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Mediator and Human Disease

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Abstract

Since the identification of a metazoan counterpart to yeast Mediator nearly 15 years ago, a convergent body of biochemical and molecular genetic studies have confirmed their structural and functional relationship as an integrative hub through which regulatory information conveyed by signal activated transcription factors is transduced to RNA polymerase II. Nonetheless, metazoan Mediator complexes have been shaped during evolution by substantive diversification and expansion in both the number and sequence of their constituent subunits, with important implications for the development of multicellular organisms. The appearance of unique interaction surfaces within metazoan Mediator complexes for transcription factors of diverse species-specific origins extended the role of Mediator to include an essential function in coupling developmentally coded signals with precise gene expression output sufficient to specify cell fate and function. The biological significance of Mediator in human development, suggested by genetic studies in lower metazoans, is emphatically illustrated by an expanding list of human pathologies linked to genetic variation or aberrant expression of its individual subunits. Here, we review our current body of knowledge concerning associations between individual Mediator subunits and specific pathological disorders. When established, molecular etiologies underlying genotype-phenotype correlations are addressed, and we anticipate that future progress in this critical area will help identify therapeutic targets across a range of human pathologies.

1. Introduction

The specification and maintenance of cell fate in multicellular organisms is critically dependent upon the precise spatiotemporal control of RNA polymerase II transcription in response to a determinative set of cell-intrinsic and –extrinsic signals. Accordingly, genetic or environmental factors that perturb physiologic transcription controls can alter cell fate decisions leading to a variety of pathologic conditions including developmental defects and cancer. Because of its central importance in organismal biology, metazoans have evolved an elaborate protein machinery to ensure proper transcription control. Work over the last decade and a half has identified Mediator as a critical component of this regulatory

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apparatus. Mediator is a conserved multiprotein interface between gene-specific transcription factors and RNA polymerase II [1]. In this capacity, Mediator serves to channel regulatory signals from activator and repressor proteins to affect changes in gene expression programs that control diverse physiological processes, including cell growth and homeostasis, development, and differentiation [2, 3]. Originally discovered in the budding yeast *S. cerevisiae*, Mediator has since been identified as an essential component of the RNA polymerase II transcriptional apparatus in metazoans ranging from worms to humans [4]. Nonetheless, consistent with the enhanced complexity of multicellular organisms, metazoan Mediator complexes are generally larger than their yeast counterparts and include both orthologous as well as metazoan-specific subunits. Among metazoans, mammalian Mediator exhibits the greatest degree of compositional and structural complexity, comprising 33 subunits, 23 of which correspond to clear orthologs in *S. cerevisiae* Mediator.

Because of its role as an integrator and processor of regulatory information conveyed by signal-activated transcription factors, Mediator represents an endpoint in a variety of fundamentally important developmental signaling pathways [2, 3, 5]. Consistent with such a role, genetic studies in mice have broadly implicated Mediator in mammalian development. Genetic inactivation of core Mediator subunits responsible for direct communication with RNA polymerase II result in very early embryonic lethality, indicating that Mediator *per se* is likely required for cell viability [6]. However, targeted inactivation or mutation of peripheral Mediator subunits, while invariably lethal, nonetheless confers broad yet distinctive defects in organogenesis and altered programs of gene expression that generally phenocopy mutations in essential developmental transcription factors [7–18]. These observations support the idea borne from biochemical and cell-based studies that Mediator transduces regulatory information conveyed by signal-controlled transcription factors that interface with distinct Mediator subunits. Thus, individual Mediator subunits can manifest activator- and/or repressor-selective functions in the regulation of developmental gene programs. It is therefore not unexpected, and emerging studies have indeed confirmed, that individual Mediator subunits are associated with wide range of human diseases spanning congenital malformations to cancer. In this review, we highlight examples in which overt mutation or altered expression of human Mediator subunits have been linked with specific pathological disorders (summarized in Table 1).

2. Mediator and Disorders of Development

2.1. Neurodevelopmental Disorders

2.1.1. MED25 and Charcot-Marie-Tooth Disease—Charcot-Marie-Tooth (CMT) disease or hereditary motor and sensory neuropathy (HMSN) comprises a large group of clinically and genetically heterogeneous peripheral nervous system disorders. CMT is the most commonly inherited peripheral neuropathy worldwide, and all mendelian modes of inheritance have been described [19]. Two major CMT forms are distinguishable based on electrophysiological and pathological criteria: the demyelinating CMT type I (CMT1) and the axonal CMT type II (CMT2) [20]. Among all forms of CMT, the autosomal recessive axonal forms (ARCMT2) are comparatively rare and severe [20]. To date, genes for three distinct and specific ARCMT2 loci have been identified on chromosomes 8q (Lamin A/C;

LMNA), 1q (ganglioside-induced differentiation-associated protein 1; *GDAP1*), and 19q (Mediator subunit 25; *MED25*) [20].

The association of *MED25* on chromosome 19q13.3 with ARCMT2 was initially established through investigation of an extended consanguineous Costa Rican family of Spanish and Amerindian ancestry [21]. Affected patients in this family presented with relatively late-onset chronic symmetric sensory-motor polyneuropathy and axon degeneration. Refined genetic mapping within the 19q13.3 region identified a critical interval of 1 Mb; sequence analysis of this region identified 53 genes, 3 of which exhibited variations that cosegregated with the recessive neuropathy in this family. Among these, a p.A335V missense mutation in *MED25* was identified as the likely disease causing variation.

The molecular basis by which a homozygous A335V missense mutation in MED25 triggers ARCMT2 is unclear. Amino acid 335 lies between two established structural and functional domains in MED25: an N-terminal 'von Willebrand factor type A' domain (aa 17-226) through which MED25 associates with core Mediator, and a C-terminal seven-stranded β-barrel activator interaction domain (aa 402–590) targeted by the viral transactivator VP16 [22, 23]. Possibly, the A335V mutation could compromise the structural integrity and/or crosstalk between these two established functional domains, although evidence to support this conjecture is currently lacking. Amino acid 335 is located in a MED25 proline-rich domain with high affinity for SH3 domains of the Abelson type; molecular and biochemical analyses have further revealed that the A335V mutation relaxes the binding specificity of this region, expanding the range of SH3-type domains with which it interacts [21]. However, the functional relevance of the SH3-binding domain for MED25-dependent transcriptional regulation remains to be established, and the significance of these findings is presently unclear. While the direct molecular consequence(s) of the A335V mutation on MED25 structure and/or protein interaction preference thus remains to be established, a likely biological outcome is disruption of MED25 as a critical Mediator interface for an unidentified transcriptional regulator of genes required for peripheral nervous system function.

