRG subtypes partitioning	STAD subtypes	YES	[82]
YB	Protein	IHC, Kaplan-Meier	CRC progression + Oxaliplatin	YES	[67]
YB	RNA	TCGA	CRC	na	[84]
YB	RNA	LncMap,GEPIA	DLBCL	na	[68]
YB	RNA	TCGA, DE ceRNA network, Kaplan-Meier	ESCA	YES*	[70]
YB	RNA	TCGA, Kaplan-Meier, DeepCC patient clustering	HCC	NO	[80]
YB	Amplification/copy number	Metastatic *vs* non metastatic	HNSCC	na	[69]
YB	RNA	TCGA	HNSCC subtypes	na	[81]
YB	RNA	TCGA, DeepCC-TCGA-ACRG subtypes partitioning	STAD	Negative in MSS,TP53$^+$	[82]
YB	RNA	TCGA	STAD	YES	[71]
YC	Splicing isoform RNA, protein	CRISPR-Cas9 sgRNA TF screening, Kaplan-Meier GEPIA2, WB	BLCA	YES	[124]
YC	RNA, protein	IHC WB qRT-PCR, Kaplan-Meier	CRC (right side)	YES	[72]
YC	RNA	TCGA, DirGeneRank, Kaplan-Meier	EC	YES*	[74]
YC	Protein	WB IHC, Kaplan-Meier	Glioma	YES	[73]
YC	RNA, Splicing isoform	TCGA, Kaplan-Meier, DeepCC patient clustering	HCC	NO	[80]
YC	RNA, Splicing isoform	TCGA	HNSCC subtypes	na	[81]
YC	Splicing isoform RNA	TCGA	LUSC subtypes	na	[78]
YC	RNA	TCGA, DeepCC-TCGA-ACRG subtypes partitioning	STAD	na	[82]

na: not assessed.
* gene identification method based on correlation with poor prognosis. RNA, Splicing ratio: RNA level and relative levels of splicing isoform are considered.

overexpression, we felt that systematic investigations on individual cancer types, and subtypes, would be appropriate: a simple query of TCGA data using the firebrowse.org browser clarifies that NF-YA is indeed increased in tumors, particularly epithelial ones. We exploited TCGA, independent GEO datasets and single-cell RNA-seq data to understand various aspects of NF-Y subunits expression, completing analysis of 8 epithelial tumors: BRCA, LUSC, LUAD, HCC, HNSCC, STAD, PCA and CRC [77–84]. Typically, each tumor type can be classified in 3–5 subtypes based on genetic and epigenetic data, as well as molecular signatures: we found commonalities and specificities.

The first feature is that CCAAT-driven genes are indeed enriched, but not in all cohorts. In LUSC and HNSCC, CCAAT is dominant in genes globally overexpressed [78,81], in BRCA and STAD, only in commonly overexpressed genes, but not in subtype-specific signatures [77,82]. In HCC, CCAAT emerged only in the iCluster 3 subtype [80] and in LUAD in genes marking the inflammatory/proliferative cohort [79]. Importantly, gene pools with CCAAT in promoters have GO signatures with *cell-cycle* terms, often with G2/M annotations [46,47,64,85], *metabolism* and *signaling*. This is in line with two types of data: profilings from RNAi-mediated NF-Y removal in cancer lines [46,47,61,64,85,86] and genomic locations of NF-YA/NF-YB, as identified by the ENCODE consortium [53,87,88].

The second feature is subunits expression, with the unifying result of NF-YA being overexpressed: the degree is somewhat variable among tumor types, but statistics comparing matched normal tissues are very robust. Stratification according to the different subtypes typically yielded similar levels of overexpression. Although fewer than RNA profilings, data on protein levels show the same, at least in STAD [59], SCC [65] and HCC [89]. The exception is EC, in which changes were reported not in overall NF-YA protein expression, but rather in the relative levels of the two major isoforms [90]. As for HFD subunits, they are overexpressed in STAD [82], HCC [80] and HNSCC, specifically in the HPV^{+} subtype [81].

