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Review

Involvement of Mediator complex in malignancy

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ABSTRACT

Mediator complex (MED) is an evolutionarily conserved multiprotein, fundamental for growth and survival of all cells. In eukaryotes, the mRNA transcription is dependent on RNA polymerase II that is associated to various molecules like general transcription factors, MED subunits and chromatin regulators. To date, transcriptional machinery dysfunction has been shown to elicit broad effects on cell proliferation, development, differentiation, and pathologic disease induction, including cancer. Indeed, in malignant cells, the improper activation of specific genes is usually ascribed to aberrant transcription machinery. Here, we focus our attention on the correlation of MED subunits with carcinogenesis. To date, many subunits are mutated or display altered expression in human cancers. Particularly, the role of MED1, MED28, MED12, CDK8 and Cyclin C in cancer is well documented, although several studies have recently reported a possible association of other subunits with malignancy. Definitely, a major comprehension of the involvement of the whole complex in cancer may lead to the identification of MED subunits as novel diagnostic/prognostic tumour markers to be used in combination with imaging technique in clinical oncology, and to develop novel anti-cancer targets for molecular-targeted therapy.

Contents

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1. Introduction

Transcriptional regulation is one of the most important steps in the control of cell identity, growth, differentiation and development. Many signalling pathways, which control these processes, ultimately target the core transcription machinery. For protein coding genes, this apparatus consists of RNA polymerase II (Pol II) and the general transcription factors (TFs) TFIIA, TFIIB, TFIID, TFIIE, TFIIF and TFIIH that contact Mediator complex (MED). MED is the essential coactivator/activator complex acting as a bridge between transcription factors bound at the upstream regulatory elements and the transcription machinery. Crucially, the pre-initiation complex (PIC) consists of MED, Pol II and TFs [1], with MED as a central scaffold within the PIC and regulator of Pol II activity [2–4]. It strongly interacts with Pol II, changes its conformation and influences the transcription initiation process as well as other transcription steps, although the whole involved molecular mechanisms have not yet fully elucidated [5,6]. At present, mammalian MED is composed of at least 31 subunits that are arranged in four structurally distinct modules, head, middle and tail modules representing the main complex core, and kinase module (CDK module), variably associated with the core (Fig. 1) [1,3,7–10]. Structural and biochemical studies have recently revealed the existence of further sub-modules [8,11]. The head and middle modules, containing CDK19 kinase, are known to interact directly with Pol II, whereas the tail module interacts with gene-specific regulatory proteins [2,4,7,8]. In particular, the head module interacts with the Pol II subunit Rpb3 through the MED17 subunit [12,13] whereas MED11 and MED22, other two important head subunits, interact with the TFIIH subunit Rad3 [14]. Finally, crystal structure

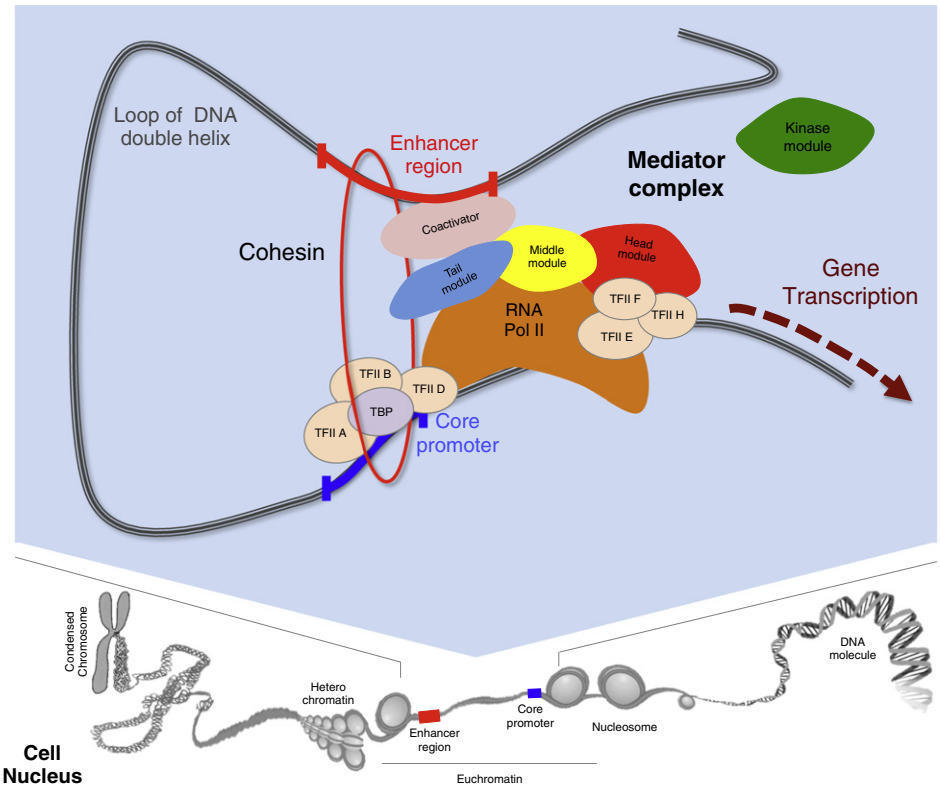

Fig. 1. MED complex involvement in cell transcriptional regulation mechanism. Biochemical and structural studies reveal that MED tightly binds Pol II enzyme thus starting pre-initiation complex formation. Transcriptional machinery is composed by several components: activator proteins, general transcription factors (TFIIA, TFIIB, TFIID, TBP, TFIIE, TFIIF, and TFIIH), Pol II and cohesin protein. Altogether these factors are assembled in a DNA loop where the start and the end are represented by enhancer region/core promoter. Generally, when the kinase module binds to the Mediator core, Pol II is released and the transcription mechanism is impeded. The Mediator modules head, middle, tail, and kinase are coloured red, yellow, blue, and green, respectively. In the lower panel a scheme depicting the structure of mammalian chromatin is illustrated.

of cyclin C subunit implied a model of the CDK8/cyclin C pair with two regions in the interface having apparently distinct roles for CDK8 function [15].

Our knowledge of Mediator assembly and its role in regulating transcription have not yet been fully determined even though studies in this field are constantly increasing in spite of the large size of the complex and the complicate network of interactions between MED and the numerous participants to the transcription. Initially, MED was considered to act predominantly during the assembling of PIC, also essential for basal transcription enhancement [8]. Then, several reports indicated that MED can also act after pol II recruitment by modulating the function of a preformed PIC thus substituting the acronym PIC with the more general term of PEC (pre-elongation complex) [3,5,8]. This model assumes that once MED complex interacts with the appropriate activators, the assembly of the complex occurs together with a reorganization of MED that leads to the loss of the kinase module. Afterwards, the transcription can continue with the elongation phase, or Pol II may be stalled until proper conditions change this stalled state into an elongation state leading to transcription. Importantly, both these states are reversible and controlled by MED [3,8].

An important issue in the MED function is the role of the regulatory CDK module. This structure was thought to generally act as a negative regulator of transcription, although several reports have been demonstrated that could also contribute to transcription activation [16–18]. CDK8 module can repress transcription by mechanisms that are not fully elucidated. Previously, CDK8 kinase activity was considered a requirement for CDK repressive function [15]. More recently, a study demonstrated that MED12 and MED13 are the critical subunits for CDK module-dependent repression, rather than CDK8 kinase activity [19]. Moreover, the same study showed that CDK module could also repress re-initiation events [19]. Finally, other mechanisms of kinase-independent transcriptional repression by the CDK module have been hypothesized [8].

Additionally, while CDK8 role has been studied extensively, little is known about CDK19 role in MED complex. This kinase subunit was identified (and named CDK11/CDK8-L) in the human MED complex using multidimensional protein identification [20]. Despite its sequence similarity with human CDK8, siRNA analyses suggest that CDK19 is not just a redundant CDK8 paralogue, but rather it may have distinct, perhaps opposite roles from CDK8 in transcriptional regulation.

MED can connect proximal or distal cis-regulatory elements, like enhancers, with promoters through the recruitment of cohesin that form rings connecting two regulatory DNA segments [21] (Fig. 1). Noteworthy, depletion of MED and cohesion subunits from embryonic stem cells resulted in altered differentiation suggesting also a role of this mechanism in pluripotency maintenance [21,22].

More recently, novel roles of MED have been emerging. For instance, MED has been involved also in the transcription of a large number of intergenic loci to generate noncoding RNAs [23]. Moreover, MED has been shown to interact with the RNA binding protein hnRNPL and regulate alternative mRNA processing via its MED23 subunit thus expanding MED function beyond transcriptional control [24].

Since MED complex has an important role in the transcription of all eukaryotic genes, the alteration of its function and/or its components may have important consequences as well as may trigger several disease types, also including cancer.

2. Mediator complex in malignancy

Carcinogenesis is a multistep process that involves alterations in various genes and cellular pathways. The altered patterns of gene expression associated with malignant transformation have generally

Table 1
Cancer specific alterations of Mediator subunits: oncologic disease classification.