2.1.2. MED17 and Infantile Cerebral and Cerebellar Atrophy—Postnatal-onset microcephaly (POM), in which a normal head circumference at birth declines to > 2SD below the mean after the neonatal period, is a feature of many neurological disorders characterized by developmental and psychomotor retardation, and it often carries a grave prognosis [24]. Recent work has uncovered a direct link between the Mediator subunit MED17 and a specific form of POM within the Caucasus Jewish community [25]. This link was initially established through genetic analysis of five infants from four unrelated families of Caucasus Jewish origin who presented shortly after birth with microcephaly, spasticity, epilepsy, and profound psychomotor delay [22]. Brain scans revealed severe cerebral and cerebellar atrophy accompanied by poor myelination. Genetic mapping was employed to identify a common homozygous region among these patients spanning 2.28 MB and 16 genes on chromosome 11. Among these genes, a single missense mutation in *MED17* (p.L371P) segregated with the disease state, and was subsequently identified in four additional patients of Caucasus Jewish heritage presenting with similar clinical and radiologic manifestations. Notably, population screening for the MED17 L371P mutation

revealed that four of 79 anonymous individuals of Caucasus Jewish origin, but none of 110 Ashkanazi Jewish or 113 Arab Muslim individuals, carried this mutation. It thus appears that L371P is a founder mutation in the Caucasus Jewish community [25].

MED17 plays an important role in Mediator architecture and function. It is critical for head module assembly, overall Mediator integrity, and association of Mediator with RNA polymerase II and promoter DNA [26, 27]. Additionally, MED17 is an established physical target and functional transducer of diverse signal-activated transcription factors, including p53 and NF-κB [28, 29]. Whether and how the L371P mutation might impact one or more of these critical functions leading to infantile cerebral and cerebellar atrophy remains to be established. Nonetheless, the *S. cerevisiae* MED17 ortholog, Srb4, engineered to carry a corresponding L371P missense mutation failed to complement a temperature sensitive *srb-4* yeast strain for growth, indicative of a deleterious impact of this mutation on general MED17 function [25]. Because of the prominent postnatal involvement of white matter in affected patients whose development prenatally is unperturbed, it has been suggested that the L371P missense mutation might disrupt a critical function for MED17 in control of genes important for oligodendrocyte development, as this process commences only after birth in humans [25].

2.1.3. MED12 and Syndromal X-linked Mental Retardation: FG and Lujan syndromes—

X-linked mental retardation (XLMR) affects 1–2/1,000 males and accounts for ~10% of all mental retardation [30]. Approximately 1/3 of XLMR cases are associated with sufficiently coincident somatic, neurobehaviorial, or metabolic features to permit diagnostic designation, and are therefore classified as “syndromal” in nature. To date, more than 140 syndromal XLMR conditions have been identified [31]. A growing number of these syndromes, originally considered distinct entities on the basis of clinical criteria alone, have instead been linked through identification of common gene mutations. Two such XLMR disorders, FG syndrome and Lujan syndrome, have recently been linked by mutations in MED12, an Xq13-encoded 230 kDa Mediator subunit.

FG syndrome, first described In 1974 by Opitz and Kaveggia, is characterized by mental retardation, complete or partial agenesis of the corpus callosum, relative macrocephaly, congenital hypotonia, craniofacial dysmorphisms (including tall and prominent forehead, downslanting palpebral fissures, and micrognathia), sensorineural deafness, constipation, seizures and behavioral disturbances, including hyperactivity, emotional lability, and autistic mannerisms [32–34]. Major anomalies are not uncommon in FG syndrome and include anorectal and urogenital malformations as well as congenital heart defects [34]. The combination of anal and cardiac defects is lethal during prenatal and early postnatal periods in some affected patients.

In the mid 1980’s, Lujan and Fryns independently described an XLMR syndrome (commonly called Lujan-Fryns, or Lujan syndrome) characterized by developmental delay, agenesis/dysgenesis of the corpus callosum, macrocephaly, hypotonia, distinct facial dysmorphisms (including prominent forehead, long narrow face, maxillary hypoplasia, and small mandible), and behavioral disturbances, including hyperactivity, emotional lability, autistic mannerisms, and psychoses [35, 36]. Although FG and Lujan syndromes share

several overlapping clinical manifestations (macrocephaly, tall forehead, tall narrow palate with dental crowding, hypotonia, mental retardation, behavioral disturbances and dysgenesis of the corpus callosum), neither syndrome was originally considered in the differential diagnosis of the other. Recent findings, however, have revealed that these syndromes are allelic and caused by different missense mutations in MED12.

FG syndrome is genetically heterogeneous, and five loci (*FGS1-5*) have so far been identified on the X chromosome [34]. Sequence analysis of candidate genes from XLMR families with linkage to Xq13 identified a recurrent p.R961W missense mutation in *MED12* responsible for FG syndrome in 6 out of 45 families, including the original family for whom the condition was named [37]. Shortly thereafter, a systematic sequencing screen of 737 annotated genes in 250 XLMR families identified a p.N1007S missense mutation in *MED12* in the original Lujan syndrome family as well as a second family that was originally diagnosed with FG syndrome [38]. Neither sequence alteration was found in over 1400 control X chromosomes [37, 38].

