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Review

Involvement of the *MEN1* Gene in Hormone-Related Cancers: Clues from Molecular Studies, Mouse Models, and Patient Investigations

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Abstract: *MEN1* mutation predisposes patients to multiple endocrine neoplasia type 1 (MEN1), a genetic syndrome associated with the predominant co-occurrence of endocrine tumors. Intriguingly, recent evidence has suggested that MEN1 could also be involved in the development of breast and prostate cancers, two major hormone-related cancers. The first clues as to its possible role arose from the identification of the physical and functional interactions between the menin protein, encoded by *MEN1*, and estrogen receptor α and androgen receptor. In parallel, our team observed that aged heterozygous Men1 mutant mice developed cancerous lesions in mammary glands of female and in the prostate of male mutant mice at low frequencies, in addition to endocrine tumors. Finally, observations made both in MEN1 patients and in sporadic breast and prostate cancers further confirmed the role played by menin in these two cancers. In this review, we present the currently available data concerning the complex and multifaceted involvement of MEN1 in these two types of hormone-dependent cancers.

Keywords: breast cancer; prostate cancer; estrogen receptor alpha; androgen receptor; the *MEN1* gene

1. Introduction

The most frequently encountered hormone-dependent cancers are breast and prostate cancers. The prevalence of breast cancer (BC) has increased such that its incidence is ranked second after lung cancer among cancers occurring in women [1], with 18.1 million new cases and 9.6 million cancer deaths in 2018. Similarly, prostate cancer (PCa), with its 174,650 new cases and 31,620 deaths estimated in 2019 in the USA alone [2], continues to represent a major cause of cancer-related mortality and morbidity in men. Hence, their global health burden is enormous, especially in developed countries, where their incidence is increasing [3]. Intriguingly, several lines of evidence have recently suggested that the tumor suppressor gene *MEN1*, the mutation of which predisposes patients to multiple endocrine neoplasia type 1 (MEN1, OMIM131100), may be involved in the development of these two cancers. In this review, we present the currently available data concerning the seemingly complex and multifaceted implications of *MEN1* in these two types of hormone-dependent cancers. We believe that a better understanding of the role played by *MEN1* should provide useful insights,

not only into the mechanisms underlying the development of these two cancers, but also into their treatment, and may provide new markers for their diagnosis and prognosis.

2. Background about Breast and Prostate Cancers

2.1. Histopathology and Classification

2.1.1. Breast Cancer

BC is histologically divided into two subtypes based on its invasive features—in situ carcinoma or invasive (infiltrating) carcinoma. BCs can also be divided into ductal or lobular types, depending on the tissue of origin, whether arising from the inner wall of the mammary ducts or the mammary glands, respectively [4]. More recently, a classification based on molecular markers such as estrogen receptor alpha (ERα), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) was purposed to facilitate the diagnosis and treatment of the four main subtypes. These include: (i) Luminal A, which represents approximately 40% of diagnosed BCs, is ERα-positive, PR-positive, or both; HER2-negative; Ki-67-low; and is associated with a slow proliferation and a significantly good prognosis, being sensitive to hormonotherapy. (ii) Luminal B is ERα-positive, PR-positive, or both; either HER2-positive or -negative and Ki-67-high; and has a worse prognosis than the luminal A subtype. (iii) The HER2-enriched subtype is ERα- and PR- negative, HER2-positive, and more aggressive than luminal subtypes. (iv) Triple-negative breast cancers (TNBCs) are ERα-negative, PR-negative, and HER2-negative [5], and are the most aggressive subtype, with the worst prognosis. Recent studies have further attempted to divide this classification into six subtypes by including basal-like and androgen receptor (LAR) subtypes, the latter displaying a high level of androgen receptor (AR) expression and an enrichment in AR signaling [6]. Treatments for BC including surgery, radiotherapy, chemotherapy, hormonotherapy, and rapidly developing targeted therapies, depend on the BC subtypes. ERα-positive BC subtypes are the most sensitive to hormonotherapy using either selective estrogen receptor modulators (SERMs) or selective estrogen receptor downregulators (SERD), whereas the treatment for HER2-enriched BCs has been greatly improved owing to therapies targeting the HER2 receptor. Unfortunately, there are very limited therapeutic options for TNBCs, although inhibitors of poly (ADP-ribose) polymerase (PARP) have shown promising results [7].

2.1.2. Prostate Cancer

PCa classifications mainly revolve around the Gleason grading system, based entirely on the histological pattern of carcinoma cells in Hematoxylin and Eosin (H&E)-stained prostate tissue sections [8,9] and the local disease state [10]. Aberrant signaling in the androgen pathway is critical in the development and progression of PCa. Androgen deprivation therapies (ADT) are the frontline treatment for PCa [11,12]. Although highly effective, ADT are characterized by the predictable emergence of resistance, termed castration-resistant PCas (CRPCs) [13,14], with a high mortality rate [15]. Genomic characterizations of CRPCs have led to the subdivision of CRPCs into two subtypes: (1) AR-dependent CRPCs, containing alterations in the *AR* gene, such as amplification, point mutations, and generation of splice variants; and (2) AR-independent CRPCs, in which resistant cells or metastatic CRPC (mCRPC) lack AR expression or signaling. The latter subtype has recently been reported to be associated with cellular plasticity and neuroendocrine (NE) molecular features. Importantly, there are mCRPCs that neither express the AR nor markers of NE differentiation ("AR null–NE null") [16,17]—their incidence has risen over the past 2 decades from 5% in 1998–2011 to 23% in 2012–2016 [18]. Neuroendocrine prostate cancer (NEPC) displays a more complex spectrum of phenotypes, ranging from anaplastic carcinomas to pure small-cell carcinomas (SCCs) [18,19]. Several studies [20–22] have shown that 10–20% of lethal PCa display SCC features with a very poor prognosis [23,24].