Cancer type	Gene symbol (alternative name)	Molecular alteration	Putative cause	Putative effect	Reference
Bladder cancer	MED19 (LCMR1; DT2P1G7)	Up-regulated		Increase of BMP-2 protein in the initial cancer invasion and anchoring in the bone tissue	[82,83]
Brain cancer	MED13 (ARC250; KIAA0593; THRAP1; TRAP240; DRIP250)	Editing pattern altered	Alteration of A-to-I editing pattern. Alu sequences in brain tumours undergo less editing compared to normal brains within the gene encoding for MED13.		[66]
Breast cancer	MED1 (ARC205; CRSP1; CRSP200; DRIP205; DRIP230; PBP; PPARBP; PPARGBP; RB18A; TRAP220; TRIP2)	Up-regulated		Transcriptional co-activator for HER2	[31,33,34]
	MED5 (MED24; ARC100; CRSP4; DRIP100; KIAA0130; THRAP4; TRAP100)	Up-regulated	Amplified at 17q11-21 in BT474 cells		[34,48]
	MED12 (OKS; FGS1; HOPA; OPA1; OHDOX; ARC240; CAGH45; MED12S; TNRC11; TRAP230)			Transcriptional co-activator for the nuclear hormone receptor ERα	[21,51]
	MED13	Amplified	Amplification of MED13 gene (17q23)		[68]
	MED14 (ARC150; CRSP2; CXorf4; DRIP150; EXLM1; RGR1; TRAP170)			Ligand-dependent ERα-mediated transactivation in a NR box (LXXLL motifs)-independent mode	[71,72]
	MED15 (ARC105; CTG7A; PCQAP; TIG1; TNRC7)			Cofactor for TGFβ/Erk phosphorylation signalling	[77]
	MED19	Up-regulated			[84]
	MED23 (RP5-914 N13.2; ARC130; CRSP130; CRSP133; CRSP3; DRIP130; MRT18; SUR-2; SUR2)			Specific link with the transactivation domain of ESX which activates the Her2 gene	[102]
	MED28 (EG1; magicin; 1500003D12Rik; FKSG20)	Up-regulated		Correlation with EGF by up-regulating the expression of MMP9; correlation with MMP2 and MEK1	[109–111]
	MED30 (THRAP6; TRAP25)	Up-regulated			[34]
Cervical cancer	MED4 (ARC36; DRIP36; VDRIP)	Down-regulated		Transcriptional activator for anti-cancer genes, like the vitamin D receptor	[44,45]
Colon cancer	MED12	Mutated	Two somatic mutations (Gly44Cys, Ala67Val) in the exon 2 of MED12 gene	Transcriptional activator for TGF-βR2 signalling	[58,61,62]
	MED28	Up-regulated			[112]
	CDK8 (K35)	Up-regulated		Direct transduction of Wnt/β-catenin signalling; indirect activation of β-catenin-dependent transcription by inhibiting E2F1	[59,124–127]
	Cyclin C (CycC; CCNC)	Up-regulated			[134]
	MED19	Up-regulated			[85]
Gastric cancer	MED19	Up-regulated			[86]
	MED23	Mutated			[104]
	Cyclin C	Up-/Down-regulated			[132,136]
Hepatocellular carcinoma	MED19	Up-regulated			[87]
	Cyclin C	Up-regulated		Link with Wnt/β-catenin signalling	[130,131,136]
Leukaemia	Cyclin C	Deleted	Deletion of t(2;6)(p21; q15) genomic region		[135]

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Table 1 (*continued*)

Cancer type	Gene symbol (alternative name)	Molecular alteration	Putative cause	Putative effect	Reference
Lung cancer	MED1	Down-regulated		Interaction with the nuclear hormone receptor ERβ; expression reduction of dapk1 gene	[38,39]
	MED12	Down-regulated		MEK and ERK signalling reduction; TGF-βR2 protein expression reduction	[61]
	MED19	Up-regulated			[88–90]
	MED23	Up-regulated		Link with Ras signalling	[105]
Melanoma	MED1	Up-regulated			[40]
	MED23	Deleted		Regulator of KiSS-1 transactivation	[69,106,108]
	CDK8	Up-regulated	Association with the loss of a histone variant macroH2A		[123,129]
Myeloma	CDK19 (CDK11; CDC2L6; bA346C16.4)	Altered			[113]
Osteosarcoma	MED19	Up-regulated			[91]
	CDK19	Up-regulated			[115]
	Cyclin C	Down-regulated			[125,137]
Ovarian cancer	MED19	Up-regulated			[92]
Pancreatic cancer	MED2 (MED29; IXL)	Up-/Down-regulated	Chromosomal 19q13 gain		[41,42]
	MED19	Up-regulated			[93]
Pheochromocytoma	MED23	Down-regulated			[107]
Prostate cancer	MED1	Up-regulated		Transcriptional co-activator for the nuclear hormone receptor AR	[35–37]
	MED5	Up-regulated		Transcriptional co-regulator for the nuclear hormone receptor AR	[35]
	MED12	Mutated	Mutations in MED12 gene		[52]
	MED14	Up-regulated		Transcriptional co-regulator for the nuclear hormone receptor AR	[35]
	MED15	Hypermethylated			[80,81]
	MED17 (ARC77; CRSP6; DRIP77; DRIP80; TRAP80)	Up-regulated			[37]
	MED19	Up-regulated		Modulation of Bid and Caspase7; Transcriptional co-regulator for AR	[94,95]
	MED28	Up-regulated			[112]
Retinoblastoma	MED4	Down-regulated	Homozygous loss alters the vitamin D signalling		[45,47]
	MED13L (A1L469, KIAA1025, PROSIT240, Q68DN4, Q71F56, Q9H8C0, Q9NSY9, Q9UFD8, Q9UPX5, THRAP2, TRAP240L)			Involvement in the Rb/E2F pathway	[70]
Tongue cancer	MED19	Up-regulated			[96]
Uterine sarcomas	MED12	Mutated	Somatic mutations of MED12 gene in uterine SMTs; heterozygous mutations in intron 1 and exon 2 in LMs, STUMPs, and uterine LMSs		[54–58]

been attributed to mutations in genes encoding cellular signalling molecules such as kinases, growth factor receptors and other intracellular molecules. Yet, rearrangements or sequence specific alterations in DNA binding motifs for protein modulators are also required for the malignant transformation of several cell types [25]. In addition to genomic, the epigenetic changes may also cause the uncontrolled cell growth and tumour formation [25,26]. Recently, cancer genome sequencing studies have revealed that mutations/alterations arise also in the RNA transcription machinery components, also containing MED subunits. However, the detailed role of these modifications and the effects that they produce to cancer development are still mostly unknown. Table 1 illustrates cancer specific MED alterations, together with putative causes and produced effects, whereby known. For an easier reading, Table 2 provides a list of MED alterations in tumours by subunit,

as described in the text below. For instance, certain MED subunits modulate distinct gene expression pathways, known to be involved in carcinogenesis, through interactions with nuclear hormone receptors (NRs) in a ligand-dependent manner [27–30]. Importantly, these MEDs/NRs interactions facilitate the transcription initiation of NR target genes [27–30]. However, other mechanisms may be involved

Table 2
Cancer specific alterations of Mediator subunits: MED component classification.

Gene symbol (Alternative name)	Cancer type	Molecular alteration	Putative cause	Putative effect	Reference
MED1 (ARC205; CRSP1; CRSP200; DRIP205; DRIP230; PBP; PPARBP; PPARGBP; RB18A; TRAP220; TRIP2)	Breast cancer	Up–regulated		Transcriptional co–activator for HER2	[31,32,33]
	Lung cancer	Down–regulated		Interaction with the nuclear hormone receptor ERβ; expression reduction of dapk1 gene	[38,39]
	Melanoma	Up–regulated			[40]
	Prostate cancer	Up–regulated		Transcriptional co–activator for the nuclear hormone receptor AR	[35,36,37]
MED2 (MED29; IXL)	Pancreatic cancer	Up–/Down–regulated	Chromosomal 19q13 gain		[41,42]
MED4 (ARC36; DRIP36; VDRIP)	Cervical cancer	Down–regulated		Transcriptional activator for anti–cancer genes, like the vitamin D receptor	[44,45]
	Retinoblastoma	Down–regulated	Homozygous loss alters the vitamin D signalling		[45,47]
MED5 (MED24; ARC100; CRSP4; DRIP100; KIAA0130; THRAP4; TRAP100)	Breast cancer	Up–regulated	Amplified at 17q11–21 in BT474 cells		[34,48]
	Prostate cancer	Up–regulated		Transcriptional co–regulator for the nuclear hormone receptor AR	[35]
MED12 (OKS; FGS1; HOPA; OPA1; OHDOX; ARC240; CAGH45; MED12S; TNRC11; TRAP230)	Breast cancer			Transcriptional co–activator for the nuclear hormone receptor ERα	[21,51]
	Colon cancer	Mutated	Two somatic mutations (Gly44Cys, Ala67Val) in the exon 2 of MED12 gene	Transcriptional activator for TGF–βR2 signalling	[58,61,62]
	Lung cancer	Down–regulated		MEK and ERK signalling reduction; TGF–βR2 protein expression reduction	[61]
	Prostate cancer	Mutated	Mutations in MED12 gene		[52]
	Uterine sarcomas	Mutated	Somatic mutations of MED12 gene in uterine SMTs; heterozygous mutations in intron 1 and exon 2 in LMs, STUMPs, and uterine LMSs		[54,55,56,57,58]
MED13 (ARC250; KIAA0593; THRAP1; TRAP240; DRIP250)	Brain cancer	Editing pattern altered	Alteration of A–to–I editing pattern. Alu sequences in brain tumours undergo less editing compared to normal brains within the gene encoding for MED13.		[66]
	Breast cancer	Amplified	Amplification of MED13 gene (17q23)		[68]
MED13L (A1L469, KIAA1025, PROSIT240, Q68DN4, Q71F56, Q9H8C0, Q9NSY9, Q9UFD8, Q9UPX5, THRAP2, TRAP240L)	Retinoblastoma			Involvement in the Rb/E2F pathway	[70]
MED14 (ARC150; CRSP2; CXorf4; DRIP150; EXLM1; RGR1; TRAP170)	Breast cancer			Ligand–dependent ERα–mediated transactivation in a NR box (LXXLL motifs)–independent mode	[71,72]
	Prostate cancer	Up–regulated		Transcriptional co–regulator for the nuclear hormone receptor AR	[35]
MED15 (ARC105; CTG7A; PCQAP; TIG1; TNRC7)	Breast cancer			Cofactor for TGFβ/Erk phosphorylation signalling	[77]
	Prostate cancer	Hypermethylated			[80,81]
MED17 (ARC77; CRSP6; DRIP77; DRIP80; TRAP80)	Prostate cancer	Up–regulated			[37]