The etiological basis by which the R961W and N1007S missense mutations in MED12 elicit cognitive dysfunction, while not fully resolved, is nonetheless suggested by recent studies that implicate MED12 in critical aspects of neural development. First, MED12 has been linked biochemically and genetically with the Notch, Wnt, and Sonic hedgehog signaling pathways that control key aspects of brain development and function, from initial patterning to neuronal plasticity [12, 39–45]. Second, in zebrafish, MED12 has been shown to be required for the proper development of the brain and neural crest, among other organs, where it plays an important role in the production of monoaminergic neurons and cranial sensory ganglia [46–49]. Third, and more directly relevant to the molecular etiology of MED12-associtiated XLMR, we recently discovered that the FG/R961W and Lujan/N1007S missense mutations in MED12 disrupt epigenetic silencing of neuronal gene expression imposed by the RE1 silencing transcription factor/neuron restrictive silencer factor (REST/NRSF), a master regulator of neuronal fate.

REST occupies a central role in non-neuronal lineage restriction through its ability to silence neuronal-specific gene expression in terminally differentiated non-neuronal cells and neural progenitor cells [50–55]. Mechanistically, REST-directed gene silencing is achieved via REST-dependent recruitment of multiple corepressors, including G9a histone methyltransferase, that collectively function to impose restrictive epigenetic modifications on the chromatin structure of REST-target genes [53, 55–57]. We found that the MED12 interface in Mediator links REST with G9a to silence REST-target genes through the imposition of transcriptionally repressive histone H3K9 dimethylation [58]. Notably, we also found that both the FG/R961W and Lujan/N1007S missense mutations in MED12 disrupt its REST-specific corepressor function, leading to unscheduled derepression of REST target genes [58]. Because REST and MED12 are both implicated in neuronal development, misregulation of REST target genes arising as a consequence of pathological mutations in MED12 could affect neuronal differentiation and possibly contribute to XLMR. Further studies in appropriate animal models will be required to validate this hypothesis.

2.1.4. CDK19 and Congenital Retinal Folds, Microcephaly, and Mental Retardation—

Along with microcephaly, mental retardation, and certain other systemic malformations, congenital retinal fold, characterized by the presence of a raised retinal fold extending radially from the posterior pole to the fundus periphery, has been considered a distinct clinical syndrome of heterogeneous genetic etiology [59]. Recently, CDK19 was linked to this condition through genetic analysis of a single female Caucasian patient [59]. Karyotpe analysis of this patient revealed a pericentric inversion of one copy of chromosome 6 causing haploinsufficiency of CDK19 [59].

CDK19 is a paralog of the *bona fide* Mediator subunit CDK8; the two human proteins share 77% sequence identity, and are nearly equivalently related to a single *Drosophila* ortholog (cdk8), suggesting their close functional relationship [59, 60]. Conditional knockdown of *Drosophila* cdk8, important for normal eye development, in multiple dendrites and neurons was shown to result in significantly reduced dendritic branching and altered morphology of the dendritic arbor, thus revealing an important function for the *Drosophila* ortholog of CDK19 in the development of structures implicated in the etiology of mental retardation [59, 61]. Based on the paralogous relationship between CDK8 and CDK19, as well as the identification of CDK19 in purified Mediator preparations, it seems probable that CDK19 might replace CDK8 as a *bona fide* Mediator subunit in specialized cellular contexts, such as in the developing nervous system [59, 60]. If so, haploinsufficiency of CDK19 in humans could deleteriously impact Mediator function and neuronal gene expression programs leading to altered neuronal development and congenital retinal folds, microcephaly, and mental retardation. Future studies will be required to clarify the mechanism(s) by which haploinsufficiency of CDK19 leads to these distinct neurodevelopmental phenotypes.

2.2. Cardiovascular Disorders

2.2.1. MED13L and Transposition of the Great Arteries—

Congenital heart disease occurs in approximately 0.7–1.0% of live births and thus represents the most common severe birth defect in humans [62]. Transposition of the great arteries (TGA) accounts for 5–7% of all congenital heart disease and is therefore the most common cyanotic heart defect diagnosed in neonates [62]. TGA is a condition marked by ventriculoarterial discordance, in which the aorta and pulmonary arteries arise from the morphological right and left ventricles, respectively, in a reversal of the normal cardiac outflow [63]. As a consequence, the systemic and pulmonary circulations operate in parallel rather than in series, resulting in the return of oxygen-poor blood to the body rather than the lungs. As TGA is incompatible with healthy survival, postnatal palliative treatment and corrective surgery is required. Despite its high prevalence, little is currently known regarding the pathogenesis of this disease. In this regard, MED13L, a paralog of the Mediator subunit MED13, was initially identified based on its disruption by a translocation breakpoint in a patient with TGA and mental retardation.

Positional mapping and sequence analysis of the region lying at the breakpoint on chromosome 12q24 revealed a novel transcription unit encoding a predicted protein with significant homology to MED13 (formerly TRAP240) [64]. On this basis, the gene was named *PROSIT240* (*pr*otein *si*milar to *T*RAP*240*), and later renamed MED13L (MED13-

like) according to the unified Mediator nomenclature [64, 65]. MED13L is broadly expressed in a variety of fetal and adult tissues, with particularly high expression in heart and brain, consistent with the clinically affected organ systems of the patient [64]. Disruption of a single MED13L allele in this TGA patient through chromosomal translocation led to haploinsufficiency at this locus. Subsequent screening analysis of 97 additional TGA patients revealed 3 missense mutations in *MED13L* (p.E251G; p.R1872H; p.D2023G) that were not present in 400 control chromosomes [64]. These findings implicate MED13L in the etiology of TGA and suggest an important role for this Mediator subunit in proper development of the heart and brain.

Based on the paralogous relationship between MED13L and MED13, the validated presence of MED13L in purified Mediator preparations, and the higher comparative expression of MED13L versus MED13 in heart (aorta) and brain (cerebellum), it seems likely that MED13L–enriched Mediator complexes could engage a unique ensemble of tissue-restricted regulators, thus enabling cardiac- and brain-specific transcriptional programs. Future studies will be required to confirm this prediction and establish how reduced expression or mutational inactivation of MED13L elicits TGA.

