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Review

MEF2 and the tumorigenic process, hic sunt leones

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ABSTRACT

While MEF2 transcription factors are well known to cooperate in orchestrating cell fate and adaptive responses during development and adult life, additional studies over the last decade have identified a wide spectrum of genetic alterations of MEF2 in different cancers. The consequences of these alterations, including triggering and maintaining the tumorigenic process, are not entirely clear. A deeper knowledge of the molecular pathways that regulate MEF2 expression and function, as well as the nature and consequences of MEF2 mutations are necessary to fully understand the many roles of MEF2 in malignant cells. This review discusses the current knowledge of MEF2 transcription factors in cancer.

1. Introduction

The discovery of genetic alterations critical for tumor cell growth and survival in patients promises to revolutionize anti-cancer approaches and usher in an era of personalized medicine. Large scale and detailed molecular analyses using multiple omics approaches have permitted a more precise characterization of tumor subtypes and can be instrumental in unveiling the Achilles' heel of individual tumors. Cancer cells are strictly dependent on deregulated transcriptional programs for sustaining their survival and impetus for growth. Such transcriptional addiction is a vulnerability that can be exploited to unveil new therapeutic opportunities [1]. Within the context of transcriptional addiction, epigenetic therapy is especially promising and has already begun to yield concrete clinical results [2–4].

The MEF2 (Myocyte Enhancer Factor-2) family of transcription factors (TFs) includes four members: MEF2A, MEF2B, MEFC and MEF2D, which play key roles in the regulation of differentiation and adaptive responses. MEF2 TFs regulate epigenetic modifications and control gene expression [5–8]. MEF2 can activate or repress transcription through interactions with co-activators or co-repressors, respectively. The four class IIa HDACs: HDAC4, HDAC5, HDAC7 and HDAC9, are important MEF2 partners. When in complex with class IIa HDACs, MEF2 are switched into transcriptional repressors and a closed chromatin conformation is accomplished [9,10]. On the opposite, the binding of MEF2 to co-activators (e.g. p300, P-TEFβ, GRIP-1, CARM1, MAML1, ACTN4, Ash2L, EBF-1, CRX) increases the transcription of MEF2-regulated loci [7–11].

In this review, we discuss evidence of the dysregulation of MEF2 as reported in the literature. There are some conflicting data about key roles of MEF2 in different malignancies. In some cases, the results appear contradictory and the contribution of MEF2 to cancer cannot be clearly categorized. Frequently the impact of MEF2 dysfunctions to the multiple protein complexes, which orchestrate epigenetic changes, is underestimated. For example, the cooperation with class IIa HDACs in fueling or restraining the transforming potential of these TFs is only marginally addressed. Understanding these aspects could open the door to new therapeutic interventions.

1.1. The MEF2 family

The MEF2 family of proteins includes widely expressed TFs controlling pleiotropic responses in adults and different developmental pathways during embryogenesis.

Saccharomyces cerevisiae, *Drosophila melanogaster* and *Caenorhabditis elegans* possess a single *Mef2* gene, whereas in vertebrates there are four *MEF2 genes*. *MEF2* genes come from a unique progenitor-seeding

Abbreviations: ABC, activated B cell-like; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ARMS, alveolar rhabdomyosarcomas; BRM, Brahma; BRG1, BRM-related gene 1; CTD, C-terminal domain; CNS, central nervous system; CLPs, common lymphoid progenitors; DLBCL, diffuse large B-cell lymphoma; ERMS, embryonal rhabdomyosarcomas; EMT, epithelial-mesenchymal transition; GCB, germinal center B cell-like; HSC, hematopoietic stem cells; HCC, hepatocellular carcinoma; MADS, MCM1, Agamous, Deficiens, Serum response factor; MEF2, Myocyte Enhancer Factor-2; NSCLC, non-small cell lung cancer; NLS, nuclear localization sequence; Ph, Philadelphia chromosome; PTM, post-translational modification; RMS, rhabdomyosarcomas; RRM, RNA-recognition motif; TAD, transactivation domain; TFs, transcription factors; TGF-β, transforming growth factor-beta

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[1] Hic sunt leones is a short Latin phrase to indicate unexplored territories.

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sequence that underwent three rounds of duplication [12]. The first two events are concomitant with the 2 big duplication events during *Gnathostomata* and *Agnatha* divergence [13]. In an evolutionary perspective *MEF2B* is the most distant member whereas *MEF2A* and *MEF2C* are the closest [12]. In vertebrates MEF2 family members are expressed in several adult tissues and data indicate that, overall, these TFs are ubiquitous. However, distinct but also overlapping expression patterns among the four family members in different tissues, lineages and differentiation stages are frequently observed [8].

In mammals MEF2 TFs play crucial roles in differentiation, cell survival, proliferation and in various adaptive responses in different tissues. The central nervous system, skeletal and cardiac muscles, bone, and bone marrow-derived cells are tissues where their functions have been investigated in detail. Initially identified as key elements of the muscle-differentiation program, the activities of MEF2 have now also been proven to be essential for the development of other lineages [5]. In the CNS, they influence neuronal differentiation, cell survival, and synapse formation [11]. Different roles are played by MEF2 in the immune system. Mef2c and Mef2d are key components of the transcriptional machinery controlling B cell development [14]. Mef2c activity is also highly regulated in T cells, where it regulates T-cell development, differentiation and thymocyte selection [15].

MEF2 TFs are subject to multiple layers of regulation, which include alternative splicing, different post-translation modifications and the ability to homo- and heterodimerize with other TFs. Taking into account this complexity, it is not surprisingly that the transcriptome under MEF2 supervision exhibits a spectacular heterogeneity and is highly variable from tissue to tissue [9,16–19].

Mutations in *MEF2* have been associated with various diseases in humans, not limited to cancer. E.g. *MEF2C* haploinsufficiency is linked to a syndromic form of intellectual disability with autistic features, thus further proving the pleiotropic nature of these TFs [20].

1.2. MEF2 structure and binding partners

All MEF2 proteins contain highly conserved MADS and MEF2 domains that lie in the N-terminus and are essential for DNA binding, dimerization and interaction with other factors (Fig. 1A/2). This region is highly conserved between the different family members and throughout evolution. The carboxy-terminal segment, which provides the transcriptional activation properties, is much less conserved [21,22]. An exception involves the highly conserved final 35 residues, where the NLS (nuclear localization sequence) is located [23,24].

MEF2 bind to the DNA as dimers (Fig. 1A) stacked head-to-head with each other and recognize the consensus sequence YTA(A/T)4TAR [25,26]. The stable folding of the MEF2 domain requires a correct folding of the MADS domain and mutations that prevent DNA binding, or alter the structure of this domain, affect the structure of the MEF2 domain [26]. As a consequence, a mutant of MEF2 deprived of its DNA binding domain is less stable, probably because of N-terminus unfolding [6,27].

As anticipated, the MEF2 domain is important not only for dimerization, but also for mediating interactions with co-factors and co-repressors. A hydrophobic groove on the MADS-box/MEF2 domain formed by Leu66, Tyr69, and Thr70 and delimited by helix H2 and the flexible linker between H2 and β3 (Fig. 1B) can rearrange to accommodate transcriptional co-activators or co-repressors, such as Cabin1 [28], class IIa HDACs [29], MyoD [26], p300 [30] and MASTR [26]. A hydrophobic residue in these partners (e.g. a Leu in HDAC4, HDAC9, Cabin1 and a Phe in MASTR) drives the insertion into the groove and contributes to the interaction with MEF2 [26]. A point mutation in this key residue is sufficient to reduce the interaction between the respective two proteins [28,29].