(*continued on next page*)

Table 2 *(continued)*

Gene symbol (Alternative name)	Cancer type	Molecular alteration	Putative cause	Putative effect	Reference
MED19 (LCMR1; DT2P1G7)	Bladder cancer	Up–regulated		Increase of BMP–2 protein in the initial cancer invasion and anchoring in the bone tissue	[82,83]
	Breast cancer	Up–regulated			[84]
	Colon cancer	Up–regulated			[85]
	Gastric cancer	Up–regulated			[86]
	Hepatocellular carcinoma	Up–regulated			[87]
	Lung cancer	Up–regulated			[88,89,90]
	Osteosarcoma	Up–regulated			[91]
	Ovarian cancer	Up–regulated			[92]
	Prostate cancer	Up–regulated		Modulation of Bid and Caspase7; Transcriptional co–regulator for AR	[94,95]
	Tongue cancer	Up–regulated			[96]
	Pancreatic cancer	Up–regulated			[93]
MED23 (RP5–914N13.2; ARC130; CRSP130; CRSP133; CRSP3; DRIP130; MRT18; SUR–2; SUR2)	Breast cancer			Specific link with the transactivation domain of ESX which activates the Her2 gene	[102]
	Gastric cancer	Mutated			[104]
	Lung cancer	Up–regulated		Link with Ras signalling	[105]
	Melanoma	Deleted		Regulator of KiSS–1 transactivation	[69,106,107]
	Pheochromocytoma	Down–regulated			[107]
MED28 (EG1; magicin; 1500003D12Rik; FKSG20)	Breast cancer	Up–regulated		Correlation with EGF by up–regulating the expression of MMP9; correlation with MMP2 and MEK1	[109,110,111]
	Colon cancer	Up–regulated			[112]
	Prostate cancer	Up–regulated			[112]
MED30 (THRAP6; TRAP25)	Breast cancer	Up–regulated			[34]
CDK8 (K35)	Colon cancer	Up–regulated		Direct transduction of Wnt/β–catenin signalling; indirect activation of β–catenin–dependent transcription by inhibiting E2F1	[59,124,125,126,127]
	Melanoma	Up–regulated	Association with the loss of a histone variant macroH2A		[123,129]
CDK19 (CDK11; CDC2L6; bA346C16.4)	Myeloma	Altered			[113]
	Osteosarcoma	Up–regulated			[115]
Cyclin C (CycC; CCNC)	Colon cancer	Up–regulated			[134]
	Gastric cancer	Up–/Down–regulated			[132,136]
	Hepatocellular carcinoma	Up–regulated		Link with Wnt/β–catenin signalling	[130,131,136]
	Leukemia	Deleted	Deletion of t(2;6)(p21;q15) genomic region		[135]
	Osteosarcoma	Down–regulated			[125,137]

Note: Subunits that are directly mutated or amplified/deleted at genomic level are highlighted in grey.

in cancer related MED alterations, as reported in Table 1 and fully described in the following paragraphs.

To date, several MED subunits have been associated with various types of tumours, as shown in Fig. 2A–B and detailed below.

2.1. MED1

2.1.1. Breast cancer

The first recognized link between MED and cancer was the association of MED1 with breast cancer [31], the second leading cause of cancer death in women worldwide [32]. Indeed, MED1 amplification and overexpression were initially observed in breast cancer tissues and cell lines [31]. This result was recently confirmed by tissue microarray analysis revealing that MED1 expression positively correlated most strongly with the human epidermal growth factor receptor 2 (HER2) status of the tumours [33]. In this study, MED1 was found to be highly phosphorylated at the critical site for its activation, in a HER2-dependent manner [33]. These data are noteworthy since it is well known that HER2 activation is one of the major mechanisms contributing to endocrine resistance in breast cancer. Thus, these findings support a key role for MED1 in HER2-mediated tamoxifen resistance and suggest its potential usage as a therapeutic target to simultaneously block both oestrogen receptor (ER) and HER2 pathways for the treatment of this tumour [33,34].

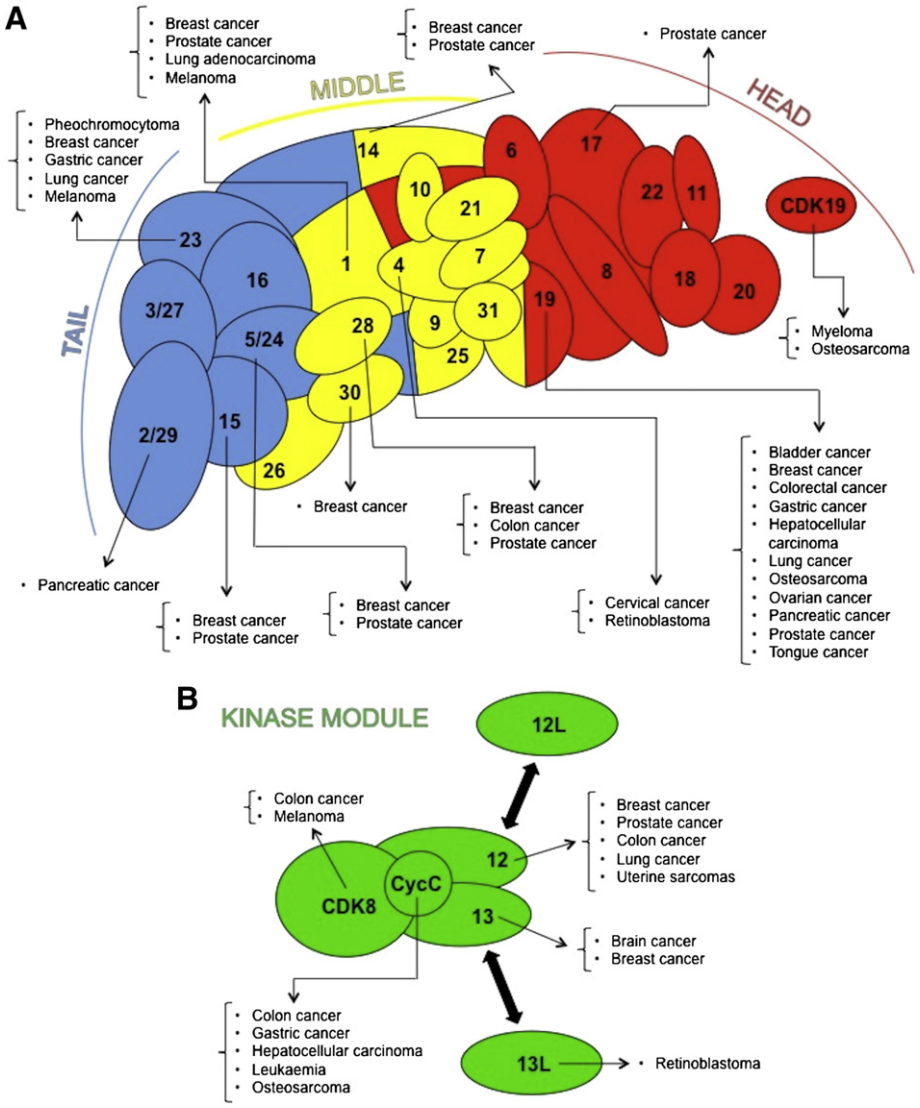

Fig. 2. Structural organization of the human Mediator complex (MED): submodules, subunits, and cancer diseases related. Panel A) shows the involvement of MED core in different cancers; MED head subunits are indicated in red colour, the middle ones in yellow, and the tail subunits in blue. Panel B) illustrates the kinase module with subunits in green colour and the tumour types involved. Black arrows indicate the homologs of MED12 and MED13: MED12-like (MED12L) and MED13-like (MED13L), respectively, which may be part of the kinase module [10]. The relative position of all subunits derives from the current knowledge even though the precise structural localization of some subunits inside the complex is still debated.

2.1.2. Prostate cancer

Analogously to breast cancer, MED1 has been shown to be a key transcriptional co-activator for androgen receptor (AR) in prostate cancer cells [35–37] although it is also overexpressed in and functionally required for proliferation of certain androgen-independent prostate cancer cell lines and primary tumours [37].