The third aspect is the connection to prognosis. High NF-YA levels are associated with worst prognosis in STAD [58,59], SCC [65] and HCC [63,89,91]. We reported no prognostic relevance of NF-YA^{high} levels in STAD [71], but it needs to be mentioned that (i) the prognostic data reported by Bie et al. are related to proteins in few −22— gastric cancer patients [59]; (ii) Cao et al. analyzed microarrays datasets smaller than TCGA and found NF-YA significant only in the "diffuse" gastric cancer cohort of the Lauren classification [58]. In our analysis, we found association of NF-YA^{high} with poor prognosis in LUSC [78] and confirmed reports in HCC [80], but found no association with worst prognosis in BRCA, LUAD, HNSCC and PCA [77,79,81,83]. Finally, NF-YA expression is reported high in sarcomas, although the paucity of matched normal samples present in TCGA (=2) does not allow direct assessment of overexpression in cancer specimens [64]. As for the HFD subunits, NF-YB^{high} levels were associated with worst prognosis in CRC [67] and STAD, correlating with increased expression of lipid metabolism, inflammatory genes and the presence of CAFs [71]; we found that NF-YB^{high} improves survival in the MSS;p53^{+} (Microsatellite Stable) subtype of the STAD ACRG classification [82], which includes tumors classified as CIN (Chromosomal Instability), EBV^{+} and GS (Genomically Stable) of the TCGA classification. NF-YB gain in copy number was found associated with metastasis in oral cancer [69], NF-YB^{high} expression to poor prognosis in ESCA [70] and in HCC iCluster 1 cohort, according to the TCGA classification [80]. In our TCGA analysis, NF-YC, notably the 48 kDa subunit NF-YC3, was associated with worst prognosis only for HCC iCluster1 patients, which lacks CCAAT in their distinctive DEG and are generally p53^{+} [80]. Finally, NF-YC was found in a negative prognostic signature of 40 genes of ovarian cancer [74].

In conclusion, these studies concur that NF-YA is generally, and the HFDs more selectively, overexpressed in cancers of epithelial origin, likely activating the more numerous CCAAT-dependent units overexpressed in these tumors. High expression of NF-YA tends to be associated with a worst prognosis, but this is not a universal feature. Rather, a relevant point emerging is differential expression of the alternatively spliced isoforms of NF-YA and, more recently, of NF-YC.

4. Alternative splicing

Both NF-YA and NF-YC mRNAs are involved in AS (Fig. 1). NF-YA has two major isoforms, NF-YAs and NF-YAl, the latter comprising an extra 28/29 aminoacids coded by exon-3 within the Gln-rich TAD [92]. NF-YC has several isoforms due to AS in exons at the 3′, also within the TAD [11]. As for NF-YA, the first indication linking splicing to cancer development dates back on normal human fibroblasts expressing uniquely the NF-YAl isoform, which, upon infection with the oncogenic SV40 virus, switch to NF-YAs [93]. This observation was overlooked until hints came from studies on EC. A first report showed specific expression of NF-YAs in aggressive ALDHA1^{+} tumors, characterized by worse prognosis, with a role in activating the ALDHA1 promoter more potently than NF-YAl [94]; a second study showed direct correlation of NF-YAs —mRNA and protein— with EMT markers in aggressive, high-grade EC and an inverse one with Lamin A and ER, markers of low-grade tumors [90]. More recently, a new isoform —NF-YAx— devoid of both exon-3 and exon-5 was found overexpressed specifically in Neuroblastomas (NB) [95]. NF-YAx lacks almost half of the TAD: this is relevant, since NF-YA devoid of the entire TAD acts as a Dominant Negative on CCAAT genes [96]. Additional considerations on this isoform will be made below.

In our analysis of TCGA data, differential AS of NF-YA in tumors was glaring, with implications on tumor classification and prognosis. In many tumor types, high NF-YAs levels are generally not prognostic, except in HCC iCluster1 and PCA LumB subtypes [80,83], and even protective in HNSCC HBV^{+} tumors. On the other hand, NF-YAl high levels are associated with negative prognosis in HNSCC and CRC [81,84]. Our studies found that more than NF-YAl —or NF-YAs— overall levels, what is clinically relevant in BRCA, LUAD, LUSC and STAD is the NF-YAl/NF-YAs *ratio* [77–79,82,97].