All of the most well characterized MEF2 partners bind the hydrophobic pocket between the MADS and the MEF2 domains where helix H2 is fundamental for the interaction. Hence, it is very difficult to image that a single MEF2 dimer is capable of binding simultaneously to many partners. Also, MEF2 binding to Cabin1, class IIa HDACs or to p300 is mutually exclusive [26] (Fig. 1B). Interestingly, all these MEF2-partners are characterized by a consensus sequence that fits in this groove and that constitutes the so-called MEF2 binding sequence. The sequence XX(V/T/I)(K/R)XZ(L/F)ZXX(V/I/L)XXX can be considered a consensus for binding to MEF2 [26].

Despite the high conservation of the N-terminus, each MEF2 shows some preferences for DNA binding. The consensus-binding is very similar for the four MEF2s, but differs in the regions adjacent to the core [25]. Wu and colleagues suggested that the specificity of the consensus of each MEF2 depends on the difference between the H3 helix of each paralogue [26]. In fact, helix H3 (Fig. 1A) is the portion less conserved inside the N-terminus of the four human MEF2. It interacts with the genomic regions flanking the core of MEF2-consensus region, conferring a certain degree of specificity to each of the four MEF2. Further levels of MEF2 DNA binding heterogeneity can be provided by the tissue and context selectivity (e.g. during different cell-cycle phases or differentiation steps). This second layer of specificity depends essentially on four factors: i) the epigenetic status of the regulatory region [9]; ii) the presence of specific partners [31]; iii) the level of specific PTMSs [32]; and iv) the expression of specific splicing variants [19] (Fig. 2). All these issues determine the tissue-specific MEF2 signature. Less information is available about the structure of the C-terminus. Deletional studies have identified two TADs (Fig. 2/3), followed by the *NLS* [21].

In summary, when mutations or other alterations of MEF2 appear in cancer, some properties of these TFs must be considered:

a) The four MEF2 are very similar in their DNA binding properties. Some differences in the consensus sequence can be explained by the selectivity of helix H3.
b) Mutations that affect the DNA binding domain and/or the dimerization domain of MEF2 are predicted to diminish the transcriptional activity [6,26].
c) The three main partners of MEF2s (the repressors, Cabin1 and class IIa HDACs, and the co-activator, p300) compete for binding to the same region of MEF2. Therefore, any mutation that affects this portion of MEF2 could have both positive and negative effects on MEF2 transcriptional activities, depending on the stability of the relative complexes in the specific cell lineage. These considerations are exemplified using small molecules, derived from BML-210 and designed to bind MEF2. In some circumstances these compounds can activate MEF2 responses by displacing class IIa HDACs [33], but in other contexts they can blunt MEF2 responses, by blocking the binding of MEF2 and p300 [34].

2. MEF2 TFs and cancer

The involvement of MEF2 in cancer is still controversial. These TFs can be converted into transcriptional activators or repressors after assembly into multi-protein complexes and under the control of the tumor microenvironment, and hence their categorization as oncogenes or tumor suppressors cannot be unequivocally defined. Genetic alterations have been observed among some members and frequently their expression is altered in different cancer types. Although the contributions to cancer related processes such as proliferation, apoptosis, angiogenesis or epithelial-mesenchymal transition have been documented for specific MEF2 members, we cannot exclude that other members may also be involved in the same processes.

2.1. MEF2A

Mef2a null mice die perinatally from a spectrum of heart defects [35]. Although the role of Mef2a in promoting muscle differentiation [36] and heart development [35,37] is well established, its involvement

in cancer has not been investigated in detail. Some cancer types are marked by altered MEF2A expression and its contribution to key adaptive responses that are instrumental for the transformation process such as invasion, refractoriness to apoptosis, proliferation, angiogenesis, metabolism and inflammation, which are instrumental for the transformation process, suggests a pro-tumorigenic role for this family member.

Initial observations noted MEF2A involvement in transducing signals elicited by fibroblast growth factors in prostate cancer cells [38]. Subsequent studies in mammary epithelial cells also identified its involvement in TGF-β signaling [39]. TGF-β promotes the activation of MEF2A directly, by mediating its acetylation, and indirectly, by decreasing the stability of class IIa HDACs. As a consequence, MEF2A favors matrix-degradative properties through the up-regulation of *MMP10*. MEF2A can also influence neuronal cell survival and it is subject to caspase-dependent processing during apoptosis [22,40,41]. A role in cell survival for MEF2A was confirmed in cardiomyocytes, where it positively regulates the expression of differentiation genes and antagonizes the expression of cell-cycle regulated genes [16]. In endothelial cells, in response to VEGF, MEF2A, as well as MEFC/D, mediate the release of repressive histone marks from enhancers of genes involved in sprouting angiogenesis [42].

In gastric cancer, MEF2A is the most expressed MEF2 family member and 10% of patients are characterized by a significant