2.2. *Estrogen Receptor-Alpha and Androgen Receptor*

2.2.1. Estrogen Receptor-Alpha (ERα)

Structure

ERα belongs to the steroid-stimulated nuclear receptors, which are transcriptional factors involved in regulating the transcription of hundreds of target genes [25]. The gene encoding ERα is called *ESR1*. This gene is highly conserved, localized on chromosome 6q25.1, and composed of 8 exons on a 140 kb genomic locus (Figure 1, upper panel) [26]. ERα consists of 595 amino acids, with two transactivation domains AF1 and AF2 located in the N-terminal domain (NTD) and domain E, respectively. The NTD is involved in both inter-molecular and intra-molecular interactions, as well as in the regulation of gene transcription, while the DNA-binding domain (DBD) allows ERα to dimerize and to bind to specific estrogen response element (ERE) sequences on DNA. The hinge domain (D region) containing the nuclear localization sequence (NLS) plays a role in receptor dimerization and in binding to chaperone heat shock proteins (Hsp). The ligand-binding domain (LBD, E/F region, C-terminal) comprises the E_2-binding domain and works synergistically with the NTD in the regulation of gene transcription (Figure 1, upper panel) [27]. At least 2 isoforms of Erα have been identified: Erα-46, lacking the AF1 domain [28]; and ERα-36, devoid of both transcriptional activation domains (AF1 and AF2) and localized in both the plasma membrane and cytoplasm, where it mediates non-genomic ERα signaling [29,30]. *ESR1* mutations, such as *ESR1* amplifications or point mutations, were found in endocrine-therapy-resistant breast tumors, and occur predominantly in the LBD, leading to constitutive hormone-independent activation of ERα [31,32].

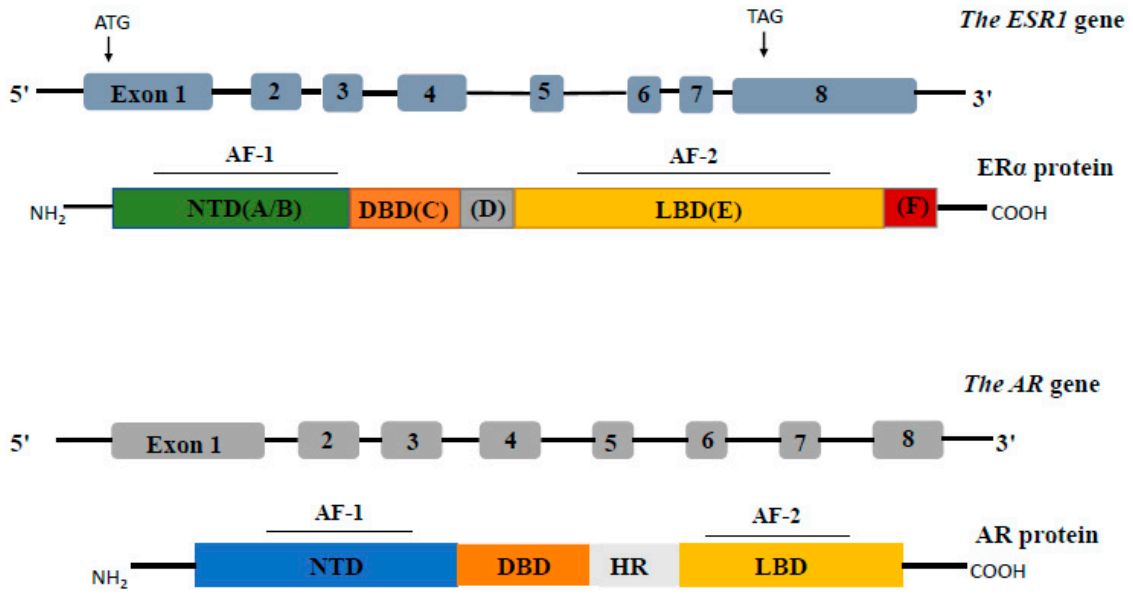

Figure 1. Schematic representation of the structure of the *ESR1* gene and the *AR* gene and their proteins. Different protein domains are indicated, including the N-terminal domain (NTD), the DNA binding domain (DBD), the hinge domain (D for ERα protein and HR for AR protein), and the ligand binding domain (LBD).

ESR1 Gene Regulation

Several studies have demonstrated that the *ESR1* promoter is positively or negatively regulated by epigenetic factors. In 1994, Ottaviano et al. showed that the lack of ERα expression in ERα-negative BC cell lines was due to the hypermethylation of *ESR1* CpG islands [33]. It was subsequently shown that the *ESR1* promoter was occupied by several complexes with inhibitory components such as DNA methyltransferases (DNMTs) and histone modifiers such as HDAC1 and msin3A [34,35].

Many studies have also reported that the *ESR1* promoter was occupied by several transcription factors, including members of the AP1 [36] and Forkhead box (FOX) family (FOXO3A [37], FOXM1 [38]), as well as metastasis-associated protein 1 (MTA1) and Twist [39]. The most extensively described ERα-associated transcription factors are GATA3 [40] and FOXA1 [41], which activate the transcription of the *ESR1* gene and are necessary for its proper functioning [40,42,43]. Recently, a study also revealed a regulation of the *ESR1* distal promoter by a loop-like complex involving GATA3, FOXA1, and menin [44]. In this study, they showed that menin binds to the *ESR1* enhancer region at sites that are also bound by FOXA1 and GATA3, and recruits the mixed lineage leukemia (MLL) compass-like complex containing MLL1/2, menin, ASH2L, RBBP5, and WDR5 [45] to these sites, thus forming a complex and regulating its expression.

Gene Targets and Gene Functions

Estrogens, through the ERα signaling pathway, play important and various developmental, physiological, and pathological roles. ERα is essential for the normal development of the female reproductive tract, including the uterus and the ovaries, as well as the proliferation and differentiation of mammary glands [46]. Furthermore, ERα plays a role in male fertility and in other non-reproductive organs, such as the neuroendocrine and cardiovascular systems and bone metabolism [46,47]. Estrogens can bind to ERα in the cytoplasm and causes their release from bound chaperones, dimerization, and their nuclear translocation, where they bind to ERE and regulate transcription of downstream ERα genes, triggering the "genomic signaling pathway". ERα can also indirectly bind to promoters via protein–protein interactions, activating a variety of transcription factors, such as the activator protein (AP)-1 or the nuclear factor-κB (NF-κB) [48]. Finally, estrogens can bind to ERα in the plasma membrane, thus inducing the "non-genomic pathway".