2.1.3. Lung cancer

In addition to its well-established relationship to breast and prostate cancers, MED1 also correlates with human lung adenocarcinoma, through the interaction with the nuclear hormone receptor ERβ. MED1 expression was found more frequently in the non-solid subtypes (bronchioloalveolar, acinar, and papillary patterns) than in the solid subtype and in the well-differentiated adenocarcinomas compared to the moderately or poorly differentiated adenocarcinomas [38]. The loss of MED1 expression was strongly associated with increased rates of invasion and metastasis in non-small-cell lung carcinoma (NSCLC) patients, with growing cell migration and invasion [38], and with loss of expression of the oncosuppressor death-associated protein kinase-1 (dapk1) in a number of primary human lung carcinomas [39]. MED1 levels were significantly lower in cancer cell lines than in normal controls and importantly, MED1 restoration induced dapk1 gene expression in these cells thus reducing their metastatic potential in vivo [39].

2.1.4. Melanoma

Finally, MED1 has also been implicated in human melanoma progression. In melanoma cell lines it is either highly or weakly expressed in melanoma cells, depending on their respectively non- or highly-tumorigenic phenotype [40]. Microarray analysis of MED1 knockdown cells showed a significant expression reduction of those genes that are well known to be involved in melanoma cell invasion [40].

2.2. MED2

2.2.1. Pancreatic cancer

Recently, MED2/29 has been found overexpressed in a subset of pancreatic cancer cells, characterized by chromosomal 19q13 gain [41,42]. MED2 silencing in pancreatic cancer cells was observed to potentiate

apoptosis and attenuate proliferation, colony formation, cell migration, and invasion in vitro, thus revealing MED2 as an essential growth and survival factor [41,42]. Unexpectedly, forced MED2 overexpression in cancer cells with low endogenous expression levels also reduced cell proliferation in vitro as well as tumour growth in vivo, and triggered concordant transcriptional changes in cell cycle regulatory genes. Taken together, these findings show that MED2 possesses both oncogenic and tumour suppressive characteristics in pancreatic cancer depending on the genetic background of the cancer cells and their surrounding environment [41].

2.3. MED4

2.3.1. Cervical cancer

The combination of gene dosage, expression profiles and gene ontology in a large sample set of cervical cancers allows identifying recurrent gene alterations and events associated with clinical outcome [43]. Integrative analysis data were provided to identify the loss and down-regulation of MED4 on 13q (13q12.2–q21.32) and associate with poor clinical outcome, suggesting that this gene could be responsible of chemoresistance. Loss of the transcriptional activator MED4 may impair transcription of genes with anti-cancer effect, like vitamin D receptor [44,45].

2.3.2. Retinoblastoma

Retinoblastoma (Rb) is caused by mutational inactivation of the RB1 gene, a tumour suppressor localized on chromosome 13q14.2. About 5–15% of the patients with Rb are heterozygous for a huge deletion that includes the entire or substantial parts of RB1 [46]. Nevertheless, relationship between phenotypic expression and loss of specific adjacent genes are unresolved yet. Recently, genotype–phenotype correlations in Rb patients with an interstitial 13q deletion have evidenced that deletions containing MED4 gene are associated with a milder phenotypic expression of Rb. MED4 encodes for a vitamin D receptor-interacting protein (DRIP) that binds nuclear receptors [45]. These data suggest that Rb precursor cells cannot tolerate the alteration of vitamin D signalling through homozygous loss of MED4 [47].

2.4. MED5

2.4.1. Breast cancer

Comparative genome hybridization (CGH) and gene expression analyses allowed identifying MED5 gene amplified and highly expressed at 17q11-21 in BT474 (a breast carcinoma cell line containing amplicons at different loci). Since it exhibited both amplification and increased expression, MED5 was hypothesized as candidate oncogene in breast cancer [34,48].

2.4.2. Prostate cancer

To date, MED5/24 has been found altered in prostate cancer cells. Indeed, Wang et al. have shown that MED5 plays an important co-regulatory role in AR-mediated gene expression in these cells, since its transient overexpression enhanced ligand-dependent transcription by AR in LNCaP prostate cancer cells. However, the mechanisms by which AR recruits MED5 have remained unclear [35].

2.5. MED12

2.5.1. Breast cancer

Both cohesin and MED complex are known to be required for the expression of the gene encoding for oestrogen receptor-alpha (ESR1) and for ER-mediated transcription [29,30,49,50]. Thus, Prenzel group hypothesized that these complexes may similarly control oestrogen-regulated gene expression. Interestingly, their results showed that depletion of the SMC3 cohesin subunit or the MED12 subunit significantly impaired the ERα-regulated transcriptome. These findings define the ESR1 gene as a cohesin/MED-dependent gene and indicate that this regulatory mechanism may be utilized for the treatment of oestrogen-dependent breast cancer [21,51]. Obviously, mouse model studies and clinical studies will help to determine the potential clinical utility of these results.

2.5.2. Prostate cancer

Common genetic alterations in prostate cancer include the loss of NKX3.1 and PTEN genes, the increase of AR gene and the fusion of ETS family transcription factor genes with androgen-responsive promoters. Recurrent somatic base pair substitutions are believed to be less responsible in prostate tumorigenesis but they have not been systematically analysed in large cohorts. In a recent study, the exomes of 112 prostate tumours and corresponding normal tissues were sequenced, and new recurrent mutations were identified in several genes, also including MED12 gene among the others, in cancer samples but not in non-cancerous tissues [52].

2.5.3. Uterine sarcomas

Smooth muscle tumours (SMT) are the most common mesenchymal neoplasms of the uterus. They include leiomyomas or fibroids, benign tumours (LM), atypical LM or Smooth muscle Tumour of Uncertain Malignant Potential (STUMP) with abnormal spotted nuclei, and leiomyosarcomas (LMS), aggressive tumours [53]. To date, the histological distinction between benign and malignant SMTs is still difficult, although in last years, new morphological criteria as immunohistochemical and molecular diagnostic tools have contributed to improve the classification, diagnosis and assessment of prognosis of these tumours. Certainly, the biology and genetics of uterine tumours are still unclear. Moreover, the majority of the uterine LMSs are assumed to develop de novo, while only a small subgroup seems to be associated with a benign component. The role of MED complex in the "sarcomagenesis" has been recently highlighted by Makinen et al., which have identified for the first time, recurrent and frequent somatic mutations of MED12 in uterine SMTs by exome sequencing [54]. Among these, heterozygous mutations in intron 1 and exon 2 of the gene were detected in a high percentage of conventional LMs [54,55], LM variants or STUMPs, and uterine LMSs [56]. Interestingly, in one study, the two LMSs harbouring the MED12 mutation also showed a benign component, with identical mutations [57]. This observation suggests that a small subgroup of LMS may derive from MED12-mutated LM. However, due to the overall low frequency of MED12 mutations observed in uterine LMS, it is conceivable that most of LMSs and LMs develop through distinct genetic pathways. Altogether these data indicate that MED12 mutations seem specific to uterine SMTs. However, to date there are no gene expression or functional studies of this protein or the MED complex in tumorigenesis and its role in uterine SMT pathogenesis is still unclear. Finally, other studies have reported that MED12 mutations cannot be detected in many carcinomas like breast, gastrointestinal tract, prostate and liver [58], benign and malignant soft tissue tumours [46,47] or haematological malignancies [58].

2.5.4. Colon cancer

The above-mentioned study reported a MED12-colorectal carcinoma correlation. Indeed, among the 1862 different tumour tissues analysed, MED12 was found mutated also in one colon carcinoma [58]. Moreover, MED12 was reported as a possible candidate biomarker of response to a range of colon cancer drugs through a role of this protein in TGF-β receptor (TGF-βR2) signalling. Interestingly, MED12 belongs to the kinase module, which also comprises CDK8, whose gene sequence is amplified in about 50% of colon cancers [59]. However, CDK8 (as well as MED13) silencing did not cause upregulation of TGF-βR2 and, therefore, did not conferred drug resistance, whereas MED12 was involved in TGF-βR2 activation and drug resistance. A portion of MED12, existing in the cytosol, negatively regulates TGF-βR2 through physical interaction with its

immature forms and inhibition of its glycosylation, thereby preventing cell-surface expression [60,61]. Consequently, MED12 loss strongly enhances cell-surface expression of TGF-βR2, by activating TGF-β and ERK signalling in the presence of several drugs, which is both necessary and sufficient for drug resistance. Moreover, MED12 suppression induces an epithelial mesenchymal transition (EMT)-like phenotype, which is associated with chemotherapy resistance in colon cancer patients. The association between MED12 and colorectal cancer (CRC) has also been recently confirmed [58,61,62]. In a study, two somatic alterations (Gly44Cys, Ala67Val) have been found in the samples of CRC patients, suggesting that MED12 exon 2 mutations may, though rarely, contribute to CRC tumorigenesis [58,62].

2.5.5. Lung cancer

MED12 role in lung cancer was hypothesized during an RNA interference (RNAi) screen carried out to identify resistance mechanisms to two anaplastic lymphoma kinase (ALK) inhibitors using the NSCLC cell line harbouring an echinoderm microtubule-associated protein-like 4 (EML4)-ALK translocation and that is sensitive to both drugs [61]. The authors found that reduced expression of MED12 results in both resistances to ALK and to epidermal growth factor receptor (EGFR) inhibitors in these cells. Activation of downstream signalling pathways is a known resistance mechanism to tyrosine kinase inhibitors. Consistently, the authors observed that MED12 knockdown increased MEK and ERK signalling, and induced resistance to MEK and BRAF inhibitors, to the multikinase inhibitor sorafenib, as well as to the standard chemotherapeutic drugs 5-fluorouracil and cisplatin [61]. The authors also elucidated the resistance mechanism conferred by MED12 loss and, through a kinase screen, they identified TGF-βR2 as a potential target. Indeed, MED12 knockdown cells showed a considerable increase in TGF-βR2 protein expression, indicating a post-translational effect. Moreover, co-immunoprecipitation studies showed an interaction between MED12 and TGF-βR2, and additional experiments suggested that MED12 could prevent the expression of a fully glycosylated form of TGF-βR2 on the cell surface. MED12 silencing induced specific changes in the expression of TGF-β target genes, involving also those regulating the EMT. Altogether, these data indicate that tumours with a reduction in MED12 activity produce a reduced proliferation of lung cancer cells [61].

