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Unraveling the Mysteries of PAX8 in Reproductive Tract Cancers

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ABSTRACT

Paired Box 8 (PAX8) is a lineage-specific transcription factor that has essential roles during embryogenesis and tumorigenesis. The importance of PAX8 in the development of the reproductive system is highlighted by abnormalities observed upon the loss or mutation of this PAX family member. In cancer, PAX8 expression is deregulated in a key set of neoplasms, including those arising from the Müllerian ducts. The roles of PAX8 in oncogenesis are diverse and include epigenetic remodeling, stimulation of proliferation, inhibition of apoptosis, and regulation of angiogenesis. PAX8 can interact with different protein partners during cancer progression and may exhibit significant function-altering alternative splicing. Moreover, expression of PAX8 in cancer can also serve as a biomarker for diagnostic and prognostic purposes. In this review, we focus on the roles of PAX8 in cancers of the reproductive system. Understanding the diverse mechanisms of action of PAX8 in development and oncogenesis may identify new vulnerabilities in malignancies that currently lack effective therapies.

Introduction

The establishment of cell lineages that give rise to specific tissues during embryogenesis requires the strict regulation of gene expression. The genesis of tissue stem cells, their maintenance, and terminal differentiation is essential for successful development and normal tissue homeostasis. These events are highly organized and require the coordinated expression of multiple factors, including the PAX family of transcription factors (1). PAX genes were initially described in the common fruit fly, *Drosophila melanogaster*, and subsequently identified in many different species (2). Their ancestral role in *Drosophila* is in embryonic development where they influence segmentation of the larvae and promote proper eye and brain development (3, 4).

The PAX family is composed of nine genes in mammals, which can be subclassified into four classes and it is described in details in **Table 1** (5). These genes encode nuclear transcription factors that include a combination of up to four functional domains: an N-terminal paired domain with DNA-binding activity, a conserved octapeptide motif, a homeodomain (which can serve as a second independent DNA-binding region), and a transactivation domain at the C-terminus (1). The paired domain, which consists of 128 amino acids, is the most conserved and most studied. It is folded into two β-sheets and six α-helices divided into two subdomains, PAI and RED. Mutations in PAI or RED subdomains disrupt the DNA-binding activity and lead to congenital abnormalities (6). Furthermore, PAX members can form heterodimers by interacting with homeodomain-containing partners, such as HOX and SOX members (7). This cooperativity alters their binding specificity and changes the set of regulated target genes that determine cell type and temporal activation. Moreover, it was also demonstrated that PAX members have pioneering activity, i.e., they can directly bind to condensed chromatin and recruit other transcription factors and histone modification enzymes that contribute to transcription factors hierarchical regulation of chromatin landscape and accessibility (8, 9).

Dysregulation of embryogenesis programs (through genetic or epigenetic changes) can lead to tumorigenesis (10). Some of these aberrant changes reactivate PAX factors and drive the emergence of a more embryonic undifferentiated state with loss of regulated growth, survival, and migratory programs (11). PAX proteins contribute to these neoplastic processes through their ability to regulate cellular networks by controlling transcription and chromatin-remodeling activities (12, 13). Herein, we focused on the transcription factor PAX8 to provide a comprehensive assessment of its importance during reproductive system development and malignant transformation.

Roles of PAX8 during Development

During embryogenesis, the PAX proteins maintain epithelial progenitor cells mitotically active before fully committing to their fate (1). The first indication that PAX8 is vital during embryonic development came from the identification of hypothyroidism due to thyroid dysgenesis or agenesis in newborns with point mutations or deletions in the *PAX8* gene (14). Of the *PAX8* loss-of-function mutations reported in different populations of patients with congenital hypothyroidism and concomitant urogenital malformation, only the G41V and D94N mutations in the critical DNA-binding domain of PAX8 have been functionally characterized. The PAX8-G41V-mutant demonstrated loss of DNA-binding activity and the inability to bind and activate the promoters of the thyroglobulin and thyroid peroxidase genes (15).