Among the thousands of ERα target genes, one of the earliest identified was *pS2/TFF1* [49,50], followed by many genes that were discovered by monitoring the global expression changes upon estradiol induction [51–55]. ERα target genes display a wide variety of functions, such that they can be divided into (i) pro-proliferative genes, such as *Cyclin D1* [56], *cMyc* [57,58], and *IGF-1* [59]; (ii) anti-apoptotic factors, such as *TIT-5* and *EIT-6* [55]; (iii) enzymes, such as the lysosomal proteinase cathepsin D [60]; (iv) and nuclear receptors, such as progesterone receptor [61], in addition to many other genes of as yet unknown function. Interestingly, these global expression experiments indicated that approximately half of ERα target genes are downregulated upon estrogen induction, reinforcing the view that estrogen promotes cell survival by downregulating pro-apoptotic genes.

2.2.2. Androgen Receptor (AR)

Structure

The *AR* gene is located on chromosome X (Xq11–12) and consists of 8 exons coding a protein of about 110 kDa (Figure 1, lower panel). The full-length AR has four domains, namely from the N-terminal, the NTD, the DBD, the hinge domain, and the LBD [62,63]. The NTD includes the transcriptional regulatory domain AF1, while the LBD includes AF2. Over 20 splice variants of the AR have been reported in the last 2 decades [64]. Most of them are lacking the C-terminal region containing the LBD [65,66] and are, therefore, functionally active independently of the presence of androgens. Among them, AR-V1 and AR-V7 are the most abundant variants [65]. Somatic AR mutations may occur selectively in response to androgen deprivation [67]. A review of 27 clinical studies revealed that AR mutations in androgen-dependent tumors ranged from 2 to 25%, while the incidence in CRPC tumors was slightly higher at 10–40% [67,68]. Furthermore, the AR LBD was described as a mutational hotspot, placing the incidence of its point mutations in CRPC at ~15–20% [69,70].

AR Gene Regulation

A better understanding of the regulation of *AR* transcription is crucial for studying prostate cell tumorigenesis. SP1, a zinc finger transcription factor, binds to GC-rich motifs of the *AR* promoter and activates the transcription of *AR*, whereas the associated antagonistic transcription factor pur-α can bind to the same region and inhibit *AR* transcription [71]. More recently, Deng et al. demonstrated that PRMT5 promotes prostate cancer cell growth by epigenetically activating the transcription of *AR* in prostate cancer cells. PRMT5 binds to the proximal promoter region of the *AR* gene and mainly contributes to the enriched symmetric dimethylation of H4R3 in the same region. Mechanistically, PRMT5 is recruited to the *AR* promoter upon its interaction with Sp1, forming a complex with Brg1, an ATP-dependent chromatin remodeler [72]. In addition, Grad and colleagues found that *AR* is regulated by AR itself in osteoblast-like U2OS cells. Indeed, two androgen response elements (AREs) were identified in exons 4 and 5 of the *AR* gene that were responsible for the androgen-mediated upregulation of *AR* mRNA [73].

Gene Targets and Functions

AR, playing a key role in both normal prostate development and prostate cancer, is a hormonal transcription factor. Upon binding to androgens, testosterone, or dihydrotestosterone (DHT), the AR localizes to the nucleus [74,75]. There, the receptor dimers bind to AREs in the promoter regions of target genes, such as prostate-specific antigen (PSA) and transmembrane protease serine 2 (TMPRSS2), to regulate transcription [76]. Similarly to other transcription factors, AR-enhanced transcription depends on the recruitment of RNA polymerase II to its target gene promoter. Some dynamic changes in the state of covalent histone modifications, relying on methyltransferase activities, are related to androgen-stimulated transcription. Fu et al. demonstrated direct interactions between p300, CBP, P/CAF, and AR. Moreover, several signaling pathways are known to enhance AR activity [77], including the EGF, IGF, IL6, Wnt, Ras-Raf-MAP kinase, PI3K/AKT, and MAPK/ERK pathways [75,78–83]. Mounir et al. reported that PMRT5 display inhibitory effects on the transactivation of differentiated genes by AR via AR methylation [84].

For prostate cancer cells, studies have shown that AR is a critical regulator of the G1-S transition in AR-dependent cell cycle progression. Indeed, Xu et al. demonstrated that androgen induces Cyclin D expression via mTOR-dependent enhancement of translation [85]. The $p21^{cip}$ has been validated as a direct AR target [86], consistent with the findings revealing that $p21^{cip}$ expression is enhanced in tumors and is correlated with a higher proliferative index and Gleason grade [87,88]. Furthermore, Knudsen et al. showed that androgen depletion induces $p27^{Kip1}$, which likely contributes to the observed reduction in CDK2 activity [89].

Rokhlin et al. found that androgen and AR signaling could directly regulate p53 to suppress apoptosis. Mechanistically, androgen suppresses TNF-α/Fas-induced apoptosis through the inhibition of p53 expression and caspase-2 activation [90]. Interestingly, Frezza et al. reported that a significant decrease in AR expression leads to an increase in caspase-3 activity in LNCaP and PC-3AR cells, suggesting that AR might suppress caspase-3 expression [91]. Liao et al. also showed that knockdown of AR via siRNA leads to apoptotic death in PCa cells [92]. Blockade of AR degradation and ectopic expression of Bcl-2 or selected caspase inhibitors can suppress this pro-apoptotic activity [93].

Zhao et al. demonstrated that AR can act as a transcriptional repressor to directly inhibit gene expression. This repression is mediated by the binding of AR to AREs, and is facilitated by EZH2-mediated repressive chromatin remodeling [94]. More recently and interestingly, Song et al. revealed that AR upregulated EZH2 expression by binding to the *EZH2* promoter and stimulating its transcriptional activity in hepatocellular carcinoma (HCC) cells. EZH2 overexpression increased H3K27me3 levels, thereby silencing the expression of Wnt signal inhibitors, resulting in the activation of Wnt/β-Catenin signaling and subsequent induction of cell proliferation and tumorigenesis [95].