2.6. MED13

2.6.1. Brain cancer

A growing body of evidences indicates that deregulation of epigenetic mechanisms cooperates with genetic alterations in the development and progression of cancer [63]. Particularly, adenosine to inosine (A-to-I) RNA editing is a site-specific modification in stem-loop structures within precursor mRNAs, catalysed by members of the double-stranded RNA (dsRNA)-specific ADAR (adenosine deaminase acting on RNA) family; ADAR-mediated RNA editing is essential for the normal development of the vertebrates [64,65]. The splicing and translational machineries recognize inosine (I) as guanosine (G). Therefore the result of ADAR editing consists of genomically encoded adenosines that are read as guanosines in the RNA sequence. A number of editing sites occur in the gene coding regions and may result in amino acid substitutions affecting the protein properties and interactions. Until recently, only a handful of such A-to-I editing sites were known in the human transcriptome. In the past few years, bioinformatics and experimental studies have revealed that the extent of editing is much higher and affects many different genes [64,65]. These A-to-I editing events occur in noncoding repetitive sequences, mostly Alu elements, and tend to undergo multi-editing in tight clusters [64,65]. Editing in noncoding sequences was proposed to be involved in general functions such as RNA stabilization, degradation and translation, splicing, RNA interference, heterochromatic silencing and protection from retro-transposition. Altered editing patterns, mainly of coding regions, were shown to be different between cancer and normal tissues [64,65]. A bioinformatics analysis was performed looking at all expressed sequence tags (ESTs), which have a specific tissue and status (normal or cancer) annotation and calculated the fraction of those ESTs exhibiting editing in at least one of the editing sites identified. The most significant result was the identification of reduced A-to-I editing in brain tumours compared to normal brain tissue. Noteworthy, by bioinformatics and experimental approaches, a research group found that the A-to-I editing pattern is significantly modified in cancer compared to normal tissues [66]. They examined the editing level in 31 different human tumours and evaluated editing levels in three coding sequence targets (CYFIP2, BLCAP, and FLNA) and two clusters of noncoding editing sites. Moreover, they observed that Alu sequences in brain tumours undergo less editing compared to normal brains and this trend is manifested specifically within the gene encoding for MED13.

2.6.2. Breast cancer

In breast cancer, several genes, localized at the 17q12 (as ERBB2), 8q24 (as MYC), and 11q13 (as CCND1) regions, are amplified in about 25% of tumours, and their amplification is associated with an advanced stage of the disease and drug resistance [67]. Moreover, studies by CGH array have allowed identifying another region, commonly amplified in breast cancer, the 17q23. Among the different putative target genes, Monni et al. found that MED13 was amplified in both breast cancer cell lines and primary breast tumours [68]. Therefore, MED13 amplification could be important for tumour development and progression and contribute to the more aggressive clinical course observed in breast cancer patients with 17q23-amplified tumours [68].

2.7. MED13L

2.7.1. Retinoblastoma

The Rb tumour suppressor gene is a fundamental negative regulator of cellular proliferation. In its active form, Rb binds to the transcription factors of the E2F family and suppresses both their transactivation function and assembles an active repressor complex [69]. Therefore, the Rb/E2F pathway is important for the cell proliferation control and it is deregulated virtually in all human tumours [70]. A study examined for the first time MED13L involvement in the Rb/E2F pathway [70]. The findings of this study indicate that MED13L reduction interferes with the function of the Rb/E2F pathway in the induction of senescence, transcriptional repression and cell cycle arrest. Thus, this MED subunit is required for the Rb/E2F control of cell growth, the complete repression of cell cycle target genes, and cell cycle inhibition. However, further works are essential to elucidate this contribution and its potential significance in carcinogenesis.

2.8. MED14

Although no direct evidences correlate this MED subunit to carcinogenesis a possible role can be hypothesized based on in vitro studies in cancer cell lines.

2.8.1. Breast cancer

MED14 enhances transcriptional activation of the ER and other NRs. Particularly, MED14 activates ligand-dependent ER alfa-mediated transactivation in a NR box (LXXLL motifs)-independent mode, in ZR-75 and MDA-MB-231 breast cancer cells, by the regulation of various tandem oestrogen-responsive elements. Analysis of multiple MED14 deletion mutants has allowed identifying a novel sequence of 23-amino-acids required for co-activation activity. Moreover, analysis of the protein crystal structure database identified a particular region at aminoacids resembling alpha-helical motifs in hepatocyte nuclear factor 1. Specific aminoacid point mutations in

alpha-helix region led to the identification of the NIFSEVRVYN region as the critical sequence required for MED14 activity [71,72].

2.8.2. Prostate cancer

MED14, together with MED1 and MED5, plays an important regulatory role in AR-mediated gene expression in prostate cancer cells. Indeed, also MED14 transient overexpression enhanced ligand-dependent transcription by AR in prostate cancer cells (LNCaP). However, the mechanisms by which AR recruits also MED14 have remained unclear [35].

2.9. MED15

2.9.1. Breast cancer

MED15 seems to be an important cofactor for TGFβ signalling suggesting a potential target for counteracting aberrant TGFβ/Smad signal transduction in breast cancer, and possibly also in other epithelial cancers. TGFβ signalling plays a critical role in the progression of human cancer [73], and the Smad2/3 co-regulatory factors can also contribute to TGFβ functions in development and tumorigenesis [74–76]. Indeed, a study showed that Med15 silencing attenuates the TGFβ-targeted gene expression, reduces the TGFβ-mediated growth inhibition, and arrests the TGFβ induced EMT, through the reduction of the phosphorylation and nuclear accumulation of Smad2/3 and by enhancing TGFβ-induced Erk phosphorylation [77]. On the other hand, western blotting analysis showed that Med15 RNAi relieved the E-cadherin down-regulation and fibronectin up-regulation after TGFβ treatment. Moreover, although the primary tumour growth seems not to change, MED15 RNAi is able to decrease the metastatic potential of highly aggressive breast cancer cells, which spontaneously metastasize from a primary tumour to lungs in vivo. Indeed, HaCaT cells expressing si-MED15 significantly inhibited lung metastasis suggesting a potential target in breast cancer and other epithelial cancers.

2.9.2. Prostate cancer

DNA hypermethylation is the most common epigenetic change and one of the most common molecular alterations in human cancer [78,79]. Through quantitative methylation-specific PCR evaluating the methylation status of gene promoter regions involved in several and different signalling pathways, some researchers found a hypermethylation of MED15 in primary prostate tumour tissues [80]. Finally, the decreased expression of MED15 in prostate carcinoma cells was associated with an increase in the malignant potential. The restoration of MED15 expression in the highly malignant prostate cancer cell line, which does not express this subunit, greatly reduced the invasiveness in vitro and the tumorigenicity in nude mice [81].

2.10. MED17

2.10.1. Prostate cancer

MED17 is overexpressed in prostate cancer cell lines and tissues and its depletion leads to a proliferation reduction by increasing apoptosis [37]. However, its role in cancer progression still needs to be clarified.

2.11. MED19

MED19 has been recently involved in many cancers [8]. Indeed, as detailed below, several studies have shown a different expression of this subunit in many tumour tissues compared to their normal counterparts, suggesting an involvement in these human cancers.

2.11.1. Bladder cancer

By in situ immunohistochemical analysis MED19 is upregulated in human bladder cancers (BCa) compared with adjacent benign tissues. To understand the role of MED19 in bladder cancer, Zhang et al. studied the effects of MED19 silencing by lentiviral vectors in 5637 and T24 cells both in vitro and in vivo [82]. A strong inhibition of MED19 expression was able to increase cell ratio in G0/G1 phases, to attenuate the growth of cancer cells in vitro and to decrease the tumorigenicity of MED19 silenced T24 cells after inoculation into nude mice [82]. Moreover, to investigate its role in promoting bone metastasis in the BCa, some researchers correlated MED19 expression with bone morphogenetic proteins (BMPs) in patients with bone metastasis and muscle invasion [83]. This study showed that MED19 and BMP-2 could be implicated in the initiation of cancer invasion and anchoring in the bone tissue. Based on the results, the authors postulated that BCa cells could increase invasiveness by high MED19 expression levels. After cell entrance into lymph or vascular circulation, the elevated BMP-2 levels, induced by MED19, could support the seeding of BCa cells in the bone tissue. Nonetheless, further investigations are warranted to identify other factors involved in this mechanism [83].

2.11.2. Breast cancer

MED19 over-expression was also revealed in breast cancer tissues compared to normal ones by immunohistochemical analysis and it resulted significantly associated with tumour grade [84]. MDA-MB-231 and MCF-7 cells infected with lentiviruses delivering small hairpin RNA (shRNA) against MED19 elicited augmentation of G0/G1 phase fraction and significantly attenuated MDA-MB-231 and MCF-7 cell growth in vitro [84]. These findings suggest an important role for MED19 in the proliferation of breast cancer cells.