2.2.2. MED15 and 22q11.2 Deletion Syndrome—Chromosome 22q11.2 deletion syndrome, eponymously called DiGeorge syndrome (DGS) or velocardiofacial syndrome (VCFS) among others, represents one of the most common multiple congenital anomaly syndromes in humans, occurring in approximately 1/3000 live births [66]. This syndrome is characterized by an extremely heterogeneous phenotypic spectrum impacting nearly every organ system and developmental function [67]. Common clinical manifestations include cardiac defects, palatal anomalies, characteristic facial dysmorphisms, immune dysfunction and hypocalcemia arising from underdevelopment of the thymus and parathyroid glands, respectively, and neuropsychiatric anomalies, including schizophrenia and psychoses [66, 67]. Many of these abnormalities are attributed to defects in early neural crest cell migration and/or differentiation in the pharyngeal arches, wherein neural crest cells contribute to morphogenesis of the heart vessels, thymus, parathyroid gland and craniofacial structures [68]. The broad range of clinical manifestations associated with 22q11.2 deletion syndrome suggests the involvement of multiple genes; consistent with this expectation, the typically deleted region (TDR) in >90% of patients spans 3.0 Mb and 60 genes, while <10% of patients harbor a smaller deletion of 1.5 Mb encompassing 28 genes [69]. These microdeletions are the most common interstitial deletions known to occur in humans, and arise as a consequence of meiotic recombination errors involving low copy repeat sequences that are reiterated along chromosome 22 [69]. Among the genes deleted in the 3.0 Mb microdeletion associated with 22q11.2 deletion syndrome is MED15, initially cloned based on its identification as a subunit of the ARC/PC2 Mediator-like complexes and named PCQAP (PC2 glutamine/Q-rich-associated protein) [70, 71]. The gene encoding MED15/PCQAP was physically mapped to the DGS/VCFS region on chromosome 22q11.2, and further genetic analysis confirmed the gene to be deleted in DGS/VCFS patients carrying the major hemizygous deletion in the TDR [71].

Human MED15 is a physical target and functional transducer of the sterol regulatory element-binding protein 1α (SREBP1α) and TGFβ-activated SMAD2/3 that control lipid

metabolism and developmental programs, respectively [72, 73]. Its pleiotropic activity as a key hub in a variety of biologically important signal transduction pathways could thus explain how haploinsufficiency and reduced expression of MED15 might contribute to the clinically heterogenous phenotypes associated with the 22q11.2 deletion syndrome.

2.3. Behavioral Disorders

2.3.1. MED12 and Schizophrenia/Psychosis—Schizophrenia is a chronic, profound, and disabling mental disorder characterized by a wide spectrum of symptoms including delusions, hallucinations, disintegration of cognitive processes, and deterioration of social behaviors [74]. The global lifetime prevalence and incidence of the disease are estimated to be 0.3–0.7% and 10.2–22.0 per 100,000 person-years, respectively [75]. Etiologically, schizophrenia is a multifactorial disorder, with a relatively high heritability (~80%) believed to derive from both genetic and epigenetic factors that are susceptible to environmental influences [76]. On the basis of data derived from candidate gene and genome-wide association studies, the number of genes potentially implicated in schizophrenia is estimated to number greater than 1000 [76]. Thus, familial aggregation of schizophrenia is best explained not by genetic variation in a few loci with strong penetrance, but instead by the contribution of variation at many loci with weak to moderate association and linkage. One such locus in which genetic variation has been linked to a moderate increase in schizophrenia is *MED12*.

The gene encoding MED12 was originally isolated during an effort to identify GC-rich candidate genes for neurodevelopmental disorders. Isolation and characterization of human genomic clones bearing large trinucleotide repeats revealed a gene encoding a carboxyl terminal OPA (opposite paired) domain, which was named human OPA-containing gene (HOPA), and later renamed MED12 following its identification as a *bona fide* Mediator subunit [65, 77]. Initial polymorphism analysis of MED12 identified a 12 bp insertion ($HOPA^{12bp}$) coding for four additional amino acid residues (QQHQ) in its OPA domain that subsequent association and transmission disequilibrium analyses revealed is associated with a modest risk (~1.5) for an endophenotype of schizophrenia [78, 79]. Further analyses revealed a second, rare deletion polymorphism within the MED12 OPA domain ($HOPA^{-15bp}$) that appears also to be associated with psychosis [79, 80].

Distinct from the $HOPA^{12bp}$ and $HOPA^{-15bp}$ polymorphisms that impact the MED12 OPA domain, missense mutations R961W and N1007S causing FG and Lujan syndromes, respectively, have also been linked to neuropsychiatric illness. In addition to mental retardation and various congenital anomalies, FG and Lujan syndromes are associated with distinctive behavioral disturbances. In FG syndrome, adolescent behavior characterized by hyperactivity, affability, and excessive talkativeness yields during early adulthood to an increased risk for maladaptive behavior, aggression, anxiety, inattention, and obsessive-compulsive disorders [37, 81, 82]. In Lujan syndrome patients, a wide variety of anomalous behaviors have been documented, including hyperactivity, emotional lability, autistic mannerisms, and frank psychosis [38, 83, 84].

The molecular basis by which genetic variation in MED12 predisposes to behavioral dysfunction is not clear, but is suggested by recent advances, highlighted earlier, that

implicate MED12 in critical aspects of neural development. MED12 is critically implicated in the development and specification of certain neuronal subtypes, including those of the dopaminergic class proposed to be a driving force in positive symptom psychosis such as that associated with the $HOPA^{12bp}$ polymorphism [48, 85]. Furthermore, MED12 is an essential transducer of both the canonical Wnt and Shh signaling pathways critical for dopaminergic neuronal differentiation [39, 40]. Finally, MED12 is implicated in neuronal cell fate specification through its functional interaction with the neuronal gene silencer REST/NRSF [58]. It is therefore possible that deficits in the number and/or function of dopaminergic and perhaps other neuronal subtypes could contribute to the aberrant behavioral phenotypes associated with pathological sequence variations in MED12.