3. The Involvement of the *MEN1* Gene in Breast and Prostate Cancers

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome characterized by the multiple occurrence of endocrine tumors of the parathyroid, pancreas, and anterior pituitary. The large tissue spectrum of the disease, affecting a dozen different endocrine cell lineages [96], indicates that the predisposition gene, *MEN1*, possesses a relevant role in all of the endocrine tissues affected. The *MEN1* gene, the mutation of which predisposes patients to MEN1 syndrome, was first identified in 1997 [97,98], and functional studies have since further improved our understanding of the gene. In particular, both genetic and biochemical experiments suggest that the *MEN1* gene has a large spectrum of expression and that the menin protein encoded by the gene plays multifaceted biological functions in a broad range of different tissues and cells, likely through physical and functional interactions with its numerous protein partners. Menin primarily has a nuclear localization, although it can also be located in the cytoplasm and membranes [99]. Menin may act as an adaptor protein involved in the regulation of gene expression via its physical interaction with several transcription factors, such as JunD, Smad1/3/5, β-Catenin, MafA/B, Foxa2, and P53, as well as epigenetic factors, including KMT2A/2B, Sin3A, and EZH2 [44,100–107]. The interactions between menin and several nuclear receptors were recently unveiled (see below). Importantly, various analyses demonstrated that menin is involved in different cellular activities controlled by many signaling transduction pathways, in particular cell proliferation, cell cycle, and cell death. Finally, the experiments using various in vivo models have also revealed that the biological functions of menin extend far beyond endocrine cells to hematopoiesis, adipogenesis, myogenesis, fibrogenesis, or even osteogenesis [108–110].

3.1. Molecular Studies

The first clues as to the possible involvement of menin in BC came from the observation that the menin protein binds physically to ERα. In 2006, Dreijerink et al. revealed that menin, owing to an evolutionarily conserved amino acid sequence LXXLL, could physically interact with several nuclear receptors, such as the vitamin D receptor, RXR, and ERα, and played the role of a cofactor. In the same study, they showed that menin binds to the AF2 domain of ERα and coactivates the transcription of *TFF1*, an estrogen-responsive ERα target gene, through the recruitment of the compass-like complex trimethylating H3K4me3 on the *TFF1* promoter [111]. In 2009, Imachi et al. confirmed the previous results by showing that menin coactivates ERα in an estrogen-dependent manner in the ERα-positive MCF7 BC cell line [112]. A recent study conducted by Dreijerink et al. demonstrated that menin regulates the expression of the *ESR1* gene (as described above) through an upstream enhancer via a looping mechanism that connects the TSS bound menin&MLL1/2 to the enhancer-bound transcription factors GATA3 and FOXA1 [44].

Almost a decade after discovering the interaction between menin and ERα, menin was identified as an important cofactor for AR signaling due to its physical interaction with AR-NTD and the recruitment of the MLL histone methyltransferase complex to AR target genes [113]. Inhibition of menin–MLL interaction with a small-molecule inhibitor (MI) impaired AR signaling and inhibited the growth of castration-resistant tumors in xenograft experiments in mice [113]. Hence, these results suggest that menin can facilitate oncogene activation through AR signaling in PCa (Figure 2).

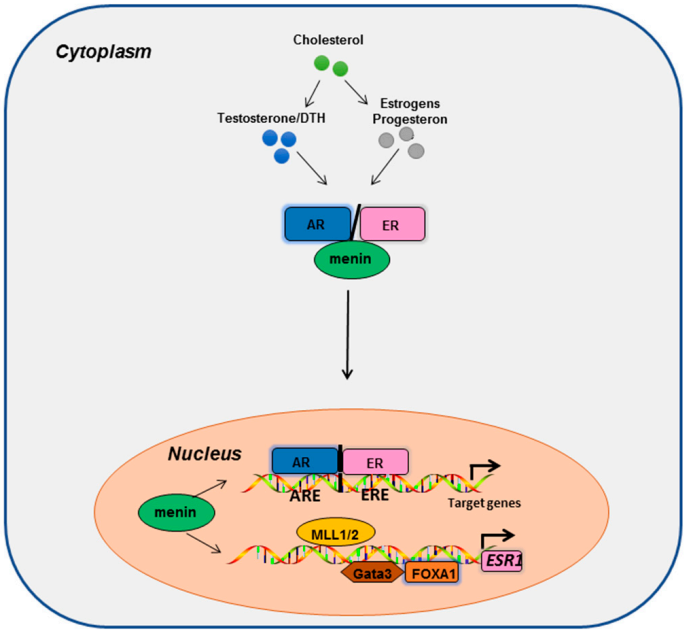

Figure 2. The menin protein interacts physically and functionally with ERα and AR, and is involved in the regulation of ESR1 transcription and the transactivation of the target genes of both ERα and AR.

3.2. Mouse Models

3.2.1. Mammary Gland Lesions in Mouse *Men1* Models

Our team is at the forefront of studies on the role of *MEN1* using *Men1* mutant mouse models. We have observed that aged heterozygous *Men1* mutant mice, in addition to endocrine tumors, developed mammary gland carcinomas in female and prostate cancers in male mutant mice at low frequencies [114]. To further confirm and understand the role of menin in the development of mammary lesions, we generated a conditional mammary-specific *Men1* knock-out mouse model by crossing the mice carrying floxed *Men1* alleles ($Men1^{F/F}$) with *WapCre* transgenic mice expressing Cre recombinase under the control of the whey acidic protein (Wap) promoter, which is known to be expressed in luminal mammary epithelial cells. Our results demonstrated that female $Men1^{F/F}$-*WapCre* mice developed substantially higher amounts of early mammary intraepithelial neoplasia (MIN), which are precursor lesions, in comparison with control $Men1^{+/+}$-*WapCre* mice. Interestingly, we found that ERα expression and the number of ERα-positive cells were clearly reduced in MIN lesions of mutant mice compared with normal mammary glands. In addition, cell membrane expression of β-Catenin and E-Cadherin was almost absent in the mammary lesions of $Men1^{F/F}$-*WapCre* mice compared with control mice; neither β-Catenin nor E-cadherin were detected in the TS1 cell line derived from a mouse *Men1* BC [115].