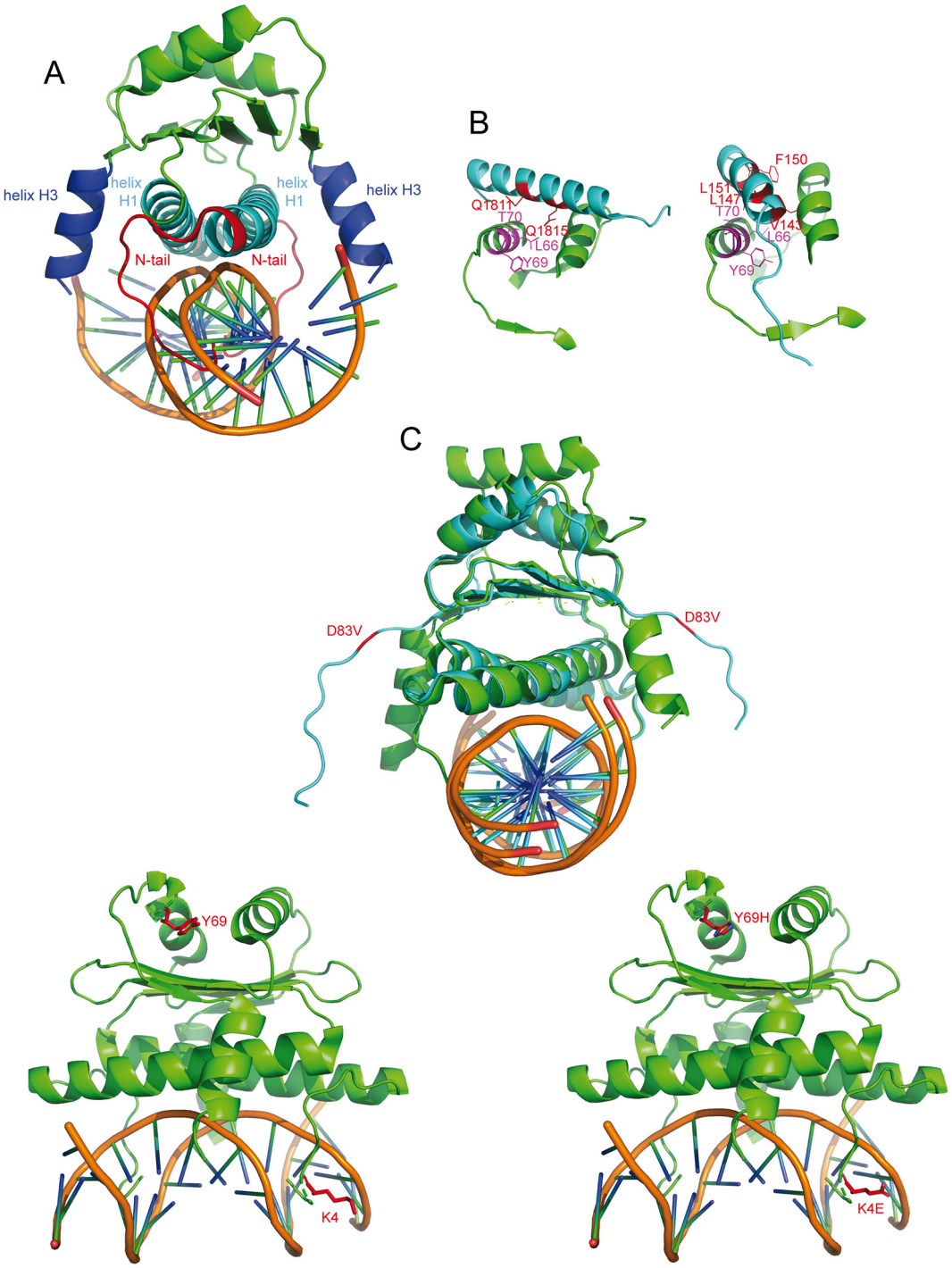

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Fig. 1. MEF2 and cancer.
A) Structure of MEF2A MADS-box/MEF2 domains bound to DNA [26] (PDB 3KOV). The MADS domain is formed by the N-terminal tail (aa 1-15 of MEF2A, in red in the picture), helix H1 (15–37, in light blue in the picture), strands β1 (41–49) and β2 (53–59). The tail and helices H1 and H3 (in blue in the picture) are involved in DNA binding. The MEF2 domain is composed by helix H2 (62–70), strand β3 (76–80), and helix H3 (82–90). This latter is involved in homo- and hetero-dimerization, including binding with co-repressors such as Cabin1 [28] and HDAC9 [29], of co-activators such as the TAZ2 domain of p300 [30] and additional partners such as MyoD [26]. The angle of binding between HDAC9 and Cabin1 and MEF2 is different from that between MEF2 dimers. Hence, Cabin1 and class IIa HDACs binding to MEF2 do not disturb its binding to DNA nor its dimerization. By contrast, the binding to co-factors and partners is strongly affected[26,30]. The minor grove (YT *A(A/T)4T* AR) of the DNA consensus sequence is directly bound by aminoacids G2, R3, K4, K5 and I6 of MEF2A. For its binding to the major grove (*YT* A(A/T)4T *AR*) only the tyrosine Y23 is not dispensable, while the positive charged R24, K30, K31 are involved in interaction with the negatively charged backbone phosphates. Many residues participate in the dimerization and any mutation in these residues could prevent correct dimerization.
B) Zoomed view of the structure of the MEF2 domain of human MEF2A (in green, PDB ID: 3P57) bound to a motif of the transcriptional co-activator p300 (left, in cyan) [30] and of MEF2B (in green, PDB ID: 1TQE) bound to a motif of the co-repressor HDAC9 (right, in cyan) [29]. The aminoacids Leu66, Tyr69, and Thr70 of the MADS-box/MEF2 domain forming a hydrophobic groove as highlighted in magenta, while the glutamines and the hydrophobic residues (Val143, Leu147, Phe150, and Leu151) respectively of p300 and of HDAC9 and that insert in the hydrophobic groove and are shown in red. The similarity of binding to MEF2 between p300 and HDAC9 highlights the incompatibility of their co-binding.
C) Effect of MEF2B D83V mutation, frequently found in DLBCL [6,60]: Superimposition of MEF2B MADS-box/MEF2 domains (green) bound to DNA (orange) [29] (PDB ID: 1n6j) and of MEF2A-MEF2B chimeric MADS-box/MEF2 domains (cyan) bound to DNA (orange) [60] (PDB ID: 6BYY), bringing the D83V mutation. In the picture it is highlighted the distortion of helix H3 induced by D83V (red) mutation. Effect of MEF2B mutations (K4, Y69), frequently found in DLBCL, affecting respectively DNA binding and dimerization. Compare the wild-type MEF2B (PDB ID: 1n6j) on the left with the mutated ones in the right. K4E mutation removes the positive charge fundamental for the interaction with DNA; Y69H decreases the hydrogen bonding between the dimers and with partners, such as p300. All the images were elaborated with PyMOL2.1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

upregulation of MEF2A mRNA levels (TCGA). In gastric cancer cells, p38 can phosphorylate MEF2A to promote glycolysis by transcribing *GLUT4* [43]. In the same cells MEF2A has tumor suppressive roles, by inducing the expression of *CDKN1A* through KLF4 [44]. Hence, MEF2A can exhibit tumor suppressive or tumor promoting activities in models of leiomyosarcomas, depending on its ability to operate as a transcriptional activator or repressor, respectively [9].

Similar data, albeit incomplete, are available for pancreatic cancer and hepatocellular carcinoma. A *MEF2A* SNP (Y105C) is frequent in pancreatic cancer and this SNP can be considered as a strong negative prognostic marker [45]. In hepatocellular carcinoma MEF2A protein levels are frequently up-regulated together with MEF2C and class II HDACs, compared to the levels in normal and cirrhotic livers [46].

Finally, MEF2A can regulate immune/inflammatory genes in different cell types [47,48]. As we will discuss below, the regulation of some aspects of the inflammatory response seems to be a leitmotif among the different MEF2 members [9,49–51].

2.2. MEF2B

From a phylogenetic and sequence homology point of view, MEF2B is the most distant family member. Although the mutation rates of the four MEF2 are extremely low, *MEF2B* evolved faster than *MEF2A/C/D* [12]. An additional MEF2B peculiarity is a change in the MADS domain, whereby a glutamic acid, that is fundamental for the binding to DNA is substituted by a glutamine (E14Q). This modification results in a reduced capacity to bind the DNA *in vitro,* and can be restored by reinserting the glutamic acid residue Q14E [52]. Despite these peculiarities, mice null for *Mef2b* do not show overt phenotypes, indicating that although *Mef2b* is the most divergent member, other *Mef2* can compensate for its absence in rodents [53].

The distinctive features of MEF2B compared to the other family members also hold true in cancer. Here point mutations are protagonists. In 2011, MEF2B mutations were found in approximately 13% of cases of follicular lymphoma and in 11% of cases of diffuse large B-cell lymphoma (DLBCL) [54]. These observations were confirmed by further studies [55–58]. Other mutations in *MEF2B* were discovered after whole genome-sequencing in mantle cell lymphoma [59].