These studies are based on bulk RNAs from solid tumors, which are formed by several cell types, including non-tumorigenic ones. The presence of cells involved in the inflammatory response, as well as fibroblasts mediating tissue rearrangements, invites to be cautious as to the interpretation of these results; this is particularly true for NF-YAl, whose levels are typically high in fibroblasts and hematopoietic cells. A further level of comprehension was gained by analysis of single cell RNA-seq data, upon deconvolution of individual cellular components, each with a specific signature. Such analysis was performed in three tumor types. In HNSCC [98], NF-YAl marks partial-EMT (p-EMT) cells located at the edge of the tumor and prone to leave the primary site to metastasize [81]. It also marks CAFs, distinct from normal fibroblasts and an important component of the tumor microenvironment [98]. In STAD and BRCA, high NF-YAl/NF-YAs ratios are found in Claudin^{low} tumors [97], a subset featuring minimal expression of Claudin3/4/7, which are membrane proteins involved in cell-cell contacts within epithelia [99]. Cell type deconvolution in STAD and BRCA yielded a parallel increase of NF-YAl/NF-YAs *ratios* in CAFs and cancer cells with a EMT phenotype, but not in other cell types of the tumors. Furthermore, by applying high values of the NF-YAl/NF-YAs *ratio* to WGCNA —Weighted Gene Co-Expression Network Analysis— a signature of 158 genes common to STAD and BRCA Claudin^{low} was derived, which proved to be significant for prognosis: this features *EMT* and *extracellular matrix* GO terms. In summary, the link between NF-YAl^{high} —or high NF-YAl/NF-YAs *ratio*— and EMT emerges and a group of associated genes are derived.

These data suggest that an unbalance in favor of NF-YAl predicts cancer subtypes with an aggressive EMT-like metastatic behavior, a point further confirmed by recent genetic experiments, indicating that NF-YA -and NF-YC- isoforms play different roles in cancer development.

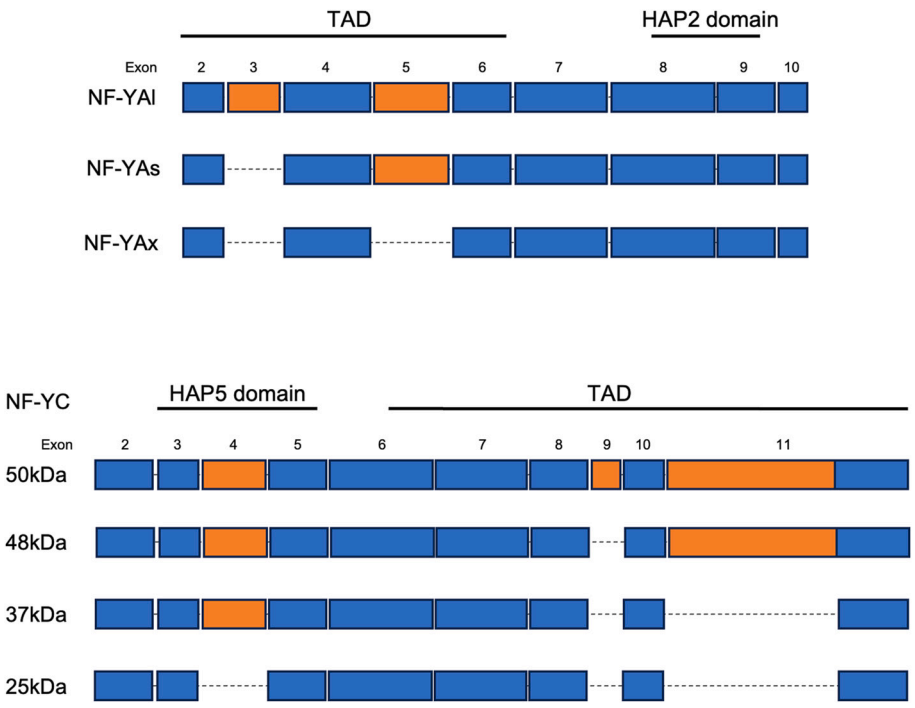

Fig. 1. Schematic representation of NF-YA and NF-YC isoforms.

5. Oncogenic NF-Y

Compelling data prove the importance of NF-Y subunits for cellular growth.

First, genetic ablation of NF-YA in mice is early embryonic lethal [100]. In fact, genomic analysis at the initial stages of development established the importance of CCAAT-driven genes in the early wave of Zygotic Genomic Activation (ZGA) in mammals [101–103]. In the case of mice, the involvement of NF-YA was formally proven by siRNA inactivation in zygotes, which abolishes a conspicuous number of DNAse I-hypersensitive sites at the 2- and 4-cells stages [101]. Consistent with this, phenotypic consequences of conditional NF-YA ablations in mice are comparatively less dramatic in tissues with large population of post-mitotic cells, such as muscle (myotubes) and neurons, than in liver and hematopoietic stem cells (Reviewed in [104], see also [105]). Data reported with the NF-Y-based MITO-LUC reporter gene in transgenic mice and zebrafish further solidified this concept *in vivo* [106,107].