3. Mediator and Cancer

Given the established role of Mediator as an integrative hub linked to a variety of signaling pathways that govern growth, development, and differentiation, it is not surprising that many of its constituent subunits have, in recent years, been increasingly linked with cancer. In the ensuing section, recent findings concerning associations between specific cancers and individual Mediator subunits are highlighted, with particular emphasis accorded those for which mechanistic relationships as opposed to strictly correlative associations have been established.

3.1. Hormonal Cancers

3.1.1. MED1 and Breast Cancer—The first clearly established link between Mediator and cancer was the association of MED1 with breast cancer. Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths among women worldwide [86]. Among a variety of established etiological factors linked to breast cancer, the steroid hormone estrogen (17-β-estradiol; E2) has long been implicated in disease pathogenesis. Numerous animal studies have revealed that E2 can induce and promote breast cancer, while estrogen ablation therapy or the administration of antiestrogens can oppose these effects [87, 88]. The physiological effects of E2 in the breast are mediated by cognate receptors that are expressed as two structurally related subtypes, estrogen receptor α (ERα) and β (ERβ) [89, 90]. Both receptors bind E2 with high affinity, and these associations trigger conformational changes in the receptors that enable direct association with coactivator complexes, including Mediator, sufficient to promote high levels of transcriptional activation from target genes bearing cis-acting enhancer sequences to which the receptors bind [89, 91]. ERα is the predominant receptor isoform expressed in breast cancer cells, and approximately 70% of breast cancer patients score positive for ERα at diagnosis [92, 93]. ERα is therefore a dominant etiologic and valuable predictive factor with respect to breast cancer development and hormone sensitivity status.

Following the discovery that Mediator was a functionally requisite coregulatory complex for diverse members of the nuclear receptor superfamily, including ERα, MED1 was firmly established as the principle direct receptor interface in Mediator [94–96]. Both in vitro transcription-based functional assays and in vivo chromatin association studies revealed that Mediator is recruited by enhancer-bound ERα to facilitate transcription preinitiation complex formation and high-level transcript synthesis from ERα-target genes [94, 97–99].

Furthermore, gene-targeted mice expressing an ERα-binding defective MED1 mutant were found to exhibit blunted estrogen-responsive gene expression and defects in mammary gland development and differentiation that partially phenocopy those arising from genetic ablation of ERα itself [11, 100]. Taken together, these observations establish MED1/Mediator as a physiologically important coactivator of ERα.

On the basis of its close functional relationship with ERα, Zhu et al. examined MED1 in ERα-positive primary human breast tumors in an effort to establish whether its expression levels may be correlated with breast cancer occurrence [96]. Notably, MED1 mRNA levels were found to be overexpressed in ~50% of breast tumors studied; in approximately one-half of such tumors, overexpression was determined to derive from amplification of the *MED1* gene located on chromosome 17q12. Thus, MED1 overexpression in breast tumors may occur by mechanisms both dependent and independent of copy number gain. Taken together, these analyses suggest that MED1, as an obligate ERα coactivator required for proper mammary epithelial differentiation, may contribute to breast carcinogenesis.

Emerging studies suggest that MED1 may additionally participate in ERα-independent signaling pathways that impact breast cancer cell growth. The adipocytokine leptin is the product of the obese (*OB*) gene and a neuroendocrine peptide with pleitropic activities, including appetite control, reproductive function, and angiogenesis, among others [101–103]. Notably, leptin has also been identified as an endogenous growth factor for breast cancer, providing a possible basis to explain, at least in part, the established epidemiological link between obesity and enhanced breast cancer risk in postmenopausal women [104–107]. Recently, leptin was shown to promote breast cancer cell growth via activation of the JAK/Stat3 axis and downstream activation of the *CYCLIN D1* promoter through a mechanism involving MED1-dependent recruitment of Mediator [108]. Thus, MED1 appears to play an essential role in leptin-induced activation of Cyclin D1 expression and breast cancer cell proliferation.

3.1.2. MED1 and Prostate Cancer—Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer deaths in men worldwide [86]. Prostate cancer onset is driven by circulating androgens through their interactions with the androgen receptor (AR), a ligand-activated transcription factor that promotes high levels of transcription from androgen-responsive genes that control prostate cancer cell growth and survival [109, 110]. Analogous to its relationship with other nuclear receptors, MED1 has been shown to be a crtical transducer of AR-dependent signaling. Liganded AR binds Mediator in a MED1-dependent manner and similar to liganded ERα, but with distinct temporal kinetics, recruits MED1/Mediator to facilitate chromosomal looping and RNA polymerase II tracking between distal enhancers and proximal promoter regions within AR-target genes, enhancing their androgen-dependent expression [110–113]. Based on the clear functional relationship between AR and MED1, Vijayvargia et al. examined MED1 expression in primary human prostate cancers [111]. Notably, MED1 was found to be significantly overexpressed in 50% of prostate cancers examined, suggesting a possible role for MED1 in prostate cancer progression. Unlike breast cancers, in which amplification of chromosomal 17q12 contributes prominently to enhanced MED1 expression, this region is not significantly amplified in prostate cancer, and other studies have reported no significant

increase in MED1 mRNA levels in primary human prostate cancers [114]. It has been speculated, though not yet proven, that MED1 overexpression in prostate cancer cells could derive from phosphorylation-induced protein stabilization. Thus, phosphorylation of MED1 by mitogen activated protein kinase (MAPK), itself constitutively activated in many prostate cancers, increases MED1 protein stability, half-life, and interaction with RNA polymerase II and other Mediator subunits, suggesting that MED1 phosphorylation could enhance both its expression and function in the prostate cancer setting [115, 116]. As it has recently been shown that MED1 phosphorylation is a critical determinant of transcription factor-mediated chromosomal looping between distal enhancer and proximal promoter elements, it will be important to determine the role of MED1 phosphorylation as a potential mechanistic link between MED1 overexpression and enhanced function in prostate cancer [117]. Notably, MED1 is also overexpressed in and functionally required for proliferation of some androgen-independent (AR-negative) prostate cancer cell lines and primary tumors [112]. It will therefore be of critical interest to establish the role of MED1 in AR-independent pathways that control prostate cancer cell growth and survival.