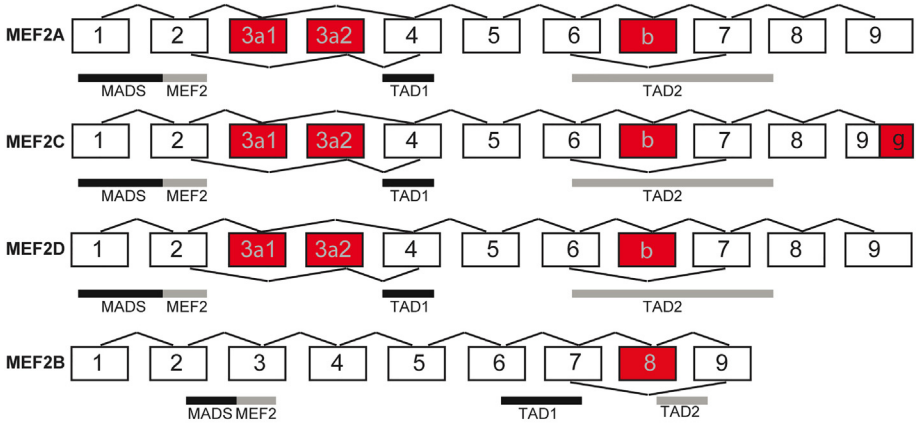

Fig. 2. Schematic representation of the splicing isoforms described for MEF2A, C, D and MEF2B; exons alternatively included are highlighted in red.
In the coding region of MEF2A/C/D there are nine common exons. There are two alternative third exons, 3α1 and 3α2, that are mutually exclusive and that are present in each gene [156]. The α1 isoform is ubiquitous and can complex with class IIa HDACs, while the α2 isoform is expressed only in fully-differentiated myocytes and is refractory to the binding by class IIa HDACs [19,156]. The alternative usage of the α2 in place of the α1 exon is under the control of the kinase SPRK3 [106] and of the splicing factors RBFox 1 and 2 [157,158]. The vertebrate MEF2 genes could have an additional exon (β) between exons 6 and 7, which is variably included in mRNAs. Finally, a γ domain fused to the last coding exon could be excluded uniquely in MEF2C by the splicing to a cryptic acceptor site in exon 9 [156]. The integration of the β domain enhances the transactivation capability of MEF2s probably through the phosphorylation of the Ser/Thr residues by ATM [116]. The β- isoforms are predominant in cycling cells, while the β+ are expressed in arrested/terminally differentiated cells of the brain, hearth and skeletal muscles [156]. The RNA-binding protein MBNL3 negatively regulates the inclusion of the β exon in differentiated myocytes, leading to muscle degeneration and myotonic dystrophy [159]. For Mef2c instead the β-γ- isoform is the most expressed also in muscles and in the brain [156]. Finally, the γ exon, which could be spliced out in MEF2C, has a repressive activity [160], due to the phosphorylation by CDK5 of Ser396 and the subsequent SUMOylation [161]. Less information is available about MEF2B. Its splicing was studied in rodents, where four isoforms where described [162]. In humans two isoforms were described, A and B, respectively made up of 9 and 8 exons [6]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Mouse models targeting Mef2c functions in the hematopoietic system.

Mouse model	Cell type	Proposed Mef2c function	Ref.
Mef2C loss-of-function allele (floxed) in the miR-223-deficient background	Myeloid-specific deletion	Expansion of granulocyte progenitors	[69]
$Mef2C^{fl/-}$ Mx^{cre} mice, in which CRE can be induced by activation of the interferon pathway by polyI:C	BM cells	Reduction of monocytic differentiation	[70]
Bone marrow cells transplanted from poly(I:C)-treated Mx1-Cre compared to $Mef2c^{fl/fl}$ mice from poly(I:C)-treated Mx1-Cre $Mef2c^{+/fl}$	HSC and progenitor compartments	Promotion of lymphoid development and repression in myeloid generation, sustainment of common lymphoid progentitor population	[66]
Vav^{Cre} $Mef2c^{fl/fl}$ mice	HSC	Control megakaryopoiesis; age-dependent maintenance of specific B-cell progenitor populations	[71]
$Mef2C^{fl/fl}$ $Cd19^{+/cre}$ mice	B cell subsets in the bone marrow and spleen, from pro-B cell stage (70%)	B cell proliferation and survival after BCR stimulation	[72]
$Mef2C^{fl/fl}$ $Cd19^{+/cre}$ mice	B cells from early in development	Regulation of B-cell proliferation after BCR stimulation	[73]
$Mef2C^{fl/fl}$ Mb-$1^{+/cre}$	Pro-B-cell stage	Regulation of B-cell numbers in bone marrow and spleen of young animals.	[74]
$Hdac7^{fl/-}$ Mb-$1^{+/cre}$ mice	Pro-B cell stage	Repression of myeloid and T lymphocyte genes in B cell progenitors through interaction with HDAC7	[75]

In DLBCL, hot spot mutations of *MEF2B* occur in aa located within the MADS/MEF2 domains required for dimerization and DNA binding (K4, Y69, D83) (Fig. 1C). Other mutations affect the transactivation domain. Using ectopically expressed MEF2B, Pon and coauthors identified MEF2B regulated genes in 293 cells and demonstrated that K4E, Y69H, D83V mutations all reduced MEF2B transcriptional activity [6]. As predicted from the structure [26] and demonstrated by the Olson group [52] the K4E mutation affects the DNA binding properties of MEF2B. Likewise, the mutation D83V, which lies within the MEF2 domain, affects MEF2B dimerization and indirectly affects its transcriptional activity [6]. A recent study indicates that this mutation shifts the conformation equilibrium of the MEF2 domain α-helix H3 to the β-strand (Fig. 1C). Furthermore, this conformational change decreases the binding to DNA as well as to cofactors and partners [60].

As discussed above, Y69 is fundamental for p300 binding [30] and therefore the decreased activity of MEF2B Y69H could depend on p300 displacement [6] (Fig. 1B/C). Further mutations cause premature truncations of the protein (R171X and Y201X) or frame-shifts (G242fs, P256fs and L269fs). As a result, these truncated mutants behave similarly to MEF2B isoform B (Fig. 2), which is produced by alternative splicing from aa 256. Isoform B shows decreased transcriptionally activity [6]. All these hot spot mutations are present in heterozygosity, but their capability to increase the migration and the malignancy of DLBCL cells suggest that they could act as dominant mutations, when homodimers or heterodimers are assembled [6].

If the impact of MEF2B mutations on the transcriptional activity is established, their implications for tumorigenesis are less clear. Among MEF2B target genes, *BLC6* was identified as an important oncogene marking GCB (germinal center B cell-like) and ABC (activated B cell-like) subtypes of DLBCL [61]. BCL6 is a transcriptional repressor that influences the expression of hundreds of genes involved in the DNA damage response, cell cycle control and differentiation. Moreover, BCL6 is required for germinal centers (GC) formation [62]. Within B-cells of GC, BCL6 also represses well-known oncogenes, and its full transforming potential was documented in cooperation with other oncogenes [63]. However, this view of BCL6 as a critical player for the transformation process elicited by mutated MEF2B is debated, since BCL6 is insufficient to rescue MEF2B knockdown cells from cell cycle arrest. This point has lead to the hypothesis that additional MEF2B-target genes could be implicated in the tumorigenic process. A recent observation points to MEF2B as a regulator of chemotaxis [6]. Undoubtedly, further studies are necessary to clarify the correlation between the two genes.