3.2.2. Prostate Lesions in Mouse *Men1* Models

By following a cohort of 47 male heterozygous *Men1* mutant mice ($Men1^{+/-}$) and 23 male wild-type ($Men1^{+/+}$), age-matched littermate mice from 18 to 26 months of age, our group found that six $Men1^{+/-}$ mice (6/47, 12.8%) developed prostate cancer, including two adenocarcinomas and four in situ carcinomas, while none of the control mice developed cancerous lesions. No prostate carcinoma was found in age-matched $Men1^{+/+}$ littermates (0/23). In addition, these carcinomas exhibited loss of the non-target *Men1* allele (LOH), therefore supporting a tumor suppressor role for the *Men1* gene in prostate glands. Moreover, the AR and p27 expression decreased in tumor lesions, likely facilitating prostate cell tumorigenesis due to *Men1* inactivation [116].

Taken together, all of the data obtained from mouse models suggest a tumor-suppressive role for menin during the initiation and development of murine breast and prostate cancers.

3.3. Human Studies

3.3.1. *MEN1* in Human Breast Cancer

Over the last two decades, several case reports have described breast cancer cases related to MEN1. In 2004, a 44-year-old Japanese woman was diagnosed with MEN1 syndrome, having hyperparathyroidism, primary aldosteronism, and also scirrhous breast carcinoma. The DNA taken from her parathyroid adenoma and breast cancer tissues showed germline *MEN1* mutation at codon 451 in exon 10, which resulted in alanine-to-tyrosine substitution (A541T), as well as LOH [117]. Another study by Jeong et al. reported a case of a patient with both MEN1-associated tumors and breast cancer. They found a germline *MEN1* mutation manifested as a 5-bp duplication in exon 3, named c.196_200dupAGCCC), which resulted in a frameshift mutation. In addition, the tested exon 10 showed a polymorphism at codon 423 with substitution of a cytidine to a thymidine (C423T), causing a change of amino acid [118]. More recently, a 41-year old patient with no familial history of breast cancer but with a mother with primary hyperparathyroidism (PHP) was found carrying a variant p.C421R/p.426R in the *MEN1* gene. The patient's histopathological study revealed hormone receptor negativity, as well as HER-2 and p53 negativity. A family study showed positive findings for MEN1 in a sister, two maternal nephews, and one of the patient's daughters, with no record of breast cancer development in any of these people [119]

Evidence of the likely involvement of menin in BC arose from the observation that female MEN1 patients were at a higher risk of developing BC [120]. In this study, Dreijerink et al. referred to the Dutch longitudinal MEN1 database to assess the incidence of BC in MEN1 patients, and found that out of 190 female patients, the relative risk of invasive BC was 2.83 ($p < 0.001$) and the mean (±SD) age at diagnosis of essentially luminal-type BC was 48 ± 8.8 years, compared with an age range of 60 to 65 years in the general population. This feature is often observed in the patients harboring a genetic predisposition. The authors validated their results using 3 other independent MEN1 patient cohorts from the United States ($p = 0.11$), Tasmania ($p = 0.22$), and France ($p = 0.03$), which provided similar values for relative risk as those obtained in the Dutch cohort, with an average age at diagnosis of 51 years. Furthermore, 8 out of 10 BC samples obtained from Dutch MEN1 patients displayed more than 50% reduction of menin expression in the nucleus, and subsequent analysis showed loss of heterozygosity at the MEN1 locus in 3 of 9 tumors. Overall, these observations strongly suggest that *MEN1* mutations could be involved in human breast tumorigenesis as a tumor suppressor.

Concomitantly to our work carried out in mice, we also observed that a substantial proportion of human sporadic BCs displayed reduced menin expression, as observed through the analyses of two series of human BCs [115]. More recently, a study in which the whole-genome sequences of 560 BCs were analyzed highlighted sporadic *MEN1* mutations, albeit at low frequency, as being among driver mutations (such as *BRCA1*, *TP53*, *PIK3CA*, *MYC*, *CCND1*, *PTEN)* in BC [121]. In addition, several other case reports identified *MEN1* mutations among sporadic BC patients, independent or not of germline mutations in *BRCA1* and *BRCA2* genes that are usually associated with hereditary BC [118,122–124].

However, in a clinical study conducted by Imachi et al. with 65 ERα-positive BC samples treated with tamoxifen for 2–5 years as adjuvant therapies, they observed that menin-positive tumors (20 patients) had a worse clinical outcome and were more resistant to tamoxifen than menin-negative tumors (46 patients) [112]. They, therefore, proposed that menin could be a predictive factor of resistance to tamoxifen. Furthermore, they found that raloxifene could inhibit the binding of menin to the AF2 domain of ERα and proposed raloxifene as the therapeutic options for menin-positive and ERα-positive BC [125]. Their works suggest an oncogenic role for menin, which raised the controversy as to its precise role in BC.

3.3.2. *MEN1* in Human Prostate Cancer

Perakakis et al. reported two cases of PCa seen in a MEN1 family with atypical tumor spectrum [126]. The DNA sequencing analysis revealed a novel mutation—Ser38Cys (TCC > TGC) in exon 2, located in a region of menin that is responsible for interaction with the transcription factor JunD. The latter has recently been associated with prostate cancer.