2.11.3. Colorectal cancer

MED19 over-expression was also found in CRC [85]. Similarly to the above-described studies, MED19 knockdown in human RKO and DLD-1, two CRC cell lines, infected with lentivirus delivering MED19 shRNA, resulted in cell proliferation inhibition and G0/G1 phase ratio amplification. Moreover, the tumorigenicity of RKO cells was also dramatically inhibited after MED19 silencing. In conclusion, these results suggest that MED19 promotes CRC cell growth, but it remains yet unknown how it can be involved in the process of CRC cell proliferation.

2.11.4. Gastric cancer

The possible correlation between MED19 expression and gastric carcinoma was hypothesized based on immunohistochemistry analyses of several gastric carcinoma specimens and silencing studies on SGC7901 and MGC803 cells, two human gastric cancer cell lines [86]. Indeed, MTT, colony formation and cell cycle analysis showed that down regulation of MED19 significantly inhibited cell proliferation and colony-formation capacity, and induced G1 phase cell-cycle arrest. Collectively, MED19 may represent a useful therapeutic target also in malignant gastric carcinoma.

2.11.5. Hepatocellular carcinoma

The role of MED19 in cancer was also explored in the proliferation and tumorigenesis of human hepatocellular carcinoma (HCC) cells. Molecular studies indicated that MED19 down-regulation expression could significantly inhibit cell proliferation, induce delay in the G1-phase transition and suppress tumour formation in HepG2 and Hep3B cells in vitro and in vivo, thereby indicating an oncogenic role also in the HCC progression [87].

2.11.6. Lung cancer

Several findings suggest that MED19 is a promising proliferation regulator in lung cancer [88]. Indeed, high expression levels of MED19 were also found in human lung cancer compared with adjacent normal tissues by immunohistochemical assay [88,89]. Moreover, A549 cells were infected with a lentivirus expressing MED19-specific shRNA to silence endogenous MED19 and the impact of MED19 knockdown was investigated on the lung cancer development in vitro and in vivo. Real-time PCR and western blot assays showed that down-regulation of MED19 expression greatly impaired

the proliferation and colony-forming ability of A549 cells. Interestingly, MED19 knockdown caused cell cycle arrest at G1/S transition of A549 cells evidenced by G1 phase accumulation and S phase decrease. More importantly, injection of A549-RNAi cells into nude mice led to inhibited growth of solid lung cancer tumours in vivo [90]. Moreover, MED19 function was investigated in the H1299, a NSCLC cell line. In this study, MED19 silenced cells showed a weak colony formation ability, lower cell growth rate, a block in the S phase of cell cycle with trouble advancing from the S phase to the M phase, and displayed a weak invasive capability [90].

2.11.7. Osteosarcoma

The molecular pathogenesis of osteosarcoma (OS) is very complicated. MED19 plays an important role in cell growth and cell cycle progression of human OS cells. Indeed, knockdown of MED19 expression in SaOS-2 and U2OS cells led to decreased cell viability, colony formation capacity, and DNA synthesis ability in both cell lines, with contemporary G0/G1 phase cell cycle arrest. Therefore, these results implied that MED19 might be an attractive candidate for the therapeutic target in OS [91].

2.11.8. Ovarian cancer

A study reported that MED19 expression was also raised in human ovarian cancer tissues by immunohistochemistry analysis [92]. After MED19 downregulation, by lentivirus-mediated RNAi, the authors observed that MED19 level correlated with the level of tumour malignancy. Furthermore, MED19 down-regulation in SKOV-3 and HEY cells significantly inhibited cell proliferation and colony formation in vitro and led to cell cycle arrest in the G0/G1 phase. Moreover, MED19 RNAi significantly inhibited ovarian cancer tumour growth in engrafted nude mice [92].

2.11.9. Pancreatic cancer

In a study MED19 silencing was reported to have an effect on pancreatic cancer cell growth. Specifically, MED19 downregulation remarkably reduced cell proliferation and colony formation capacity of Aspc-1 and Panc-1, two pancreatic cancer cell lines, and induced G1-phase cell cycle arrest and apoptosis [93]. These findings allowed supposing that MED19 may act as an oncogene functioning during pancreatic cancer development. However, to explore the underlying mechanism by which MED19 modulates pancreatic cell growth, further examinations are required.

2.11.10. Prostate cancer

To understand the functional role of MED19 in human prostate cancer, its presence was examined in prostate cancer specimens by immunohistochemical assay. MED19 was found to be specifically and highly expressed in the prostate tumour tissues compared to the paired non-neoplastic ones. MED19 silencing significantly inhibited the proliferation of PC-3 and DU145, two prostate cancer cell lines. Finally, targeting MED19 resulted in lower colony formation ability and attenuated tumour formation and growth in PC-3 xenografts. Knockdown of MED19 caused S-phase arrest and induced apoptosis modulating two pro-apoptotic proteins, Bid and Caspase 7 [94]. Moreover, simultaneous depletion of protein kinase HIPK2 and MED19 decreased AR target gene expression and, importantly, reduced the proliferation of androgen-dependent and castration-resistant prostate cancer cells [95].

2.11.11. Tongue carcinoma

Tongue carcinoma is one of the most common types of oral cancer. Down-regulation of MED19 by shRNA resulted in inhibition of cell proliferation, induction of G0/G1 phase cell cycle arrest and diminished colony formation and migration abilities. Furthermore, the antitumor effects of MED19 were elucidated by in vivo tumorigenicity experiments. Despite that the mechanism involved is far from the explanation, it is conceivable that there may be interactions between MED19 and cell growth transcription factors via direct or indirect binding that influences their correct functioning [96].

2.12. MED23

MED23 is essential to link insulin signalling to the adipogenesis. Moreover, MED23 controls the cell fate preference that directs differentiation from the multipotent mesenchymal stem cells into smooth muscle cells or adipocytes [97]. As stated above, it has also been demonstrated to interact with the RNA binding protein hnRNPL to regulate alternative splicing [24]. Altogether, these functional properties render MED23 a possible player of carcinogenesis.

2.12.1. Breast cancer

Overproduction of the Her2 protein has been found in almost 30% of breast tumours, and patients who have Her2 excesses typically have more aggressive disease. One of the critical transcription factors that activate the Her2 gene in breast cancers is ESX, an epithelial restricted transcription factor that is specifically expressed in epithelial cells including mammary glands [99,100]. ESX binds and strongly activates the Her2 promoter [98], and the ESX-binding site in the Her2 promoter is absolutely required for the high-level expression of Her2 in breast cancer cells [101]. A few years ago MED23 was found to bind specifically the transactivation domain of ESX and the disruption of the interaction between these two cancer-linked proteins decreases the expression of the Her2 gene and downregulates the proliferation and viability of Her2 expressing breast cancer cells [102]. The association of ESX with MED23 is mediated by a small hydrophobic portion of an 8-aa helix in ESX, suggesting a therapeutic approach to weaken the Her2 gene through small organic molecules.

2.12.2. Gastric cancer

To date, approximately the 1–3% of patients with gastric cancer (GC) have a familial predisposition to the disease and the 30–40% of hereditary diffuse gastric cancers (HDGCs) can occur for defects in CDH1, a gene encoding for the cell adhesion protein E-cadherin. Both genetic and epigenetic mechanisms can act to silence CDH1 gene in GCs [103]. Exome sequencing analysis applied to identify new genes involved in gastric cancer allowed detecting mutations in MED23 and MED12 genes among the others [104].

2.12.3. Lung cancer

A correlation between MED23 and lung cancer was found through a screening of a large panel of human lung cancer cell lines with or without a Ras mutation [96]. In this study MED23 RNAi specifically inhibited the proliferation and tumorigenicity of lung cancer cells with a strong Ras activity. Moreover, MED23 deficiency selectively inhibited the oncogenic transformation of fibroblast cells induced by Ras but not by c-Myc. A transcriptome analysis revealed that MED23 and the transcription factor ELK1 (known to connect Ras signalling to MED23) co-regulate a common set of target genes enriched in those regulating cell cycle and proliferation functions supporting the Ras dependency. Furthermore, MED23 was up-regulated by Ras transformation and was found to be overexpressed in both Ras-mutated lung cancer cell lines and primary tumour samples. Interestingly, lower MED23 expression predicted better survival in Ras-active lung cancer patients and xenograft mice. Therefore, collectively these findings demonstrated a critical role for MED23 in facilitating the “Ras-addiction” of lung carcinogenesis, thus providing a vulnerable target for the treatment of Ras-active lung cancer [105].

2.12.4. Melanoma

MED23 is also correlated with melanoma. Indeed, the region encoding MED23, 6q16.3–q23, is commonly lost during progression of melanoma. KiSS-1, a metastasis tumour suppressor is also strongly correlated to the progression of metastases in melanoma [69,106]. Starting from these considerations, KiSS-1 and MED23 roles were

examined with specific assays. Chromosomal deletion of MED23 in melanoma cells was found to be associated with reduced promoter activation and decreased production of downstream suppressor KiSS-1 [107]. Significantly, MED23 expression not only restored KiSS-1 expression, but also induced an inhibition of the invasive and migratory behaviours in highly metastatic melanoma cells. Similarly, induction of KiSS-1 overexpression decreased invasive and migratory properties of highly metastatic melanoma cells [108]. Therefore, MED23 represents a key regulator of KiSS-1 transactivation in normal tissue, and its loss may provoke increased tumour metastasis.