Apart from the role of MEF2B in malignant transformation, DLBCL patients with mutated MEF2B respond better to the HDAC inhibitor Panobinostat, even though the explanation for this sensitivity is unknown [64]. Less information is available for solid tumors. In colon cancer the presence of the fusion gene TADA2-MEF2B was reported, but not characterized [65].

2.3. *MEF2C*

Animal models have shown that *Mef2c* is essential for the development and differentiation of multiple tissues including bone, neuronal cells and cardiac and skeletal muscles [8]. In addition, when lineage specific conditional knock-outs were generated, new functions of *Mef2c* were discovered [66]. The contribution of MEF2C in driving the development of hematopoietic cancers has been pursued in recent years. A role of *Mef2c* as oncogene was initially suggested by Du and co-authors [67]. They applied oncogenic-retrovirus-induced insertional mutagenesis to discover new genes able to cooperate with *Sox4* in eliciting myeloid leukemia. Although dysregulation of *Mef2c* alone was not sufficient to trigger leukemia, its increased expression accelerated the development of Sox4-induced leukemia [67].

This evidence for a contribution of MEF2C to leukemia development was corroborated by the findings of key roles of MEF2C in regulation of the immune system. In bone marrow, Mef2c is highly expressed by common lymphoid progenitors (CLPs) and B cells, whereas Mef2c expression is minimal in T cells, granulocytes and erythrocytes. It is also expressed, at lower levels compared to CLPs, in hematopoietic stem cells (HSC) and common myeloid progenitors [68].

Several mouse models were developed and used to dissect the role of *Mef2c* in the hematopoietic system[66,69–75]. Data are summarized in Table 1. These models clearly show that Mef2c is required for B cell homeostasis, by transducing proliferative and survival signals in response to BCR stimulation [66] and, by cooperating with early B cell factor-1 (EBF1), NF-kB and NFAT in transcribing B cell-specific genes, including the anti-apoptotic *Bcl-2* family members *A1* and *Mcl1* [73,76,77].

Mef2c stimulates lymphoid over myeloid differentiation principally through two mechanisms: a) by activating lymphopoiesis synergistically with Pu.1 [66], thus promoting B-cell progenitors survival [77,78]; b) by repressing myelopoiesis, through the engagement of Hdac7 on myeloid gene regulatory regions [75,79]. A repressive influence of Mef2c can also favor the differentiation of B cells over T cells [80]. Here, Mef2c seems to exert a repressive function, by binding Malm1 and competing with Notch1 signaling, which promotes T cell differentiation [68].

Although within the hematopoietic lineage MEF2C might be considered as a B-cell specific transcription factor, its deregulated expression can contribute to malignancies of T cells, e.g. acute lymphoblastic leukemia (T-ALL), and of myeloid cells, e.g. acute myeloid leukemia (AML). T-ALL is elicited by chromosomal alterations that cause the activation of different oncogenes. The outcome is a block of T cell

differentiation and the development of leukemogenesis. T-ALL subgroups are classified by their oncogenes [81]. In T-ALL, high expression of NKX2-1/NKX2-2 or MEF2C typifies two clusters, which comprise 20% of all T-ALL cases. The MEF2C cluster is marked by a very immature immunophenotype [82]. This subtype was named early T cell precursor ALL. In leukemia cells MEF2C can be aberrantly activated as a result of cardiac homeobox gene NKX2-5 expression or of genomic deletions in the MEF2C promoter region. This deletion possibly abrogates a binding site for STAT5, critical to exert a repressive influence [82–84]. Other studies have unveiled further mechanisms responsible for MEF2C de-regulation [84]. The leukemogenic activity of MEF2C could stem from uncontrolled pro-survival signaling. Repressing *NR4A1/NUR77* expression, possibly by binding class IIa HDACs, could be a mechanism. Alternative strategies exploited by MEF2C to sustain T cell survival could involve the expression of *BCL2* family members [83,85].

MEF2C has also been reported to be a driver oncogene in AML. Indirect evidence of a mitogenic role of MEF2C in the myeloid lineage, first arose from the observation that miR-223 null mice are characterized by a marked neutrophilia caused by the expansion of granulocyte progenitors. This phenotype was proved being mainly due to elevated *Mef2c* levels [69]. This finding is consistent with the fact that MEF2C is strongly up-regulated during the commitment of granulocyte-monocyte progenitors into leukemic stem cells (LSCs), as a consequence of MLL-AF9 chimera overexpression [86]. The rise in MEF2C is necessary but not sufficient for the maintenance of stemness and the tumorigenicity characteristics of LSCs [86]. Knock-out of *Mef2c* in MLL/ENL mice confirmed that it is dispensable for leukemogenesis and for the establishment of LSCs. Instead, Mef2c shortens the latency of the disease and increases the infiltration of leukemic cells into the spleen, by rising the homing and motility of LSCs [87]. Another layer of complexity concerns MEF2C phosphorylation. MEF2C phosphorylation at serine 222 marks chemoresistance in AML patients. Furthermore, Mef2c S222A/S222A knock-in mice were resistant to leukemogenesis induced by MLL-AF9. These findings point to a dominant tumor suppressive role of MEF2C when not phosphorylated at serine 222, and a contribution to chemoresistance when phosphorylated [88]. This hypothesis is consistent with the mild phenotype of the KO described above.

AML cells were also found to be addicted to a salt-inducible kinase (SIK) family member, SIK3, in large part due to its MEF2C-preserving function [89]. In fact, AML cells with down-regulated SIK3 and/or LKB1 showed an increase in the binding of HDAC4 to MEF2C on some genomic enhancers [89]. In this context the authors proposed an anti-proliferative effect of HDAC4 through the repression of the MEF2 pro-oncogenic and pro-proliferative properties [86]. Curiously, as discussed below for MEF2D-fusions, HDAC9 is among the genes regulated by SIK3-MEF2C [89]. Whether HDAC9 up-regulation represents an operative feed-back mechanism to buffer some MEF2C functions and how much of this buffering could be required for cancer fitness is presently unknown. Differently from what is reported in 293 cells [90], in AML cells the kinase activity of SIK3 was required to export HDAC4 to the cytoplasm and trigger MEF2-dependent transcription [89].

The leukemia genes under MEF2C orchestration are still to be defined in detail. In murine hematopoietic precursors, Mef2c drives the up-regulation of *Socs2* that limits unrestricted myelopoietic response and the exhaustion of long-term HSC [91]. Mef2c was found to control the expression of metalloproteinases and various chemokines [87]. These MEF2-target genes were also identified by other studies and indicate the pervasive MEF2-signature [9,51,92–95]. Whether the secretory repertoire activated by MEF2C is directly involved in the regulation/functionality of the stem compartment remains to be investigated. Even less explored is the contribution of MEF2C to the metabolic reprogramming of leukemic cells. It was observed that MEF2 sustained the expression of oxidative phosphorylation genes in normal Foxp3$^+$ T-regulatory cells [96]. This finding was also seen in leukemic cells [97] and MEF2C was shown to trigger a robust anti-oxidative response [97].