Only limited sporadic *MEN1* mutations have so far been reported in human sporadic PCa [127]. Manson-Bahr et al. found that missense mutations of the *MEN1* gene were detected in 2 of 8 formalin-fixed prostate needle biopsy materials [125]. Interestingly, Grasso et al. analyzed 58 human CRPC samples by aCGH and found that 17.2% of all samples (10 of 58) harbored mutations in the *MLL* complex, including the *MEN1* gene [69]. MLL functions as part of a multi-protein complex containing menin [128]. Many members of the complex have different levels of aberrations in CRPC [69]. Noticeably, Chen et al. analyzed 150 cases for advanced and metastatic human PCa. They observed that the percentage of *PTEN* and *MEN1* co-loss was almost the same as the co-loss of *PTEN* and *PML* (*Promyelocytic Leukemia*), which is around 11% in all cases [129]. Conversely, Paris et al. reported that the MEN1 locus was amplified in some patients and was predictive of post-operative recurrence [130]. The similar observation was made Kerstin et al. [131]. Moreover, *MEN1* knockdown resulted in a decrease in cell proliferation in DU145 cells [132,133], but curiously not in the PC3 cell line [132].

In total, the current data obtained from human studies suggest that the *MEN1* gene could play a complex even opposite role in the development of human breast and prostate cancers.

4. Further Clues for the Role of Menin in Breast and Prostate Cancers

As we mentioned above, many different factors and signaling pathways are involved in mammary and prostate cell tumorigenesis. By investigating the possible molecular links between the former and menin, we speculated that we might gain further insight into the possible role played by menin in these cancers (Figure 3).

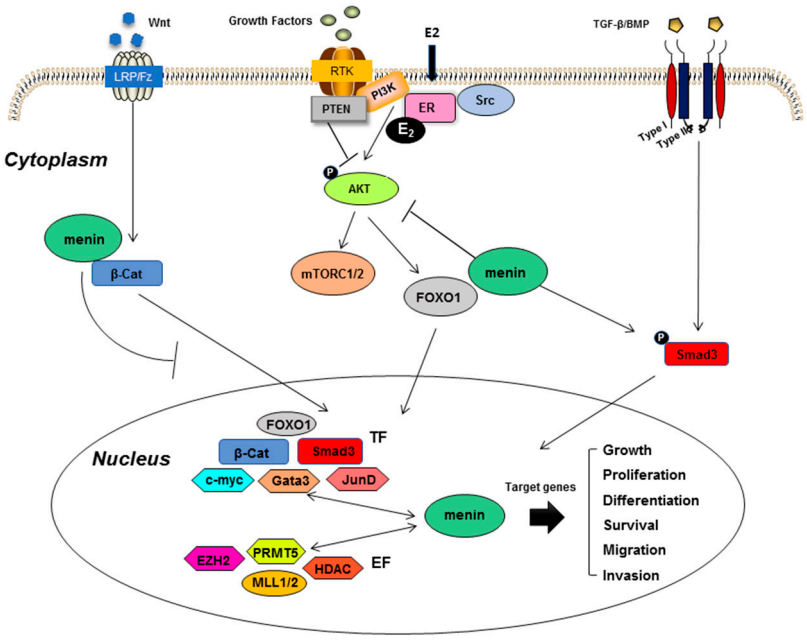

Figure 3. Mechanistic clues underlying the involvement of menin in mammary and prostate cell tumorigenesis. Menin interacts with numerous menin-interacting factors, consequently participating in the regulation of many target genes and interfering with different signaling pathways strongly implicated in breast and prostate cancers. EF: epigenetic factors; TF: transcriptional factors.

4.1. Epigenetic Factors

Interestingly, several epigenetic factors reported to be involved in mammary cell tumorigenesis are known to be partners of menin. Histone methylase MLL1 (*KMT2A*) and MLL4 (*KMT2B*), which are the most characterized partners of menin, were shown to act synergistically with ERs (ERα and ERβ) to mediate the estrogen-induced transcriptional activation of the *HOXB9* gene, which is critical for mammary gland development and BC [134]. Menin was also shown to upregulate several members of the same family (mainly *HOXA9* gene) in leukemia by associating with the compass-like complex and lens-epithelium-derived growth factor (LEDGF) [45,135]. The HDAC family, which contains known partners of menin [54,55], is implicated in the regulation of ERα expression, mainly by silencing the *ESR1* gene. It was proposed that HDAC may be responsible for loss of ERα expression in ER-negative BC [34,35]. EZH2 and PRMT5 are two shared partners of menin [100,136,137] and the ERα pathway. Indeed, EZH2 inhibits the transcription of estrogen-responsive genes through its association with the transcriptional corepressor repressor of estrogen receptor activity (REA) [138]. Although there is no direct evidence of the interaction between PRMT5 and ERα, PRMT5 plays an important role in BC by methylating programmed cell death 4 (PDCD4), a tumor suppressive protein with anti-proliferative functions on arginine residue 110 [139].

4.2. Transcription Factors

JunD, a member of the AP-1 family that interacts physically with menin [140,141], has a higher level of expression in BCs [142]. JunD and menin co-expression was found in the mouse submandibular gland, an AR-responsive tissue, with their expression pattern and localization changing with cell differentiation status [143]. Moreover, JunD physically binds to ERα and facilitates its binding to target genes [36]. Intriguingly, it has been shown that prostaglandin E_2 (PGE_2) induces JunD and JunB expression, resulting in the activation of the aromatase promoters I.3/II, while JunD and c-Jun mediate the suppression of the aromatase promoter I.4, leading to high levels of local estrogen, and thus to BC progression [144]. JunD is crucial for cell proliferation in PCa cells, as it controls cell cycle regulatory genes [145,146]. Their analyses further suggest that the essential role played by JunD in prostate cancer cell proliferation is mediated by *MYC* signaling [147]. Furthermore, Mehraein-Ghomi et al. highlighted JunD as an AR co-activator, as it triggers the oxidative stress pathway in prostate cancer cells by regulating the *SSAT* promoter, which produces large amounts of metabolic reactive oxygen species (ROS) [148].