3.1.3. MED28 and Breast Cancer—Along with MED1, MED28 has also been linked to breast cancer, and an emerging body of literature concerning MED28 function suggests possible bases for its involvement in this disease. Originally identified as an endothelial cell gene stimulated by tumor-conditioned media and thus named *endothelial-derived gene 1 (EG-1)*, its encoded protein was subsequently determined to be a *bona fide* Mediator subunit and so named MED28 according to the unified Mediator nomenclature [65, 118, 119]. Based on the angiogenic nature of human tumors and its initial endothelial origins, MED28 (EG-1) expression was initially examined in breast, colon, prostate, and lung cancers. MED28 expression was found to be elevated in cancerous as opposed to benign epithelial cells of the breast, colon, and prostate, with little differential expression observed between normal and cancerous lung epithelia [120]. More recently, MED28 expression was evaluated on a population basis using a larger breast cancer patient sample, and the association of MED28 expression with histopathological subtypes, clinicopathological variables, and disease outcomes was assessed. MED28 protein levels were found to be elevated in ductal carcinoma *in situ* and invasive ductal carcinoma of the breast relative to nonmalignant breast epithelium of glandular and ductal origin. MED28 protein levels were found to be elevated in ductal carcinoma *in situ* and invasive ductal carcinoma of the breast relative to nonmalignant breast epithelium of glandular and ductal origin [121]. Furthermore, MED28 expression proved to be a strong prognostic indicator of disease outcome, with higher MED28 expression associated with a greater risk of death in both early and late stage breast cancers [121].

Consistent with a role for MED28 in breast carcinogenesis, its overexpression or knockdown was found to enhance or inhibit breast cancer cell proliferation, respectively both in vitro and in vivo [121, 122]. Notably, MED28-mediated control of breast cancer cell growth was independent of estrogen receptor (ER) status, and MED28 expression in human breast tumors was found to be significantly associated with ER negativity [121–123]. Thus, unlike MED1, functional collaboration with ER cannot explain how MED28 controls breast cancer cell proliferation and tumor growth. In this regard, it is notable that MED28 was

independently identified as a binding partner of the cytoskeletal neurofibromatosis 2 (NF2) tumor suppressor merlin [124]. Furthermore, MED28 appears to partition between the actin cytoskeleton in association with merlin, and the nucleus as a resident subunit of the Mediator head module. Based on its bipartite compartmentalization dynamics and unique protein interaction profile, it has been proposed that MED28 might function to couple receptor-mediated signals at the cell surface to gene expression changes through cytoskeletal reorganization. Mechanistically, this could involve signaling crosstalk between the Src tyrosine kinase and mitogen activated protein kinase (MAPK) families, since cytosolic MED28 was found capable of stimulating both pathways and catalytically active c-Src is known to activate MAPK signaling [121, 125–128]. Significantly, both pathways are implicated in breast cancer development and/or progression [129, 130]. Further work will be necessary to clarify whether and how crosstalk between the Src and MAPK signaling pathways possibly contributes to ER-independent control of breast cancer cell growth by MED28.

3.2 Non-Hormonal Cancers

3.2.1. CDK8 and Colon Cancer—Worldwide, colon cancer is the second and third most commonly diagnosed cancer in women and men, respectively, and a leading cause of cancer-related deaths [86]. While early surgical excision of non-invasive tumors is essentially curative, few effective treatment options are available for advanced stage disease, which carries a grave prognosis. Colon tumors arise from intestinal crypts, from whence progenitor-derived epithelial cells commence differentiation as they initiate their ascent up intestinal villi [131]. Maintenance of the crypt progenitor phenotype is dependent upon the expression of genes programmed by the canonical Wnt/β-catenin pathway, and constitutive activation of this pathway is a driving force in the immortalization of intestinal epithelia and the initiation of colon cancer [131–134]. While the upstream events in this pathway linked to signal-induced stabilization and activation of β-catenin in the cytoplasm have been deciphered in considerable detail, the mechanistic basis by which β-catenin activates gene transcription upon translocation into the nucleus is comparably poorly understood. In this regard, a series of recent studies implicating the Mediator kinase module in Wnt/β-catenin signaling have converged to clarify these mechanistic issues, and further identify potential therapeutic targets in β-catenin driven cancers.

The Mediator kinase module was initially implicated in Wnt/β-catenin signaling based on the observation that the β-catenin C-terminal transactivation domain physically and functionally targets the MED12 interface in Mediator to activate transcription [40]. Subsequently, the *Drosophila* homologs of MED12 and MED13 were shown to be physical and functional targets of the essential β-catenin co-activator Pygopus, suggesting a model in which the two principal activation surfaces within the β-catenin transcriptional complex, the C-terminus of β-catenin and the N-terminal homology domain in Pygopus, both target MED12 within the Mediator kinase module [135]. These observations have important mechanistic implications for β-catenin-dependent gene activation because MED12 fulfills important architectural and biochemical roles within the kinase module of human Mediator. Structurally, MED12 effectively links CDK8/CyclinC with Mediator, since MED12 depletion leads to reductions in the steady state levels of CDK8/CyclinC as well as their

incorporation into Mediator [40, 58]. Biochemically, MED12 activates the CyclinC-dependent CDK8 kinase [136]. Taken together, these considerations suggest the involvement of enzymatically active CDK8 in β-catenin-driven gene regulation, a possibility since confirmed by recent work notable for its revelation of a direct link between the kinase module in Mediator and colon cancer.

In an effort to identify within the human kinome prospective modulators of β-catenin important for colon cancer, Firestein et al. conducted parallel high-throughput RNAi-based loss of function screens to identify kinases/phosphatases required for both β-catenin transactivation and colon cancer cell proliferation [137]. Among nine candidate genes found to be required for both functions, only CDK8 on chromosome 13 was observed to reside in a region of copy number gain in a significant subset of colon cancers. Further work revealed that CDK8 kinase activity was required for cell transformation as well as β-catenin-regulated target gene transcription and colon cancer cell proliferation. These observations thus identify CDK8 as a colon cancer oncogene and mechanistically implicate its kinase activity in β-catenin-driven gene regulation and colon carcinogenesis [137]. Because β-catenin binds directly to MED12, but not to CDK8 (or CyclinC) [40], β-catenin transactivation potential must be transduced through MED12 to CDK8, most likely via MED12-dependent stimulation of CyclinC-dependent CDK8 kinase activity. Future studies will be necessary to confirm this prediction and to identify CDK8 substrates downstream of β-catenin important for it oncogenic activity.