Second, a CRISPR-Cas9 screening on 1427 TF genes in 33 cancer cell lines —leukemias, sarcomas, lung and pancreatic cancers— pointed at the three individual NF-Y subunits as the —relatively few—TFs essential for growth [108]; similarly, the DepMap consortium, interrogating cancer cell lines genetic dependencies, has NF-Y subunits ranking high among essential genes (https://depmap.org/portal).

Third, functional inactivation of NF-YA by RNAi was performed by different labs, and in different cellular contexts, resulting in inhibition of proliferation *in vitro* and *in vivo* [58,61,64,86,89,109–112]. A list of such experiments is shown in Table III. In addition, an apoptotic response has been reported [105,109,113,114]. As for HFD subunits, targeting of NF-YB inhibits xenografts growth *in vivo* [67] and proliferation of CRC cells *in vitro* [105]; of NF-YC, growth and migration of NB cells *in vitro* [73].

In summary, it is clear that NF-YA is essential for proliferation, but this does not immediately imply that it acts as an oncogene when overexpressed. Several results now point in this direction. NF-YA overexpression has been shown to increase migration and invasion of osteosarcoma [112], melanoma [115], hepatocarcinoma cells [89,116] *in vitro*; increased xenografts growth *in vivo* was reported for cervical carcinomas [65] and colon cancer cells [117]. Note that the inactivations/overexpressions were performed in cells expressing either NF-YAs or NF-YAl, thus the role of the single isoforms was not considered: in essence, it is unclear which isoform was targeted/overexpressed. Studies more focused on this issue have recently appeared on NB, HCC, PCA, BRCA and CRC, as discussed [83,84,89,95,97,117].

Another clinically relevant aspect regards a specific role of NF-Y in resistance to pharmacological treatments. NF-YB was retrieved in an RNAi screening for genes enhancing Paclitaxel activity in BRCA cells [118]. A study on the NF-Y/E2F1 partnership highlighted their relevance to confer increased resistance to Oxaliplatin in CRC [67]: interestingly, inactivation of both TFs led to a DNA-damage response, as found for NF-YA [114] and one of the mechanisms proposed was the shared activation of CHK1. In another study, profilings of U2OS cells inactivated of NF-YB or E2F1 yielded a common genes signature, whose most obvious feature, other than being "cancer" genes, was *drug resistance* (particularly for Irinotecan and Parabinostat); note that this signature was absent in NF-YB- or E2F1-specific DEG [119]. Concerning lymphomas, NF-YB is overexpressed in DLBCL cisplatin-resistant cells, contributing to drug resistance, *via* activation of STK33 [55]. It partakes in a tumorigenic "axis" of cells resistant to Doxorubicin, along with H19 lncRNA and MBTD1 [68]. Analysis of TFBSs responsible for Docetaxel resistance, based on single cell RNA-seq data in PCA, identified NF-Y as one of the ten nodes [120]. Finally, treatment of PDAC cells with a CDK7 inhibitor —LDC4297— causes down-regulation of cell-cycle genes —CDK1/2 and CDC25A/C— and a decrease of NF-YA and NF-YB at the mRNA and, for the latter, also at the protein level [121]. In summary, it can be speculated that NF-Y increased levels are conferring cells with increased resistance to drugs; it is intriguing, but it might be coincidental, that (i) NF-YA is not detected in the unbiased studies mentioned, and (ii) that NF-YB, but not NF-YC, emerges. Further experiments on NF-YC are required to verify whether there is a specific role of NF-YB, independently from its partner, or it is merely an issue of insufficient probing of NF-YC.

6. NF-Y isoforms in cancer development

The first functional indication of a specific role of an individual NF-YA isoform in cancer was reported on NF-YAx, which activates key genes —Nestin, SOX2, Nanog— that lead to selection of NB CSCs, in turn

Table III
NF-Y subunits modulation in cancers.