Another important factor is *cMyc,* a well-known estrogen-regulated oncogene [149,150], which is overexpressed in approximately 20–30% of BCs [151] and has also been shown to interact with ERα to modulate estrogen-mediated signaling [152]. The cMyc overexpression in PCa has been a well-recognized phenomenon since 1986, when Fleming et al. showed a significantly higher level of its expression in adenocarcinoma of the prostate than in benign prostate hyperplasia by Northern blotting [153]. Furthermore, Sato et al. reported that *cMyc* amplification is strongly associated with higher histopathological grades and Gleason scores, as well as with earlier disease progression and cancer-associated death [154]. It is now known that cMyc is a partner of menin and that they collaborate to either activate or repress the expression of certain genes. The most recent report shows that menin can directly interact with the transactivation domain (TAD) of cMyc, and that they in turn bind to E boxes to enhance the transcription of cMyc target genes [155]. Interestingly, menin can interact with the *cMyc* promoter to regulate its transcription in HEK293 cells [156].

Finally, menin was recently shown to interact with GATA3 and FOXA1 [44] in BC to regulate the *ESR1* promoter (see details above), both of which are markers of luminal BC, especially for the luminal A subtype [42,43,146], and which are highly associated with ERα and are required for the proper function of most of its target genes [40,157,158]. Menin interacts with GATA3 to activate Th2 cell maturation in primary human peripheral blood T cells [159] and to physically interact with a member of the FOXA family, namely FOXA2 [103]. It is worth mentioning that FOXA1 plays a crucial role in the AR signaling, and possibly in CRPC occurrence [160].

4.3. Signal Transduction Pathways

Menin is known to interfere with different signaling pathways that play important roles in breast and prostate cancers.

4.3.1. The PI3K/PTEN/AKT/mTOR Pathways

Activation of the PI3K/PTEN/AKT/mTOR pathways occurs in 70% of BCs overall [161]. *PIK3CA* (a subclass of the PI3K family of genes) is the most commonly mutated gene in ER-positive BCs [162]. This mutation is present in approximately 35% of HR-positive BCs, 20–25% of HER2-overexpressing BCs, and with a lower frequency (8.3%) in TNBCs [163].

PTEN is one of the most commonly deleted and mutated genes in human breast and prostate cancers. Loss of *PTEN* in BC is negatively correlated with ERα and PR status, and is associated with the basal-like phenotype [164,165], with more aggressive behaviors (tumor size, lymph node metastasis, etc.), and with worse outcome (disease-free survival DFS and overall survival OS) [166]. Accumulating evidence has highlighted an association between loss of *PTEN* and the development of CRPC, likely due to AR phosphorylation [167,168]. Moreover, loss of PTEN and AR expression has been clinically correlated with increased mortality in CRPC patients [169]. More recently, Wong and colleagues generated mouse models with insulin-specific biallelic inactivation of *Men1* and *Pten* in β-cells, and showed that concomitant loss of *Pten* and *Men1* accelerated islet cell tumorigenesis. Co-mutations of *MEN1* and *PTEN* were observed in a small percentage of human PanNETs [170,171], suggesting that menin and Pten may function synergistically to suppress tumorigenesis.

Several studies have focused on the relationship between the PAM (PI3K/Akt/mTOR) and resistance to endocrine therapy in pre-clinical BC models [172], in which the authors showed that Akt can activate the ERα pathway independently of estrogen availability and that the combination of mTOR inhibitors and endocrine therapy can overcome this resistance [173,174]. In addition, the PAM pathway has also been implicated in trastuzumab resistance in HER2-overexpressing BCs [175]. Interestingly, menin interacts with AKT1, downregulates its kinase activity and suppresses both AKT1 induced proliferation and anti-apoptosis in endocrine and non-endocrine cells, mainly by reducing the translocation of AKT1 from the cytoplasm to the plasma membrane during growth factor stimulation [176]. Another study showed that menin can interact with FOXO1, a downstream effector of Akt, in the hepatocytic cancer cell line HepG2 and in MEFs [177]. In the same year, a study also showed that *MEN1* and genes from the mTOR pathway are frequently altered in pancreatic neuroendocrine tumors [170]. A recent study revealed that menin regulates milk protein synthesis through mTOR signaling in normal mammary epithelial cells [178]. According to the authors, menin overexpression caused significant suppression of factors involved in the mTOR pathway, as well as milk protein κ-casein (CSNK). All of the abovementioned data suggest that menin may regulate the PI3K/Akt/mTOR pathway in mammary cells.

4.3.2. Cell Cycle, Growth, and Death Control

Kaji et al. demonstrated that menin could suppress cell proliferation via the transforming growth factor-β (TGF-β) pathway in the rat pituitary cell line by interacting with Smad3 [179]. Agarwal et al. reported that menin is essential for JunD-mediated inhibition of cell proliferation [140]. Ratineau et al. showed that menin represses cell proliferation in rat intestinal epithelial cells [180] by inhibiting the expression of Cyclin D1, Cyclin D3, and CDK4. Based on a transcriptomic study of differentially expression genes, our team demonstrated that *Men1* ablation in mouse islet cells greatly affected the expression of factors involved in cell cycle and cell growth control, such as Cyclin A2, B2, and D2 for the former; and IGF2, IGFBP3, and 6 for the latter [181]. Menin can also repress cell proliferation by interacting and inhibiting ASK (S-phase kinase) [182]. In addition, menin was reported to upregulate the expression of Cyclin-dependent kinase inhibitors $p18^{ink4c}$ and $p27^{kip1}$ with the help of the MLL compass-like complex, which adds H3K4 trimethylation marks on their promoters, thus activating

gene expression [183–185]. Interestingly, p18 has recently been shown to be a downstream target of GATA3 in luminal BC and to suppress luminal progenitor cell proliferation and tumorigenesis [186]. P27 is ranked as one of the 18 most significantly mutated genes in luminal A BC, and loss of p27 was associated with poor outcome in BC patients [187].

Schnepp et al. revealed that the infection of cells using menin-expressing adenoviruses could trigger apoptosis in MEFs [188,189] by activating an apoptotic pathway that depends on Bax [186]. They also highlighted that *Men1* disruption in vivo increased resistance to TNFα-induced apoptosis, further supporting a vital role for menin in regulating apoptosis.