2.12.5. Pheochromocytoma

A likely correlation between MED23 and pheochromocytoma was suggested by a real-time PCR study on 15 benign and 10 malignant pheochromocytomas showing a significantly downregulation of MED23 in malignant compared to benign pheochromocytomas [107].

2.13. MED28

This subunit was initially identified as an endothelial gene stimulated by tumour-conditioned media and for this reason named endothelial-derived gene 1 (EG-1). Based on the angiogenic nature of human tumours and the endothelial origins of MED28, its expression was investigated in several malignancies, such as breast, prostate, colon and lung cancers.

2.13.1. Breast cancer

An increased expression of MED28 was found in breast cancer; despite the small patient size analysed, this study suggests that MED28 could be a novel and strong independent prognostic indicator of survival for breast cancer [109]. Indeed, MED28 protein expression levels were increased in ductal carcinoma in situ and invasive ductal carcinoma of the breast compared to non-malignant glandular and ductal epithelium [110]. Recently, MED28 was reported to enhance epidermal growth factor (EGF)-induced migration by up-regulating the expression of the metalloproteinase MMP9 in human breast cancer cells [109]. Moreover, suppression of MED28 expression inhibited migration and this event coincided with lower expression levels of MMP2 and MEK1, whereas MED28 overexpression enhanced MEK1-mediated MMP2 expression and cell migration in human breast cancer cells. On the other hand, ectopic employment of MEK1 cDNA or MMP2 protein rescued the inhibitory effect of MED28 or MEK1 knockdown on invasion [111]. Altogether, these findings indicate that MED28 is a predictor of disease outcome, with higher expression predicting a greater risk of disease-related death.

2.13.2. Prostate cancer

MED28 expression was also increased in cancerous as opposed to benign epithelial cells of the prostate, although the sample size of the analysed population was small [112].

2.13.3. Colon cancer

High expression of MED28 was also observed in cancerous cells in comparison with benign epithelial cells of the colon by immunohistochemistry of several human pathological specimens. This observation supports the hypothesis that MED28 gene is associated with the malignant phenotype of the common epithelial-derived cancer of the colon. In a small sample size, colon cancer seems to consistently have elevated MED28 signals, whereas the increased staining pattern is more variable in breast and prostate cancer types. Interestingly, lung cancer does not appear to express elevated MED28 levels [112].

2.14. MED30

2.14.1. Breast cancer

To date the only evidence of a possible implication of this subunit in cancer diseases comes from a study on various breast carcinoma cell lines that express abundant amounts of MED30, other than MED1 and MED5 [34].

2.15. CDK19

This kinase subunit CDK19 was firstly identified as CDK11/CDK8-L in the human MED complex using multidimensional protein identification technology and it is very similar to human CDK8 [20,113]. It possesses a serine/threonine kinase domain with 97% identity to CDK8, and the full sequence of CDK19 has approximately 80% identity to CDK8 [20]. Importantly, this MED subunit exists predominantly in the nucleus, similarly to CDK8, even though it forms distinct MED complexes lacking CDK8 [114]. Northern blotting analysis revealed that CDK19 was expressed in a limited number of tissues in contrast to the ubiquitous expression of CDK8. To elucidate the functional differences between CDK8 and CDK19, further examination of the in vitro transcription mechanisms is required.

At present, the HUGO Gene Nomenclature Committee (HGNC) has assigned a unique name CDK19 to the previous gene CDC2L6/CDK11, to indicate the gene mapping on human chromosome 6 and encoding a protein component of the MED complex (http://www.genenames.org/). Indeed, it is to note that the Mediator-associated CDK19 (CDC2L6/CDK11), with Accession Number NP_055891, is distinct from the cyclin-dependent kinase PITSLRE, which has also been called CDK11 in some publications.

2.15.1. Osteosarcoma

OS cells display high levels of CDK19 expression. Moreover, CDK19 expression knockdown inhibited cell growth and induced apoptosis in OS cells. Moreover, immunohistochemical analysis showed that patients with OS displaying high CDK19 tumour expression levels were associated with significantly shorter survival than patients with OS and low levels of tumour CDK19 expression. In vivo administration of CDK19 siRNA reduced the tumour growth in an OS subcutaneous xenograft model. In conclusion, CDK19 signalling resulted essential in OS cell growth and survival [115].

2.15.2. Myeloma

To identify critical molecular targets, a genome-scale lethality study in multiple myeloma cells using siRNAs has allowed identifying 57 potent multiple myeloma survival genes in multiple myeloma cells. Among these, CDK19 exhibited differential expression in primary plasma cells compared with other human primary somatic tissues [113].

2.16. CDK8 (kinase or module)

To understand the functions of CDK8, it is important to distinguish the activities of CDK8 kinase with the activities of the CDK8 module, because CDK8 may function outside of the MED complex. Indeed, CDK8, Cyclin C (CCNC), MED12, and MED13 form the CDK8 module in a 1:1:1:1 stoichiometry in vitro [116]. In mammals, there are also two described homologs of MED12 and MED13, which are MED12-like (MED12L) and MED13-like (MED13L), respectively [20].

All deletions of CDK8 module components have similar phenotypes, and share common transcriptional defects, suggesting a uniform function for the four subunits [117]. In mammals, CDK8 knockout mice are lethal prior to compaction and implantation at embryonic days 2.5, suggesting a critical role of CDK8 for cell-fate determination in early embryos, whereas knockout mice for other subunits of the CDK8 module have not been reported [118]. Furthermore, only a fraction of CDK8 is associated with MED12 and MED13 subunits in mammalian cells, thus CDK8 may function outside of MED [116,119,120]. These observations suggest that the four subunits of the CDK8 module do not have identical roles and possibly that CDK8-CCNC could have MED-independent functions that remain to be discovered. On the other hand, CDK8 module can inhibit transcription independent

of the CDK8 kinase activity. Current hypothesis suggest that CDK8 is linked to promoters with the small MED complex through MED13 subunit of the CDK8 module [5]. Thus, it can inhibit transcription through the CDK8 module, which can induce a conformational change of the small MED complex, thereby disrupting the interaction between the large MED complex and Pol II enzyme [5,120,121]. However, this effect is independent of the CDK8 kinase activity. Therefore, the activities of CDK8 kinase and transcription function of CDK8 module are not the same and they may have important implications in developing therapeutic approaches. Genes encoding CDK8 and CCNC are frequently deregulated in numerous cancers but only in some conditions the role and the potential mechanisms of their deregulation have been studied precisely, such as in human colorectal cancers and melanoma [122,123]. Nevertheless, the function and regulation of CDK8 and CCNC in vivo are still poorly understood.

2.16.1. Colon cancer

In colon carcinogenesis, CDK8 was identified as a potent oncogene with a double function [124]. It is known that canonical Wnt/β-catenin pathway plays an important role in colon cancers. Indeed, abnormal activation of this pathway occurs in almost all colorectal cancers by contributing to their cell growth, invasion and patient survival. However, relatively little is known about the regulatory mechanism of β-catenin. Firestein group found a significant positive correlation between CDK8 and β-catenin expressions [59]. Indeed, the suppression of CDK8 expression inhibited proliferation in colorectal cancer cells characterized by high levels of CDK8 and β-catenin hyperactivity. Noteworthy, CDK8 suppression inhibited the expression of a subset of Wnt/β-catenin target genes in these cells [59]. Afterwards, the same authors conducted a study to examine CDK8 expression in a large cohort of colorectal cancers by immunohistochemistry and detected CDK8 expression in 70% of tumours [125]. In this analysis CDK8 expression was independently associated with β-catenin activation that is significantly associated with poor prognosis in colon cancer [125]. Similar immunohistochemistry data were obtained in an independent study although β-catenin expression was not completely suppressed by CDK8 interference in the analysed cell lines [126]. Altogether, these observations suggested that therapeutic interventions targeting CDK8 could confer a clinical benefit in such malignancies. In addition to its role as a direct transducer of Wnt/β-catenin signalling, there is also new evidence showing that CDK8 can indirectly activate β-catenin-dependent transcription by inhibiting E2F1, an apoptosis activator, through direct phosphorylation [127].

Finally, and of particular interest, CDK8 was demonstrated to be required for both tumour growth and maintenance of tumour dedifferentiation in vivo thus suggesting a common role for CDK8 in controlling cancer and stem cell function [128]. Indeed, CDK8 inhibition in colon cancer cells led to a significant decrease in the expression of embryonic stem cell-related genes. These genes were particularly enriched for MYC target genes yet identified in embryonic stem cells. The subset of MYC target genes, whose expression was CDK8 dependent, was unique in its ability to predict tumour differentiation and clinical outcome [128]. These data suggest that the CDK8-regulated subgroup of MYC embryonic stem cell target genes is co-ordinately expressed in poorly differentiated, poor prognosis primary colon tumours. However, it remains to be determined whether CDK8 is directly responsible for maintaining this coordinated expression. These observations raise the possibility that the stem cell-like properties of cancer cells may be specifically inhibited by therapeutically targeting CDK8.