Additional data supporting a pro-oncogenic function of MEF2C were obtained in some solid tumors, though data are somewhat fragmentary and require confirmation. In colorectal cancer, MEF2C was found to be up-regulated during disease progression [98]. In breast cancer, MEF2C expression was associated with tumor invasion [99]. MEF2C was found to be up-regulated in hepatocarcinomas [46,100,101]. In this tumor MEF2C displays both oncogenic and tumor suppressive properties. It mediates migration/invasion and VEGF-dependent angiogenesis on one hand, whereas on the other hand it negatively affect cell proliferation, by blocking β-catenin nuclear translocation and WNT signaling [100]. The injection in mice of hepatocarcinoma cells overexpressing MEF2C gave rise to slowly proliferative but highly malignant tumors [100]. An intronic SNP in MEF2C that could affect its splicing was recently associated with VEGF levels in a genome-wide association study on 16,112 individuals. This association confirmed the pro-angiogenic role of MEF2C [102]. A link with β-catenin was also evoked in breast cancer. Here tumor-associated macrophages release exosomes containing high levels of miR-223 that promotes the invasion of breast cancer cells. As MEF2C is a target of miR-223, increased cell invasiveness could be due to the MEF2-dependent control of β-catenin nuclear accumulation [103]. A different scenario has been proposed in Hodgkin lymphoma, where MEF2C is down-regulated and, as a consequence, its inhibitory influence on the homebox gene SIX1 was constrained. SIX1 is aberrantly activated in 12% of patients and this alteration supports lymphomagenesis via deregulation of developmental genes [104].

The double nature of MEF2C is exemplified in rhabdomyosarcomas (RMS), the most common soft tissue sarcoma in children. Pediatric RMS can be subdivided into two major histological subtypes: the embryonal (ERMS) and the alveolar (ARMS) tumors [105]. The two major splicing variants of MEF2C are derived by the mutually exclusive exons α1/α2, which generate the ubiquitously expressed MEF2Cα1 and the muscle-specific MEF2Cα2 isoforms (Fig. 2 and Table 2). In RMS cells, the ratio of α2/α1 is dramatically diminished compared with normal myoblasts. MEF2Cα1 interacts more strongly with HDAC5, thus recruiting the deacetylase to myogenic gene promoters to repress the expression of muscle-specific genes. Reintroduction of the MEF2Cα2 isoform fosters the differentiation of RMS cells [106]. Whether the alternative splicing is a cause or a consequence of RMS development is a fundamental question, especially since changes in MEF2C splicing have also been documented in other tumors [6,9,106].

In addition to the activation splicing mechanism, the down-regulation of MEF2C levels has been reported in RMS. A murine model of

Table 2
MEF2 splicing in cancer

Gene	Aberrant splicing event	Cancer type	Effect	Ref.
MEF2B	Isoform A is most commonly expressed (91.7%), but some patients have truncations that resemble the B isoform	Diffuse Large B-Cell Lymphoma (DLBCL)	The truncated isoforms, similarly to B isoform, show impaired transcriptional activity	[6]
MEF2C	Increased levels of α1, decreased levels of α2	Rhabdomyosarcoma (RMS)	HDAC5 interacts strongly with α1 keeping off the transcription of myogenic genes	[106]
MEF2D	Increased levels of α1, decreased levels of α2	Leiomyosarcoma (LMS)	Aggressive LMS cells express high levels of α1 isoform which interacts strongly with HDAC9 keeping off transcription	[9]

RMS indicates that neoplastic cells do not arise from differentiated Mef2c-expressing cells, but from mesodermal immature progenitors [107]. The defect of MEF2C expression in RMS initiating cells could be caused by the loss of MYOD binding in its promoter and regulative regions [108]. Down-modulation of MEF2C in RMS was confirmed by a second study. In a zebrafish model of ERMS and in human ERMS cell lines, the activation of NOTCH1 triggered the up-regulation of *SNAIL (SNAI1)*, which blocks muscle differentiation, thus keeping ERMS cells undifferentiated. Most of this dedifferentiation is due to the repression of MEF2C at both transcriptional and activation levels. Importantly, suppression of MEF2C was required to maintain the self-renewal capacity of ERMS cells [109]. The cross-talk between MEF2C and NOTCH1 pathways was first described in myoblasts; however further studies are needed in order to clarify whether these pathways synergize or antagonize [110–112].

Another example of MEF2C antiproliferative signalling was observed in vascular smooth muscle cells whereby the over-expression of miR-223 increases their proliferation and migration, at least in part through the repression of MEF2C and of its target *RHOB* [113]. miR-223 also plays a tumor suppressive role in mycosis fungoides/cutaneous T-cell lymphoma by downregulating *E2F1, MEF2C* and *TOX* and blocking the progression of the disease [114]. However, in myeloid cells, as noted earlier, miR-223 is repressed in chronic myeloid leukemia through a BCR/ABL mediated mechanism and the consequent up-regulation of Mef2c contributes to disease development [69,114]. In conclusion, the complex effects of MEF2C, involving both pro-oncogenic and tumor suppressive actions, likely stem from, or are strongly influenced, by the specific cellular context in which it operates.

2.4. MEF2D

The initial generation of *Mef2d*-null mice did not result in any overt phenotype; mice were viable, showed no overt histological abnormalities, and under normal conditions had normal lifespan, behaviour, weight and fertility [115]. However, cardiac hypertrophy and fibrosis induced by pressure overload were suppressed in *Mef2d-/-* mice, and cardiac over-expression of *Mef2d* caused severe cardiomyopathy and fibrosis [115]. Moreover, *Mef2d* has a non-redundant protective role in cerebellum [116]. Compared to wild-type controls, cerebellar granular cells from *Mef2d-/-* mice manifest increased susceptibility to DNA damage induced by etoposide or irradiation. Mechanistically, DNA damage activates Atm, which phosphorylates and activates Mef2d, promoting expression of the pro-survival gene *Bcl-xL*. *Mef2d* deletion prevents the expression of *Bcl-xL* and increases cell-death upon DNA damage [116]. In *Mef2c+/-* heterozygous mice, the absence of one allele of *Mef2d* exacerbated bone defects [117]. In a second, tissue-specific *Mef2d* knock-out mouse model, a key role of this family member was observed in the retina; here *Mef2d* was necessary for the survival of photoreceptor cells [31,118].

The first evidence of the involvement of MEF2D in the transformation process arose from studies of childhood pre-B acute lymphoblastic leukemia (ALL). In ALL, the introns of MEF2D and DAZAP1 show infrequent chromosomal translocations t(1;19)(q23;p1) [119–121], generate both MEF2D-DAZAP1 and DAZAP1-MEF2D transcripts, and give rise to in-frame fusions (Fig. 3). MEF2D-DAZAP1, but not DAZAP1-MEF2D, can interact with MEF2D and HDAC4. DAZAP1 is a RNA binding protein involved in mRNA splicing regulation and is characterized by two N-terminus RRM (RNA-recognition motif) and a low complexity C-terminal domain (CTD) proline-rich [122]. Both chimeric proteins promoted cell proliferation when ectopically expressed [119]. Curiously, while DAZAP1/MEF2D loses the capability to bind the MEF2 consensus-site on DNA, the fusion of DAZAP1 to the C-terminus of MEF2D increases the transcriptional capabilities of MEF2D [121]. Despite opposite effects in terms of MEF2 activation, the two chimeras display similar oncogenic properties in NIH-3T3 cells and can cooperate [120]. A difference was reported for the ability to protect from apoptosis; this task was afforded only by MEF2D-DAZAP1 [120].