In addition to its role as a direct transducer of Wnt/β-catenin signaling, there is also convincing evidence that CDK8 may indirectly stimulate β-catenin activity through suppression of negative β-catenin regulators. Using a genetic screen in *Drososphila* to identify in vivo regulators of E2F–dependent apoptosis, Morris et al. recently uncovered an antagonistic relationship between E2F1 and β-catenin [138]. Either protein was found capable of suppressing the phenotypic effects wrought by overexpressing the other, and importantly, E2F1-induced apoptosis was found to be dependent upon its ability to inhibit β-catenin-dependent gene activation. In a consequent genetic screen for upstream regulators of E2F1, CDK8 was identified as a potent E2F1 suppressor. Subsequent biochemical analysis revealed that CDK8 kinase activity could suppress the inhibitory effect of E2F1 on β-catenin-dependent transcription. Taken together, these studies uncover twin regulatory functions for CDK8 within the Wnt/β-catenin pathway- one as a direct transducer of β-catenin-dependent gene activation and the other as an indirect suppressor of negative pathway regulators [137, 138]. It is likely that both of these activities contribute to the function of CDK8 as a colorectal cancer oncogene.

3.2.2. CDK8 and Melanoma—Melanoma is the least common but the most deadly form of skin cancer, accounting for only ~4% of skin cancer cases but >75% of skin cancer deaths [139]. Over the past 40 years, the incidence of melanoma has increased more rapidly than any other cancer [140]. While highly curable in its early stages, there is no effective treatment for metastatic melanoma, and a greater appreciation of the genetic and epigenetic changes involved in melanoma progression is therefore essential to advance these limited options. Recent work in this regard has uncovered a new link between CDK8 and melanoma, a finding with significant prognostic and therapeutic implications, and one that

also provides evidence of an expanding role for the Mediator kinase domain in the etiology of human cancers.

To explore histone variant exchange as a possible epigenetic determinant of melanoma progression, Kapoor et al. probed the H2A variant profile, including macroH2A (mH2A) and H2A.Z, H2A isoforms typically associated with transcriptionally silent and active chromatin states, respectively, during the course of melanoma progression [141]. Strikingly, this analysis revealed a global decrease in mH2A expression, along with chromatin decondensation, coincident with a reciprocal increase in H2A.Z expression, suggesting possible H2A variant exchange during the course of melanoma progression. Notably, forced reduction of mH2a in minimally malignant melanoma cells enhanced their proliferative and migration capacities in vitro as well as their growth and metastatic potential in vivo, consistent with a role for mH2A as a suppressor of malignant melanoma. To assess the transcriptional consequences of chromatin decondensation elicited by mH2A loss, Kapoor et al. profiled gene expression changes in mH2A knockdown cell lines, and identified CDK8 as an mH2A–repressed gene and, thus, a potential mediator of malignant melanoma progression. Accordingly, CDK8 knockdown in mH2A–depleted melanoma cells suppressed the proliferative advantage provoked by mH2A loss, and an inverse correlation was observed between mH2A and CDK8 expression in melanoma patient samples. Together, these findings implicate CDK8 as a major effector of mH2A–mediated melanoma progression [140].

The molecular basis by which CDK8 promotes melanoma progression is presently unclear. As a critical transducer of Wnt/β-catenin signaling, CDK8 could enable this pathway, which is constitutively activated in melanoma [142]. However, if this is the case, the mechanistic basis by which CDK8 mediates β-catenin-dependent gene activation and cell proliferation must fundamentally differ between melanoma and colon cancer, since CDK8 kinase activity is irrelevant in the former but indispensable in the latter [137, 141]. Future studies focused on CDK8 function and regulation in melanoma will undoubtedly help to clarify these intriguing distinctions. Interestingly, MED1 has also recently been implicated in melanoma progression. MED1 expression was found to be inversely correlated with degree of melanoma cell tumorigenicity, with high and low MED1 expression levels observed in melanoma cells of low and high tumorigenic potential, respectively [143]. Furthermore, MED1 depletion in non-tumorigenic melanoma cells increased their invasive properties in vitro as well as their tumorigenic potential in vivo, with no effect on their proliferative capacities [143]. Finally, enhanced tumorigenicity triggered by MED1 suppression was accompanied by expression changes in established melanoma invasion genes, implicating MED1 in regulation of gene expression programs important for melanoma progression [143]. Whether and how MED1-dependent gene expression networks important for melanoma progression crosstalk with those under control of mH2A and CDK8 will represent an important area of future inquiry.

3.2.3. Other Mediator Subunits and Cancer—Mediator has been implicated in a growing list of additional human malignancies based on association studies linking aberrant expression of its constituent subunits with a variety of different cancers. In most instances, detailed molecular insight sufficient to explain how Mediator contributes to tumor

development and/or progression is lacking. Therefore, these studies are only briefly outlined below.

In addition to its well-established relationship to breast and prostate cancers, MED1 has been linked to lung cancer. Yun et al. recently identified MED1 expression in ~1/3 of human lung adenocarcinomas surveyed, and determined that MED1 expression is positively associated with more favorable histological subtypes, fewer lymph node metastases, positive ERβ receptor status, and enhanced survival [144]. Very recently, MED19, a key architectural component of the Mediator middle module, has been linked to lung, bladder, and breast cancers. Consistent with the expression profile underlying its initial discovery as a lung cancer metastasis related protein (LCMR1), MED19 is overexpressed in lung, as well as in bladder and breast tumors; in the latter, MED19 expression was significantly positively correlated with high tumor grade [65, 145–148]. Notably MED19 depletion reduced proliferation and colony formation of lung, bladder, and breast cancer cells in vitro as well as the tumorigenicity of lung and bladder cancer cells in vivo [145–147]. Thus, by mechanisms not yet established, MED19 appears to be an important regulator of lung, bladder, and breast tumorigenesis.