NF-Y subunit	Cell line / Organism	Modulation	Validation method	Ref.
YA	BRCA: SUM159 mouse xenograft PyMT mouse	CrispR KO, isoform KO	cell proliferation, spheroid formation, lipid metabolism, *in vivo* tumor size, tumor number in PyMT mice	[122]
YA	BRCA: SUM159PT, BT549 zebrafish xenograft	CrispR isoform KO	spheroid formation, wound healing; *in vivo* extravasation, metastasis	[97]
YA	Clear Cell Renal Carcinoma: A498; ACHN; 786-O; 769-P	siRNA KD	colony formation, MTT	[61]
YA	CRC: HCT116, SW480	siRNA KD, OE + S100A2 KO	cell migration, invasion, Ecadh expression, YA nuclear import	[117]
YA	CRC: HCT116; zebrafish xenograft	isoform OE	scratch assay, spheroid formation; *in vivo* infiltration, metastatic dissemination	[84]
YA	HCC: SK-Hep1	CrispR KO, isoform OE	cell number, glucose deprivation apoptosis, ROS,	[122]
YA	HCC: HepG2, Huh7	siRNA KD, OE + CDC8A KD	colony formation, migration, invasion	[89]
YA	liver: L-02, L02-AID-NF-YA	shRNA KD, protein KD	post-mitosis transcription reactivation, chromatin accessibility, cell proliferation, GE genomic stability, DNA repair, telomere maintenance; micronuclei, nucleoplasmic bridges proportion	[169]
YA	MEFs $p53^{-/-}$, $p73^{-/-}$, $E2F1^{-/-}$; HCT116, HCT116 $p53^{-/-}$, MCF10A, SKBR3	OE	colony formation, cell proliferation (negative regulation), apoptosis (induction)	[126]
YA	PCA: PC3; mouse xenograft	shRNA KD, CrispR isoform KO, OE	anchorage independent growth, MTS growth; *in vivo* tumor incidence, size, dissemination	[83]
YA	SCC: SiHa, C33A mouse xenograft	OE, siRNA KD	tumor spheres formation, chemical resistance *in vivo* tumor size, survival	[65]
YA	STAD: MGC803 (Diffuse) *vs* SGC-7901 (Intestinal)	siRNA KD	cell growth; colony formation	[58]
YB	CRC: Oxaliplatin-Resistant: OR-DLD1, OR-RKO mouse xenograft	OE, siRNA KD, shRNA KD	OXA cell survival, apoptosis, colony formation; tumor size	[67]
YB	DLBCL: OCI-Ly1-R, SUDHL4-R Cisplatin resistant cells	OE in sh-STK33 cells	Cisplatin cell survival IC50, apoptosis, DNA damage	[55]
YB	Lymphoma: OCI-Ly8/DOX, SU-DHL-2/DOX mouse xenograft	OE in sh-lncRNA H19 cells	DOX survival, colony formation, apoptosis, *in vivo* tumor size, Ki67	[68]
YB	OS: U2OS-ER-E2F1, U2OS	siRNA KD, OE,	Sarcoma, drug resistance GE signature	[119]
YB	OS: U2OS, HOS	Oncomine GE analysis OE, shRNA KD	wound healing, invasion	[112]
YC	BLCA:T24, BIU-87, UMUC3; patient derived primary cell lines mouse xenograft	CrispR isoform KO + OE, shRNA KD	cell proliferation, colony formation; *in vivo* tumor size, incidence	[124]
YC	Glioma: U87MG	siRNA KD	cell proliferation, cell cycle, colony formation, wound healing, invasion, sphere migration, *E*-Cad/Vim expression	[73]

KD: functional inactivation by RNAi experiments; KO: genetic inactivation by genome editing; OE: Overexpression.

contributing to tumorigenesis *in vivo* [95]. Currently, there is no indication of differential levels, or impact, of NF-YAx in tumors other than NB.

In PCA, Belluti et al. showed that NF-YAs overexpression spurs proliferation, both in the original tumor and in metastasis, whereas NF-YAl promotes migration [83]. Importantly, a high NF-YAl/NF-YAs *ratio* was found in circulating PCA cells. This suggests that increased expression of NF-YAs, generally associated *in vivo* with pro-growth gene signatures, is involved in the initial phases of tumor growth, as well as in the expansion of metastasis at later stages, yet it is NF-YAl that mediates exit from the original site and migration at distance.