More recent studies, aimed to explore the oncogenic mechanisms responsible for ALL in children, adolescent and adults, provided further evidences of MEF2D alterations and in-frame fusions that could impact its activity (Fig. 3 and Table 3). In the first study, a large cohort of B-ALL patients (92 adult and 111 pediatric cases) underwent genomic characterization by NGS. 29 new fusions were identified; fusions involving MEF2D were among the most frequent, affecting 6.7% of adults and 3.4% of pediatric patients. The MEF2D-BCL9 and MEF2D-HNRNPUL1 fusions upregulated HDAC9, which could cooperate with the fused MEF2D to repress genes essential for B-lineage differentiation, like *RAG1* [123]. Suzuki and co-authors found MEF2D-BCL9 translocations in children with relapsed or primary refractory B-ALL. These patients were relatively older in age (between 10 and 13 years), had a worse prognosis and were resistant to chemotherapy. Their leukemic blasts mimicked morphologically mature B-cell leukaemia with markedly high expression of HDAC9. Interestingly MEF2D-BCL9 leukemic cells were resistant to dexamethasone but responsive to HDAC inhibitors [124].

The co-existence of high levels of HDAC9 and MEF2D is an apparent and unresolved paradox. MEF2D binds the promoter of *HDAC9* and favours its transcription. In physiological contexts it represents a negative feedback mechanism that assists the down-modulation of MEF2D activities, as a consequence of HDAC9-dependent repression [125]. In a physiological context this repression should also affect HDAC9 expression, since HDAC9 is a MEF2-target gene. However, this circuitry is altered in tumors, allowing high levels of both MEF2D and HDAC9 expression (Fig. 4).

These results were confirmed in a larger cohort of 560 ALL cases [126]. Some, 42 out of 560 cases, revealed fusions and rearrangements between MEF2D and BCL9, CSF1R, DAZAP1, HNRNPUL1, SS18 or FOXJ2. All fusions engaged the MADS/MEF2 domains of MEF2D, whereas TAD1 was only partially retained and TAD2 at the carboxy-terminus was lost (Fig. 3). However, when tested for transactivation capacity on an artificial MEF2 reporter, MEF2D-BCL9 and MEF2D-HNRPULL1 fusions showed strong transcriptional activities [126]. Tumors with MEF2D fusions were characterized by similar gene expression profiles and repression of WNT signalling. Here again, the MEF2-target gene *HDAC9* was highly expressed while *MEF2C* was strongly repressed and leukemic cells were vulnerable to HDAC inhibitors [123,126].

In an RNA-seq analysis of Philadelphia chromosome (Ph)-negative ALL specimens from adolescent and young adults (n = 73), 7% of cases showed MEF2D translocations. The prognosis of these patients was worse compared to patients bearing other fusions, and similar to that of patients with Ph-like ALL. As with the other study, MEF2D-BCL9 and MEF2D-HNRNPUL1 fusions were recurrently found in the cohort. The chimeric MEF2D showed enhanced transcriptional activity and the ability to transform NIH-3T3 cells. Expression of MEF2D-BCL9 in pro-B cells triggered leukemia with low penetrance (~50% of mice developed leukemia during the observation period of 290 days). MEF2D-BCL9 failed to confer a growth advantage on pro-B cells *in vivo*, but both MEF2D chimeras hampered B cell differentiation beyond the pro-B cell stage [127]. Similarly to the MEF2D-BCL9 fusion, the MEF2D-S18 chimera was found to arrest the differentiation of B cells at the pre-pro B cells. This block was marked by the repression of some B-cell differentiation genes, like *RAG1*, and by the up-regulation of *HDAC9* transcription[128].

Lilljebjörn and colleagues, also using again RNA-seq of a primary pre B-ALL, identified a novel in-frame MEF2D/CSF1R fusion between the N-terminus of MEF2D and the tyrosine kinase domain of CSF1R. It is plausible that dimerization through the MADS domain generated a constitutive active TK, which renders the leukemic cells susceptible to imatinib treatment [129].

Dysregulations of the MEF2-HDAC9 axis are not limited to ALL. The chromatin remodelling multiproteins complexes SWI/SNF are

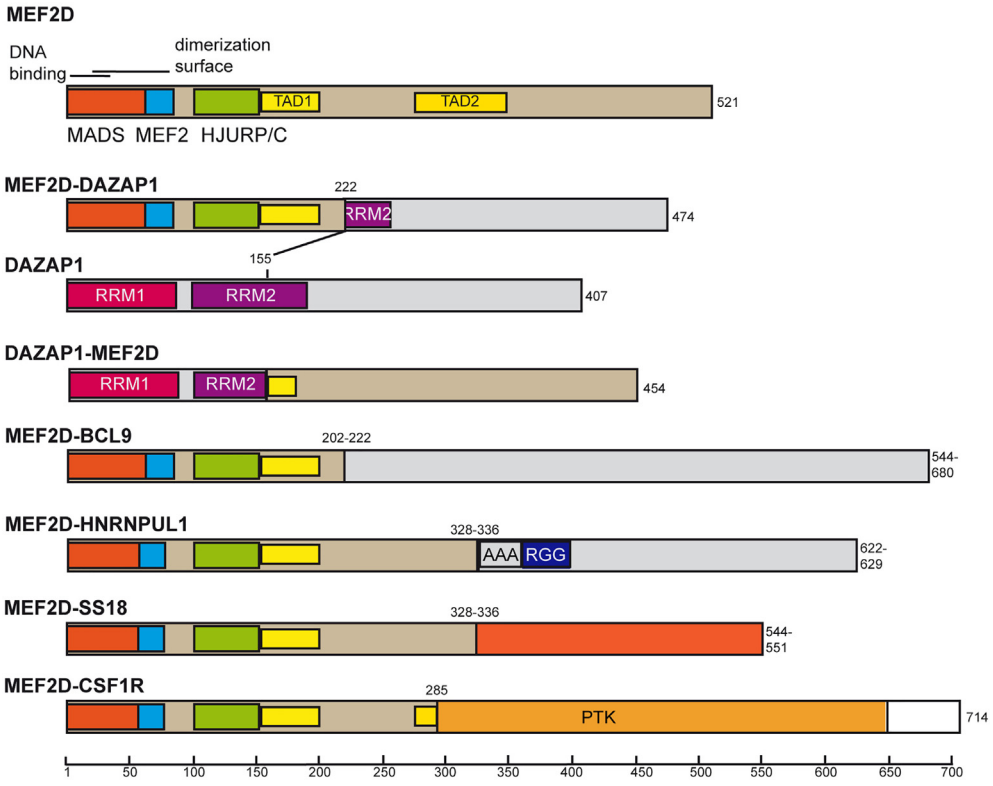

Fig. 3. MEF2D fusions in cancer.
Schematic representations of important MEF2D in-frame fusions found in malignant cells. The relevant domains of MEF2D and of the chimera are indicated. TADs are in MEF2C TAD1: aa 143-174 and TAD2: aa 247-327 and in MEF2D TAD1: aa 143-184 and TAD2: aa 261-341.