2.16.2. Melanoma

Since Wnt/β-catenin signalling is also constitutively activated in melanoma and CDK8 is a critical transducer of this signalling pathway, it was hypothesized to influence also melanoma progression. Indeed, CDK8 silencing was found to decrease melanoma cell proliferation, whereas CDK8 activation promoted melanoma progression [123]. However, the molecular basis of this mechanism is presently unclear. Recent evidences showed the loss of histone variant macroH2A (mH2A) in over 80% of metastatic melanomas and evidenced CDK8 as one of the mostly increased genes in mH2A-deficient melanoma cells by expression analyses. Moreover, CDK8 knockdown suppressed the proliferative advantage induced by mH2A loss in melanoma cells both in vitro and in vivo. These findings suggest that CDK8 can be considered a melanoma oncogene associated with the loss of a histone variant mH2A [129]. However, future studies focused on CDK8 function and regulation in melanoma cells will absolutely help to clarify these interesting findings.

2.16.3. Other tumours

Although CDK8 is mostly aberrantly overexpressed in many human cancers, also loss or reduction of CDK8 can be found in a few types of cancers, such as in esophageal squamous cell carcinoma, bladder cancers and other tumour samples, as a result of deletions or point mutations; these results suggest that CDK8 may not always behave as an oncogene in all human cancers, and its activity is tightly regulated [122].

2.17. Cyclin C

CCNC is the major regulatory partner of CDK8 and it is part of the kinase module. Altered expression, both up-regulation and down-regulation, of this subunit has been found in several human cancers [130–137].

2.17.1. Colon cancer

CCNC was found overexpressed in 88% of the colon cancers analysed [134]. Moreover, extra gene copies of CCNC gene were detected in about the 27%, showing a significant correlation between protein overexpression and gene amplification. Nevertheless, amplification of the CCNC gene was related to an unfavourable prognosis in colon adenocarcinoma [134].

2.17.2. Gastric cancer

Discrepant results on the CCNC status have been obtained for gastric cancers probably due to the different patient samples analysed and methods used in the two studies where it was found significantly either up- or down-regulated [132,136]. Nevertheless, these findings suggest that CCNC deregulation may play important roles in this type of tumours.

2.17.3. Leukaemia

The CCNC gene is also deleted in a subset of acute lymphoblastic leukaemia, including a patient sample containing a t(2;6)(p21;q15), with no apparent cytogenetic deletion. Single-strand conformational polymorphism analysis of the remaining CCNC allele from patients with a deletion of one allele established that there were no further mutations within the exons or the flanking intronic sequences. These results suggest that either CCNC haplo-insufficiency is enough to promote tumorigenesis or an important tumour suppressor gene is linked to the CCNC locus [135].

2.17.4. Hepatocellular carcinoma

The first observation on the involvement of CCNC gene in HCC was obtained on a hepatoma cell line (HLE) that displayed up-regulation of this gene [130]. A further study examined the gene expression of cancer related genes in HCC, particularly cell cycle and growth regulators, and showed a stronger tendency toward cell proliferation with CCNC up-regulation also in another hepatoma cell line: BEL-7402 [131]. To study possible signalling pathways, involving CCNC, siRNAs against β-catenin were transfected into HepG2 and SMMC-7721, two HCC cell lines, and cell cycle and CCNC protein expression were examined. Cell cycle was arrested at G0/G1 until 72 h after transfection and it began to move from G0/G1 to G2/M through S with a trend to revert

at 96 h. CCNC expression increased at 72 h whereas it decreased at 96 h [136]. These findings suggested that β-catenin gene silencing could induce changes of cell cycle and CCNC protein expression. Thus, Wnt/β-catenin signalling pathway probably takes part in the genesis and development of HCC through regulation of the cell cycle and the expression of CCNC. Obviously, further studies are required to understand the precise relationship between CCNC gene alterations and correlation with the pathogenesis of HCC.

2.17.5. Osteosarcoma

The molecular pathogenesis of OS is associated with a lot of chromosomal abnormalities. In a study aimed to identify chromosomal imbalances in OS, two distinct commonly deleted regions on chromosome 6, were found by comparative genomic hybridization [137]. Fine mapping of the deletion refined the region containing a putative tumour suppressor gene. The expression analysis of genes located at the deleted region was performed, and decreased mRNA expression of the CCNC gene was revealed. Moreover, the growth of three OS cell lines was significantly suppressed after CCNC cDNA transfection [137]. This association of CCNC depletion with cancer points to a possible role as a governor of CDK8 activity. Indeed, any deregulation of CDK8 activity, either by the loss of control or modest increase in total kinase activity, may be oncogenic. However, the control of CDK8 activity still remains poorly understood [125].

3. Conclusions and future perspectives

Overall, the literature findings suggest an important role of MED complex in cancer development and metastasis formation. Indeed, MED has been implicated in a lot of human malignancies through studies connecting altered expression, or, in some cases, mutations of genes coding for its subunits, with numerous types of cancers. However, in most cases, detailed molecular mechanisms involved in the role of MED in cancer development and/or progression are still unknown or they have been investigated only in in vitro models. Indeed, well-established mechanisms essentially exist only for those subunits participating to the transcription regulation with members of the NR superfamily [27,28]. A significant example is MED1 subunit, which is an essential coactivator for several hormone receptors, including ER [29,30], and it has been associated with many cancers, both hormonal (like breast and prostate cancers) and non-hormonal (such as lung cancer and melanoma) [31,33,37,38,40]. Another well-recognized mechanism involves the subunits of the kinase module, particularly MED12, CDK8 and CCNC subunits, which play also a role in the Wnt/beta-catenin signalling. Specifically, a direct oncogenic role of CDK8 in colorectal cancer through the regulation of beta-catenin activity has been demonstrated [59]. Also of note is the involvement of MED12 in uterine sarcomas [54–58]. This subunit is also fundamental for ERα-regulated transcriptome; indeed, similarly to cohesin, MED12 depletion significantly impairs this pathway suggesting that this regulation could be employed for the treatment of oestrogen-dependent breast cancer [51]. Recently, a growing body of evidences indicates new physiological roles for MED complex. For instance, MED23 has also been demonstrated to interact with hnRNPL to regulate alternative splicing, a post-transcription regulative process that is also altered in many tumours [24]. Thus, the whole comprehension of the mechanisms and functions of MED can also help to clarify the causative role of its individual subunits in human malignancies and open new fields of investigation.

A further issue to be elucidated is the function of each individual subunit as regard to the oncogenic or tumour suppressor properties. Indeed, available data indicate that each subunit may display a different behaviour depending on the tissue type and also on the genetic background of the cancer cell. One emblematic example is MED2/29 that exhibits a dualistic role in pancreatic cancer with both oncogenic and tumour suppressive characteristics [41]. Thus, it would be of interest to understand also the feature of the entire complex in this context.

Besides the literature results on the already described cancer types, it is conceivable that the expression of one or more MED subunits can be modified in all malignancies and, hence, that a specific MED alteration pattern can characterize each cancer type. Indeed, this complex contains various submodules and several subunits and has a mobile structure with a vast surface; thus, it is possible that MED acts by interacting with different proteins involved in multiple stages of the deregulated transcription during cancer development and metastasis. Since several regulators of Pol II-dependent transcription have a fundamental role in malignant transformation, MED complex can act as a key principal coordinator, by organizing different factors in the gene expression regulation.

However, to date the whole MED complex has not been explored yet in most of cancers and the role of other subunits is still unknown. Indeed, very recently we have reported the complete picture of MED subunit gene expression in human OS by comparing three OS cell lines with normal osteoblasts. Interestingly, in our study we found expression alteration in most of the MED genes. Noteworthy, we noted a general increase in the expression of subunits belonging to the head module and a decrease in those of the kinase one. Moreover, among the significantly differently expressed subunit genes we observed a very high overexpression of MED20 and MED31 in all the analysed OS cells, thus suggesting for the first time a potential role of these subunits in human malignancies [138]. Accordingly, future investigations aimed to depict this important complex in the different tumour types are required.

Finally, given the role of several MED subunits in cancer, insights on their role in malignancies can provide both novel tumour markers for the diagnostic tools as well as novel targets for cancer therapy. For instance, the CDK8 dysregulation in many cancers like melanoma and colorectal carcinoma has stimulated a great interest in developing drugs specifically targeting CDK8 for cancer therapy. A possible strategy is the search for small molecule inhibitors of CDK8 kinase activity, even though such inhibitors could affect also other CDKs given their high similarities or they could produce adverse effects on cell viability [139]. An alternative approach would be to design methods to only reduce the protein levels of CDK8 or CCNC, by delivering specific shRNAs that target their mRNAs in cancer cells [140]. However, this strategy is still far from the clinical usage. If successful, these approaches may be specifically advantageous for patients with increased levels of CDK8 or CCNC and, similarly, they can be also extended to other patients with increased expression of specific MED subunits, such as MED19 [83–97].

The involvement of MED12 in cancer is also particularly relevant for treatment of many tumours. Beyond the findings of several mutations in some cancers, recently MED12 has also been demonstrated to control the response to multiple cancer drugs through the regulation of TGF-β receptor signalling. Specifically, MED12 suppression was found to confer resistance to a variety of cancer drugs, including chemotherapy, in colon cancer, melanoma, and liver cancer [61]. Thus, small-molecule drug inhibition of this pathway in cells with MED12 disruption has been suggested to reverse resistance to targeted cancer drugs.

Also MED1 could be potentially used as an advantageous therapeutic target for the treatment of tamoxifen resistant human breast cancer. Indeed, it is required for the expression of both oestrogen and EGF dependent ERα target genes in HER2-overexpressing cells [33]; thus, it can be used to simultaneously block these two pathways for the treatment of endocrine resistant breast cancer.

Conflict of interest statement

The authors do not have any conflicts of interest to declare.

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