Genomic ablation of exon-3 in two BRCA Claudin^{low} lines —BT549 and SUM159— with predominant NF-YAl generated clones expressing only NF-YAs: the cells displayed normal growth, but reduced motility/migratory capacities *in vitro* and in Zebrafish embryo extravasation assays, widely used as a proxy to measure metastatic potential [97]. Okada et al. generated NF-YA-null cells by CRISPR-Cas9 in SUM159 by a different strategy involving exons 1/2, obtaining cells impaired in essentially all growth parameters *in vitro* and *in vivo*: upon overexpression of NF-YAl —termed by these Authors NFYAv1— growth was restored. They went on to show upregulation of lipid anabolic genes, specifically FASN and ACACA, in conjunction with SREBPs, well established partners of NF-Y in this pathway [122]. The same Authors used liver SK-Hep1 cells —mostly expressing NF-YAl/NFYAv1— to generate cells expressing NF-YAs/NF-YAv2, which is induced by glucose deprivation and functions as a growth suppressor by activating PCK1 [123]. These observations assess a role of NF-YAl/NFYAv1 in conferring metastatic potential in BRCA in mice and suggest a tumor suppressor role of NF-YAs in liver cancer. In another HCC study, shRNA inactivation of NF-YAl/NFYAv1 has a stronger inhibitory effect on proliferation than a shRNA directed against both isoforms [116]. In general, it remains to be verified which isoform is associated with aggressive HCC: whether NF-YAs, as suggested by gene expression data [80], or NF-YAl, as in the above studies. A relevant point is that ablation of NF-YA by targeting exon-1/2 —as reported in breast and liver cells— seems at odds with the numerous indications pointing at the essentiality of NF-YA for cancer cells viability and growth, as mentioned above: further experiments are required to confirm this point and extend it to the HFD subunits.

In CRC cells, overexpression of the two isoforms has quite different effects: NF-YAl reduces proliferation, modifies the shape of cellular spheroids, making them irregular, with increased cell migration out of the structure as a result of decreased adhesion [84]; this is not observed with NF-YAs, which maintains cell adherence and compaction of spheroids. Zebrafish embryo extravasation assays confirmed *in vivo* the pro-migratory phenotype induced by NF-YAl.

Finally, a recent contribution points at NF-YC isoforms as important

in BLCA. These tumors express mostly the 37 kDa isoform and its inactivation/overexpression has more profound effects on tumor cells growth, *in vitro* and *in vivo*, than that of the 50 kDa isoform [124]. The Authors further investigated the mechanisms, which will be commented below. We have failed at detecting differential expression of NF-YC isoforms at the mRNA level in other epithelial cancers: it remains to be seen whether their role is limited to BLCA or extended to other cancers.

In summary, a coherent view of the role of the isoforms emerges: increased expression of NF-YAs spurs proliferation, whereas NF-YAl is associated with an EMT-like behavior, entailing loss of cell-cell contacts, increased migration and capacity to leave the original site to metastasize. NF-YAx and NF-YC 37 are involved in specific tumors, NB and BLCA, at least at present. The genetic and gene expression data gathered so far suggest that AS of NF-YA —and possibly NF-YC— is not merely an epiphenomenon of EMT, but rather a focal point of it, able to change cellular programs profoundly.

7. Oncogenic targets

DEG of cancer specimens resulted in lists of NF-Y-regulated genes, many of which were previously established targets, according to functional experiments in which CCAAT boxes were mutated in promoters or NF-Y subunits inactivated. In general, the two most recurrent GO categories under NF-Y control are *cell-cycle progression* and *metabolism* [46,47,61,64,86]. As to the first term, we mention the G2/M "*mitotic trait*" signature, whose overexpression is common to most tumors, conferring a negative prognosis [46]: the majority, if not all, such genes are NF-Y targets. The importance of this "*mitotic trait*" is further illustrated by genomic experiments commented below in the "Mechanisms" section. Other targeted cell-cycle regulators whose overexpression is associated with cancer development are NUSAP [125], MAPK3 [126], UBE2C [127], CDC25B [128–130], PLK1 [131], PRR11/SKA2 [132–134], CDC152 [135], CycD1/CDK4 [61], S100A2/KPNA2 [117] and CDCA8 [89,136]. Experiments on CDCA8, a component of the complex essential for microtubule stabilization and spindle formation, represent a paradigm. Chen et al. identified DEG in HCC and further selected genes whose overexpression is associated with poor prognosis [89]; many of the 36 "hub" genes were known oncogenes, but a "new" entry was CDCA8, whose overexpression/depletion confirmed its oncogenic role in hepatoma cells *in vitro,* as well as *in vivo* (xenografts and pulmonary metastasis following tail vein injection). Thereafter, NF-YA, one of the CDCA8 activators [136], was correlated in expression and increased protein levels scored in tumor samples. Comparing tumors with CDCA8^{high}/NF-YA^{high} to CDCA8^{low}/NF-YA^{low} levels, robust statistics emerged both in OS and DFS, granting a clinical impact of the association. Inactivating and overexpressing NF-YA confirmed its role in growth of HCC cell lines, and the importance of CDCA8 in NF-YA-mediated growth stimulation *in vitro*. This line of experiments is illustrative of just one of the many oncogenic NF-Y targets likely acting in different cellular contexts.