MED29, the human homolog of the *Drosophila* Doublesex coactivator Intersex, was recently found to be recurrently amplified and overexpressed in a subset of pancreatic cancers characterized by chromosomal 19q13 gain [149–152]. MED29 depletion in pancreatic cancer cells with high endogenous expression due to gene amplification was observed to potentiate apoptosis and attenuate oncogenic phenotypes in vitro, including proliferation, colony formation, cell migration, and invasion, thus revealing MED29 to be an essential determinant of pancreatic cancer cell growth and survival [151, 153]. Unexpectedly, forced overexpression of MED29 in pancreatic cancer cells with low endogenous expression levels also reduced cell proliferation in vitro as well as tumor growth in vivo, and triggered concordant transcriptional changes in cell cycle regulatory genes [153]. Together, these findings imply complex, and possibly context-dependent, dual oncogenic and tumor suppressive properties for MED29 in the regulation of pancreatic tumorigenesis.

Finally, at least two Mediator subunits, MED1 and MED23, have been implicated in suppression of tumor metastases. Loss of MED1 expression in lung carcinoma or MED23 in malignant melanoma, the latter through chromosomal deletion and loss of heterozygosity, was found to be associated with diminished promoter activation and reduced expression of the metastasis suppressors DAPK1 and KiSS-1, respectively [154, 155]. Mechanistically, tumor-specific loss of MED1 or MED23 depletes an interface in Mediator for the C/EBP-β or Sp1 transcriptional activators that drive expression of DAPK1 and KiSS-1, respectively [154–156]. Thus, pathologic reductions in the levels of key coactivators can drive cancer progression through diminished production of downstream suppressors of tumor metastases.

4. Conclusions and Future Perspectives

Functional and comparative genomics analyses have revealed a deep evolutionary origin for the multiprotein Mediator as a central conduit of regulatory information that converges on

eukaryotic protein coding gene promoters [4]. These analyses suggest the presence some 1–2 billion years ago of 17-subunit core “protocomplex” that served as structural framework upon which additional Mediator subunits have been added, rearranged, and occasionally duplicated during evolution to yield the unique species-specific Mediator assemblies present today. The diversification and expansion in both the number and sequence of Mediator subunits during the course of eukaryotic evolution represents a two-edged sword. While it very likely contributed to the expanding genetic circuitry of increasingly complex multicellular organisms, it also undoubtedly introduced new points of ontogeneic and oncogenic susceptibility. Given its central role as an integrative hub for diverse developmental signaling pathways, we expect the list of human diseases linked to mutation or dysregulation of Mediator subunits to continue its rapid expanse, and likely encompass the range of physiological systems in which Mediator is an indispensable component. Further, we also expect an increase in the number of reported virus-Mediator interactions, an emergent area of considerable interest and direct relevance to human disease. Since initial observations that human Mediator is a physical and functional target of the adenovirus E1A and herpes simplex virus VP16 transactivator proteins, a growing list of human pathogenic viruses, including Kaposi’s sarcoma associated herpesvirus, varicella-zoster virus, and bunyamwera virus, have been shown to target Mediator and thus reprogram the host cell transcription machinery for purposes of viral latency, immune evasion, or lytic replication [28, 70, 157–164]. Fortunately, as a direct transducer of oncogenic and viral pathogenic induced signaling, we may also expect that Mediator and its constituent subunits will hold important keys to future therapeutic intervention in a range of human pathologies.

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Highlights

1. Mediator subunits are associated with human developmental defects.
2. Neurodevelopmental and behavioral disorders has been linked to Mediator
3. Dysregulation of Mediator subunits are linked to cancer development and progression.
4. Mediator kinase module is implicated in both cancer and neuropsychiatric illness.
5. Mediator is potential therapeutic target for a range of human pathologies.

TABLE 1

Molecular Disposition of Human Mediator Subunits Linked to Pathological Disorders

Disease/Disorder		Mediator Subunit	Molecular Disposition	References
NEURODEVELOPMENTAL DISORDERS				
X-Linked Mental Retardation	FG syndrome	MED12	missense mutation (R961W)	[37]
Syndromes	Lujan syndrome	MED12	missense mutation (N1007S)	[38]
Infantile Cerebral and Cerebellar Atrophy		MED17	missense mutation (L371P)	[25]
Autosomal recessive axonal Charcot–Marie–Tooth disease		MED25	missense mutation (A335V)	[20], [21]
Congenital Retinal Folds, Microcephaly, and Mental Retardation		CDK19	haploinsufficiency (pericentric inversion)	[59]
CARDIOVASCULAR DISORDERS				
Transposition of the Great Arteries (TGA)		MED13L	haploinsufficiency (chromosomal translocation)	[64]
		MED13L	missense mutation (E251G; R1872H; D2023G)	[64]
22q11.2 Deletion Syndrome		MED15	deletion	[69], [71]
BEHAVIORAL DISORDERS				
Schizophrenia; Psychosis		MED12	polymorphism ($HOPA^{12bp}$; $HOPA^{-15bp}$)	[78–80]
CANCER				
Bladder		MED19	overexpression	[146]
Breast		MED1	overexpression (with/without gene amplification)	[96]
		MED19	overexpression	[147]
		MED28	overexpression	[120], [123]
Colon		MED28	overexpression	[120]
		CDK8	overexpression (gene amplification)	[137]
Lung		MED1	reduced expression	[144], [155]
		MED19	overexpression	[145]
Melanoma		MED1	reduced expression	[143]
		MED23	loss of heterozygosity (chromosomal deletion)	[154]
		CDK8	overexpression (secondary to mH2A loss)	[141]
Pancreas		MED29	overexpression (gene amplification)	[151], [153]
Prostate		MED1	overexpression (without gene amplification)	[112], [114]
		MED28	overexpression	[120]