4.3.3. Wnt Signaling

It is well known that the Wnt pathway plays a crucial role in the development of breast and prostate cancers, in particular at late stages [190]. We observed that in *Men1*-deficient mice insulinomas, β-Catenin expression switched from a membrane expression to a cytoplasmic or even nuclear expression [187]. Along with our collaborators, we also showed that menin physically interacts with β-Catenin, and menin overexpression reduced the nuclear accumulation of β-Catenin and suppressed its transcriptional activity in *Men1*-null MEFs [104]. Jiang et al. further demonstrated that β-Catenin ablation leads to the suppression of tumorigenesis and significantly improved hypoglycemia and the survival rate of *Men1*-deficient mice [105]. Applying the small molecule inhibitor, PKF115–584, in *Men1*-deficient mice to antagonize β-Catenin signaling suppressed tumor cell proliferation in vitro and in vivo [105]. Kim et al. reported that menin promotes ubiquitin-mediated degradation of β-Catenin and menin overexpression downregulates the transcriptional activity of β-Catenin and target gene expression, as well as the proliferation of human renal carcinoma cells with an activated β-Catenin pathway [191].

5. Finishing Words

5.1. The Dual Role of Menin

The abovementioned data provide clues on the complex and sometimes paradoxical role of the *MEN1* gene in mammary and prostate cell tumorigenesis (Figures 2 and 3). Dreijerink et al. proposed a hypothesis on the dual role of menin in BC, which may shed light on these discrepancies and the surrounding confusion [44]. They proposed that menin could act as a tumor suppressor in normal luminal mammary epithelial cells and as an oncogene in sporadic ER-positive BCs, the key point being its essential role in the regulation of the *ESR1* gene mediated by the MLL–menin complex via H3K4me3 sites. Therefore, when *MEN1* is mutated or inactivated in normal mammary and prostate cells, it could result in dysregulated ERα and AR pathways, leading to aberrant cell proliferation and differentiation, and to tumor development with the participation of other oncogenic alterations. Conversely, in ER-positive BC and AR-positive prostate cancer cells, menin could act as a co-activator of these two nuclear receptors, playing a crucial role in promoting cell proliferation by the latter.

5.2. Remaining Questions

The currently available data and the abovementioned molecular clues suggest that menin may play a multifaceted but non-negligible role in the tumorigenesis of both mammary and prostate cells. However, concerning the detailed mechanisms underlying its involvement, many questions remain. Among them, one may wonder about the molecular pathophysiological consequences of *MEN1* inactivation in these two tissues during the initiation of tumorigenesis. In addition, since menin interacts and regulates the ERα and AR pathways, does menin play different roles in HR-positive than in HR-negative cancers? Last but not least, as menin acts as a scaffold protein, what are the other factors, in particular interacting partners, involved in the process?

To further understand the involvement of menin in these two cancers, there is an urgent need to generate adequate cell, tissue, and animal models in order to better investigate the distinct roles played

by menin during the initiation of carcinogenesis on the one hand, and during cancer progression on the other hand. Concurrently, strengthening *MEN1* mutation detection and menin expression analysis for breast and prostate cancer samples collected from young and aged patients or in different subtypes would be informative. The availability of more relevant models and crucial data from clinical samples, together with the rapidly improved tools in molecular study, should be of great help in obtaining rightful answers for the abovementioned questions.

6. Summary

Even though the role of menin in the development of neuroendocrine cancers is well known, its role in human breast and prostate cancers is slowly emerging. Based on the literature presented above, we speculate that future research could unveil further crosstalk between menin and the ERα and AR pathways. Finally, a better understanding of the mechanisms underlying its role in the mammary and prostate cell tumorigenesis could also make menin a potential therapeutic target for the treatment of these cancers, as well as a new marker for their diagnosis and prognosis.

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Abbreviations

ADT	Androgen deprivation therapies
AP-1	Activator protein 1
AR	Androgen receptor
AREs	Androgen response elements
ASK	Activator of S-phase kinase
BAX	BCL2 Associated X
BC	Breast cancer
BRCA1&2	Breast cancers 1 and 2
CDK	Cyclin-dependent kinase
CRPC	Castration-resistant prostate cancer
DBD	DNA-binding domain
DHT	Dihydrotestosterone
DNMTs	DNA methyltransferases
EIT-6	Estrogen Induced Tag-6
ER	Estrogen receptor
ERE	Estrogen response element
EZH2	Enhancer of zeste homolog 2
FOX	Forkhead box
H3K4me3	Tri-methylation at the 4th lysine residue of the histone H3 protein
HCC	Hepatocellular carcinoma
HDAC	Histone deacetylase
HER2	Human epidermal growth factor receptor 2
HOX	Homeobox

Hsp	Heat-shock proteins
IGF-1	insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor-binding protein 3
LAR	Luminal-androgen receptor
LBD	Ligand-binding domain
LEDGF	Lens epithelium-derived growth factor
LOH	Loss of heterozygosity
mCRPC	Metastatic CRPC
MEF	Mouse embryonic fibroblast
MEN1	Multiple Endocrine Neoplasia type 1
MI	Molecule inhibitor of menin-MLL interaction
MIN	Mammary intraepithelial neoplasia
MLL1&2	mixed lineage leukemia 1&2 (KMT2A and 2B)
MTA1	metastasis-associated protein 1
mTOR	Mammalian target of rapamycin
NEPC	Neuroendocrine prostate cancer
NF-κB	nuclear factor-κB
NLS	Nuclear localization sequence
NTD	N-terminal Domain
PCa	Prostate cancer
PR	Progesterone receptor
PRMT5	Protein arginine N-methyltransferase 5
PSA	Prostate-specific antigen
PTEN	Phosphatase and TENsin homolog
ROS	Reactive oxygen species
SCC	Small cell carcinomas
SERDs	Selective estrogen receptor downregulators
SERMs	Selective estrogen receptor modulators
TGF-β	Transforming growth factor beta
Th2	T- helper type 2
TIT-5	Tamoxifen Induced Tag-5
TMPRSS2	Transmembrane protease serine 2
TNBC	Triple negative breast cancer
TNFα	Tumor necrosis factor alpha
TSS	Transcription start site
Wap	Whey acidic protein

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