The second term —*metabolism*— is relevant because of the profound alterations in metabolic pathways found in cancer cells. NF-Y is known to activate several "rewired" pathways, as determined by RNAi experiments [64,86]: (i) glycolysis and TCA cycle [86], including ALDHA1 [94], ALDH1A3 [137] and the cancer stem cell marker ALDH2 [138]. (ii) Lipids anabolic pathways, notably by activating the oncogenic FASN [112,122]: all genes of rate-limiting steps in fatty acids and cholesterol synthesis which are under the control of NF-Y and of the master SREBP TFs. The relevance of lipid genes as NF-Y targets in transformation has become evident [62,122,139], and further confirmed by the report on the mevalonate pathway in BLCA mentioned above [124]. (iii) Pathways of certain amino acids, such as genes mediating the Serine/Glycine One Carbon cycle and GLUL, a key enzyme in the biosynthesis of glutamine [86,140]. Altogether, NF-Y appears to activate genes mediating the "Warburg effect", as well as others whose expression is typically increased in cancer cells, particularly in solid tumors.

A third term present in the NF-Y regulome is *transcriptional regulation*. The collection of sequence-specific TFs and cofactors controlled includes STAT3 [115], EZH2, PRMT5, EHMT2, MEP50, MBTD1 [68,111,138,141–144], all having oncogenic potential. The "axis" with E2F1 was in part dissected [67,119,145]: Jiang et al. showed that overexpression of E2F1 increases NF-YB levels in sarcoma cells, by binding to and activating the NF-YB promoter; conversely, E2F1 inactivation leads to NF-YB decrease. In turn, NF-YB inactivation enhances apoptosis mediated by overexpression of E2F1. Fang et al. showed that NF-YB inactivation leads to decreased activity of the E2F1 promoter, which has important CCAAT boxes, lower E2F1 levels and decreased growth. Together with the conjunct enrichment of E2F/CCAAT sites in "cancer" genes, the large overlap of respective genomic locations as *per* ChIP-Seq data [53], and the common link to the drug resistance promotion mentioned above, there is a clear indication that this *duo* plays a crucial role in driving unrestricted cell-cycle progression.

Another TF gene controlled by NF-Y is SOX2, widely overexpressed in solid cancers, considered as a marker of CSC in numerous tumors [146] and required for development of sarcomas [147]. The SOX2 promoter is under NF-Y control [148–151] and NF-YA overexpression in cervical cancer leads to increased cell proliferation, spheres formation *in vitro* and xenograft tumors *in vivo*: this effect is partly mediated by increased SOX2 expression [151].

Not included in the three categories discussed above, and in addition to the genes reviewed by Gurtner et al. [152], other NF-Y targets involved in growth control are COL11A1 [153,154], EFNB2 [155], PTEN [156], LIN28B [157], SATB1 [158], STK33 [55], PNPT1 [91], Notch1 [159], MDR1 [160,161].

8. The mechanisms

Recent experiments provide advancements in our understanding on how increased NF-Y levels can impact on tumor development and growth by altering cell-cycle regulation or differentiation.

De Veale et al. investigated the transcriptional "phasing" of gene units important for differentiation of embryonic cells, identifying ATAC-seq accessible location in G1/S and G2/M cells [162]: NF-Y/CCAAT are enriched together with the CHR/MYB sites typical of G2/M promoters. However, unlike the latter, NF-Y/CCAAT shows no bias for G1/S *vs* G2/M accessibility, indicating that its role is not limited to regulate G2/M genes. Interestingly, the study showed that the growth suppressor CDKN1B (p27) delays cell-cycle phasing and differentiation.

In the terminal differentiation system of granulocytes, two B-Zip are known to play a key role, CEBPa and CEBPe: Theilgaard-Monch et al. studied by genetic means the mechanisms of cell-cycle exit mediated by these TFs: ChIP-seq shows that CEBPe binds to NF-Y/E2F modules, repressing MYC-driven G1/S and G2/M promoters through association to an activatory NF-Y, and not to the repressive CDE/CHR elements [163]. Among E2Fs, E2F4 is part of the DREAM complex which acts on the CDE/CHR [164], so it is likely that other E2Fs team-up with NF-Y to mediate CEBPe recruitment and repression in G2/M, at least in the terminal differentiation considered. These findings indicate that repression of this class of genes upon differentiation is not relying on —or solely on— the CHR/CDE/DREAM complex. In addition, CEBPe also stimulates CDK inhibitors, including p27 and the related p57, both NF-Y targets [165,166]. Note that it was previously reported that p27 overexpression down-regulates a gene signature in various types of cancers, with CCAAT as common element in their promoters [19]. Hence, the role of NF-Y in CDKI expression, and consequently exit from cell-cycle and differentiation, appears to be relevant, but still poorly understood.