Table 3
MEF2D fusions in cancer.

MEF2 fusions	Disease	Cases	Tot.	%	Functions	Ref.
MEF2D-DAZAP1	B-ALL	1	376	0,3	hyperactive (luciferase on HDAC9 promoter), but it represses RAG1; bad prognosis	[123]
MEF2D-DAZAP1	B-ALL	1	560	0,2	not investigated	[126]
MEF2D-BCL9	B-ALL	8	376	2,1	hyperactive (luciferase on HDAC9 promoter), but it represses RAG1; bad prognosis	[123]
MEF2D-BCL9	B-ALL	4	55	7,3	increased transcription of HDAC9	[124]
MEF2D-BCL9	B-ALL	16	560	2,9	hyperactive (luciferase on 3xMEF2 reporter), but it represses MEF2C; bad prognosis	[126]
MEF2D-BCL9	AYA-ALL	2	149	1,3	hyperactive (luciferase on artificial MEF2 reporter)	[126]
MEF2D-HNRNPUL1	B-ALL	8	376	2,1	hyperactive (luciferase on HDAC9 promoter), but it represses RAG1; bad prognosis	[126]
MEF2D-HNRNPUL1	B-ALL	3	560	0,5	hyperactive (luciferase on 3xMEF2 reporter), but it represses MEF2C; bad prognosis	[126]
MEF2D-HNRNPUL1	AYA-ALL	3	149	2	hyperactive (luciferase on artificial MEF2 reporter)	[126]
MEF2D-SS18	B-ALL	2	376	0,5	hyperactive (luciferase on HDAC9 promoter), but it represses RAG1	[126]
MEF2D-SS18	B-ALL	1	560	0,2	not investigated	[126]
MEF2D-CSF1R	B-ALL	1	560	0,2	increased TK activity of CSF1R?	[126, 129]
MEF2D-FOXJ2	B-ALL	1	560	0,2	not investigated	[126]

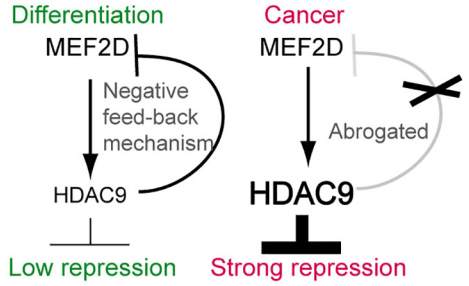

Fig. 4. Schematic representation.
Overview of the feedback mechanism acting on the promoter of HDAC9 in normal but not cancer cells.

important regulators of chromatin status and gene expression in several contexts [130]. Alterations in these complexes are frequently found in cancer. For example, in highly aggressive malignant rhabdoid tumors that affect young children, a critical perturbation involves the tumor suppressor SMARCB1/BAF47[131]. Expression of Brahma (BRM) or BRM-related gene 1 (BRG1), which encodes for the subunit with ATPase activity, is lost in 15% to 40% of many primary solid tumors [132,133]. Frequently this loss is triggered by epigenetic mechanisms [133,134]. In lung cancer cell lines, MEF2D and HDAC9 supervise BRM silencing [135,136]. Moreover, HDAC9 was overexpressed in rhabdoid cancer cell lines and in primary BRM-deficient rhabdoid tumors. Both MEF2D and HDAC9 bound *BRM* promoter close to two insertional polymorphisms that create two MEF2 binding sites (BRM-741:TTAAA and BRM-1321:TATTTTT), which contribute to *BRM* silencing[136]. These results were confirmed in non-small cell lung cancer (NSCLC) and the decrease in BRM expression is associated with worse overall survival

[137]. Under these conditions, regeneration of the MEF2D transcriptional activity by inhibiting HDAC9 promises to be a fruitful strategy to restore BRM expression and inhibit. A similar mechanism is operative in oral squamous cell carcinoma [138] and in high-grade leiomyosarcoma [9]; in both cases, high levels of HDAC9 are required to repress MEF2D, selectively on the promoters of a subset of genes that probably antagonize cell transformation.

In hepatocellular carcinoma (HCC) high levels of MEF2D are associated with poor prognosis [139] and these high levels could be related to the reduced expression of miR-122. In HCC cells, MEF2D sustains cell proliferation and is required for tumorigenicity [139]. Additional mechanisms augmenting MEF2D expression could involve the activity of Pokemon, a transcription factor with proto-oncogenic activity constituted by an N-terminal POZ/BTB domain and a C-terminal kruppel-type zinc finger domain [140]. Curiously, in HCC cells, MEF2D binds the promoters of genes (*RPRM*, *GADD45A*, *GADD45B* and *CDKN1A*) involved in the negative regulation of G2/M transition, and in complex with an unknown co-repressor keeps them silenced. This action promotes proliferation and mitosis [139]. It is not yet known if this MEF2 co-repressor is a class IIa HDAC [27,141,142], although these genes are frequently up-regulated together with MEF2C and MEF2D in HCC samples [46].

As observed for other family members, MEF2D can influence angiogenesis and EMT. In hepatocytes, TGF-β treatment activates the PI3K/AKT pathway and induces EMT [101]. As a consequence of this activation, levels of MEF2A, C and D are increased. MEF2s promote EMT and invasiveness and induce the expression of TGF-β that sustains the process, contributing to a feed-forward circuit [101]. Moreover, MEF2D is reported to control transcription of the EMT driver gene *ZEB1,* by facilitating histone acetylation at the *ZEB1* promoter [143,144]

Several reports have pointed to pro-proliferative/pro-oncogenic functions of MEF2D in different cellular models of solid tumors [9,145–150]. However, MEF2D also has tumor suppressive properties, as shown for rhabdomyosarcomas, low grade uterine leiomyosarcomas [9,151], and breast cancers [142]. In these tumors, MEF2D could be critical to cell cycle progression, as confirmed by knock-down experiments in cardiac myocytes [152] and fibroblasts [27]. In a model of embryonal rhabdomyosarcoma induced by YAP1, the expression of MEF2C and MEF2D is repressed. YAP1 induces the expression of Twist1 and Cabin1, two MEF2 repressors, and redirects residual MEF2C and D activities away from the promoters of myogenic differentiation genes [153]. Curiously, in all these cases MEF2D was found to promote the expression of the cell-cycle genes *CDKN1A* and *GADD45A* that were found to be repressed in HCC cells [139].

3. Concluding remarks

Much of the data concerning the tumor suppressive or pro-oncogenic functions of MEF2 TFs are based on gain or loss-off-function experiments. Less frequently the binding of MEF2 to their partners was investigated in parallel, as well as the compensatory intervention of a paralogue [154,155]. Hence, whether the origin of their oncogenic activities arises from the assembly of MEF2 proteins into transcriptional activator or repressor complexes is still an open question.

The list of tumors in which MEF2 TFs exhibit oncogenic or tumor suppressive functions is extensive and points to the need for further analyses of the molecular biology and biochemistry of these TFs. In the future, the dissection of activating or inhibitory signaling pathways converging on MEF2s in different cancer types will likely shed light on the still cryptic role of MEF2s in cancer and their potential importance as therapeutic targets.

Conflict of interest

Authors declared no conflict of interest.

Authors' contribution

C.B. conceived the idea for the review. E.D.G., W. W. H. and C.B. wrote the article.

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