Bookmarking of chromatin by TFs during mitosis is related to crucial cellular decisions of re-entering the cell-cycle, or exiting for differentiation. NF-Y binding to the Cyclin B1 promoter during mitosis was reported two decades ago [167] and several TFs and General Transcription

Factors —TFIIB, TFIID— are known to behave similarly [Reviewed in [168]]. Consistent with this, the activity of promoters is more resilient compared to enhancers during mitosis. Recent results in liver cells lend a new dimension to this topic. Using single cells expression analysis, Yu et al. showed dynamic waves of accessible *loci* during the different phases of mitosis, with a core set of metaphase sites organized by NF-Y [169]. KD by shRNA and inducible Degron elimination of NF-YA led to a generalized impairment of post-mitotic transcriptional reactivation. Intriguingly, some bookmarked genes, among the first wave targets, are TFs with known hepatic function, such as GATA4/6, PROX1, JUN: in turn, these TFs might be responsible for the second and third waves of re-activation. In addition, NF-YA depletion leads to down-regulation of genes involved in DNA-damage repair, formation of micronuclei and genomic segregation defects. These experiments were performed in proliferating cancer cells, so it remains to be seen whether the role of NF-Y is similar in normal cells and what happens upon differentiation.

Sarcomas are often characterized by genomic rearrangements of genes creating the production of fusion proteins acting as powerful oncogenes. One paradigmatic example is rhabdomyosarcoma (RMS), often caused by the PAX3-FOXO1 fusion under the control of the PAX3 promoter in myoblast progenitors; it is known that inactivation of PAX3-FOXO1 leads to cellular arrest and differentiation to myotubes [170]. Sroka et al. used a CRISPR genetic screening based on FACS-mediated isolation of myocytes differentiated from RMS lines: the use of an sgRNA library restricted to TFs and cell signaling genes led to the identification of the three NF-Y subunits among the top hits whose inactivation drives myo-differentiation [171]. In brief, although NF-Y inactivation caused a drop of expression of cell-cycle targets, the Authors showed that the mechanism abolishing RMS proliferation is caused by transcriptional inactivation of the PAX3 transcription unit, containing two CCAAT boxes, hence disappearance of the oncogenic PAX3-FOXO1 fusion. The evidence featured a plethora of genomic assays, including inducible base editing of one of the two CCAAT boxes of the PAX3 promoter. In addition to having potential consequences for management of RMS, this work elegantly illustrates the importance of NF-Y/CCAAT interactions in driving even a single oncogenic unit.

Collectively, these data place NF-Y, and its relative levels, at the center of crucial decisions whether to exit from mitosis and enter G0, as in differentiating cells, or re-entering and progress to another cycle, as in cancer cells.

Finally, the aforementioned report on NF-YC isoforms in BLCA provides interesting molecular mechanisms: the activation of NF-YC-37 is apparently exerted through recruitment of the CBP co-factor and synergy with the SREBP2 TF, resulting in activation of the mevalonate pathway genes: NF-YC-50, instead, harbors additional parts (Fig. 1) contacting CARM1, a co-factor known to methylate arginines in histones, whose recruitment prevents CBP/SREBP2 interactions and therefore activation [124].

9. Perspectives

While the subunits are —in most cases— not primary genetic drivers of cancer, the current data converge on NF-Y, specifically NF-YA, as an important nodal point in cancer development, through activation of growth-promoting genes with direct oncogenic potential. Several questions are raised: (i) what are the mechanisms driving increased expression of NF-YA —and in some cases NF-YB/NF-YC— in cancers? Is this due to transcriptional or post-transcriptional mechanisms (or both)? Along the same line, what is the role of miRNAs —and lncRNAs— in the control of the subunits? (ii) To elicit function, NF-Y is considered a "pioneer" TF teaming up with other "activator" TFs, as well as co-factors, a list of which is being progressively established by multiple approaches [53]: what are their 3D structures and molecular relationships on regulatory DNA elements? Can knowledge of structures lead to development of compounds that interrupt the activity of the complexes? (iii) Concerning AS, what are the Splicing Factors mediating altered NF-YA and NF-YC splicing in aggressive tumors and how are they regulated? To this end, there is evidence that the oncogenic RBFOX2 and U2AF1 might be involved [97,172], but a long road lies ahead before a complete understanding on this topic is reached.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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