Subsequent genetic studies showed that *Pax8*$^{-/-}$ mice presented with pronounced thyroid hypoplasia were drastically underdeveloped and died shortly after weaning (16). Early thyroid hormone replacement allowed female *Pax8*$^{-/-}$ mice to survive; however, they were infertile. The mice also showed abnormalities in the Müllerian duct-derived tissues, such as atresia of the uterus, vaginal opening, and impairment of the oviducts due to hydrosalpinx (17). During development, Pax8 expression in wild-type mice is present in the kidney, the thyroid gland, and the normal epithelium of the Müllerian ducts, the origin of the female reproductive system (18). In adult tissues, PAX8

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Table 1. Overview of the PAX family.

Class	Gene	Chromosomal location	Structure	Posttranslation modification	Isoforms	Translocations	Mutations
I	PAX1	20p11	Paired domain Octapeptide	Amidation Hydroxylation Glycosylation Sumoylation or Ubiquitination Phosphorylation	3 isoforms		A277V A277T
	PAX9	14q12			1 isoform		A24D/T G96D/S
II	PAX2	10q24	Paired domain Octapeptide Partial homeodomain	Methylation Amidation Acetilation Phosphorylation Glycosylation	6 isoforms		V26G R403G
	PAX5	9p13		Sulfatation Sumoylation or Ubiquitination Glutathionylation	11 isoforms	PAX5–ETV6 PAX5–FOXP1 PAX5–ZNF521	V26F/G R104C/H/L R239C/H
	PAX8	2q12			6 isoforms	PAX8–PPARG	G41V D94N R64S
III	PAX3	2q35	Paired domain Octapeptide Homeodomain	ADP-ribosylation Amidation Phosphorylation Carboxylation Glycosylation	8 isoforms	PAX3–FOXO1 PAX3–NCOA1	R220S F294S A411E
	PAX7	1p36			4 isoforms	PAX7–FOXO1	S155L P408L/S/T G459A/C/S
IV	PAX4	7q32	Paired domain Homeodomain	ADP-ribosylation Glycosylation Amidation Ubiquitination Phosphorylation	3 isoforms		R166L/Q/W E180K
	PAX6	11p13			4 isoforms		H376T H390T P389H

Note: Data obtained and modified from https://www.ncbi.nlm.nih.gov/, http://dbptm.mbc.nctu.edu.tw/, and https://www.cbioportal.org/.

expression is found in the kidney, thyroid gland, Müllerian derived tissues (cervix, fallopian tube, and endometrium), and male reproductive tissues (seminal vesicle and epididymis; ref. 19). Interestingly, PAX8 staining is localized in the nuclei of healthy fallopian tube secretory epithelial cells (**Fig. 1**), which can self-renew and differentiate into normal fallopian tube epithelial ciliated cells to preserve the functional oviduct structure (20). PAX8 is expressed in human and mouse oviductal epithelial progenitor cells, which are the cell of origin of the majority of high-grade serous carcinomas (21, 22).

As suggested by its expression pattern, PAX8 also plays a pivotal role in the development of the male genital system and is expressed in the Wolffian ducts during the embryonic period (23). Treatment of male *Pax8*$^{-/-}$ mice with thyroxine restored the general deficits of congenital hypothyroidism, but these mice were infertile due to the absence of efferent ducts, epididymis, and spermatozoa (24). Therefore, PAX8 plays an important role during mouse development to guide the proper formation of the reproductive organs of both sexes.

Alterations of PAX8 Expression in Cancers of the Reproductive System

PAX8 is overexpressed in genital malignancies, enhancing both the survival and the proliferation of tumor cells (25). The upregulation of PAX8 in endometrial and ovarian cancer tissues is accompanied by a higher risk of death (lower 5-year survival) and disease recurrence (26, 27). Pan-cancer analysis of PAX8 expression showed higher expression in ovarian and endometrial cancer than in cervical, testicular, or prostate cancers (**Fig. 1**). In particular, PAX8 expression is higher in ovarian and uterine cancers of serous histology than those of endometrioid histology and in testicular seminomas compared with nonseminoma. Interestingly, PAX8 expression trends higher as disease stage increases (Supplementary Fig. S1A–S1D).

To begin deciphering the function of PAX8 in ovarian cancer, RNA-seq analysis of high-grade serous ovarian carcinoma (HGSOC) cell lines following PAX8 knockdown was performed to define the transcriptional network directly regulated by PAX8 (12). Surprisingly, this

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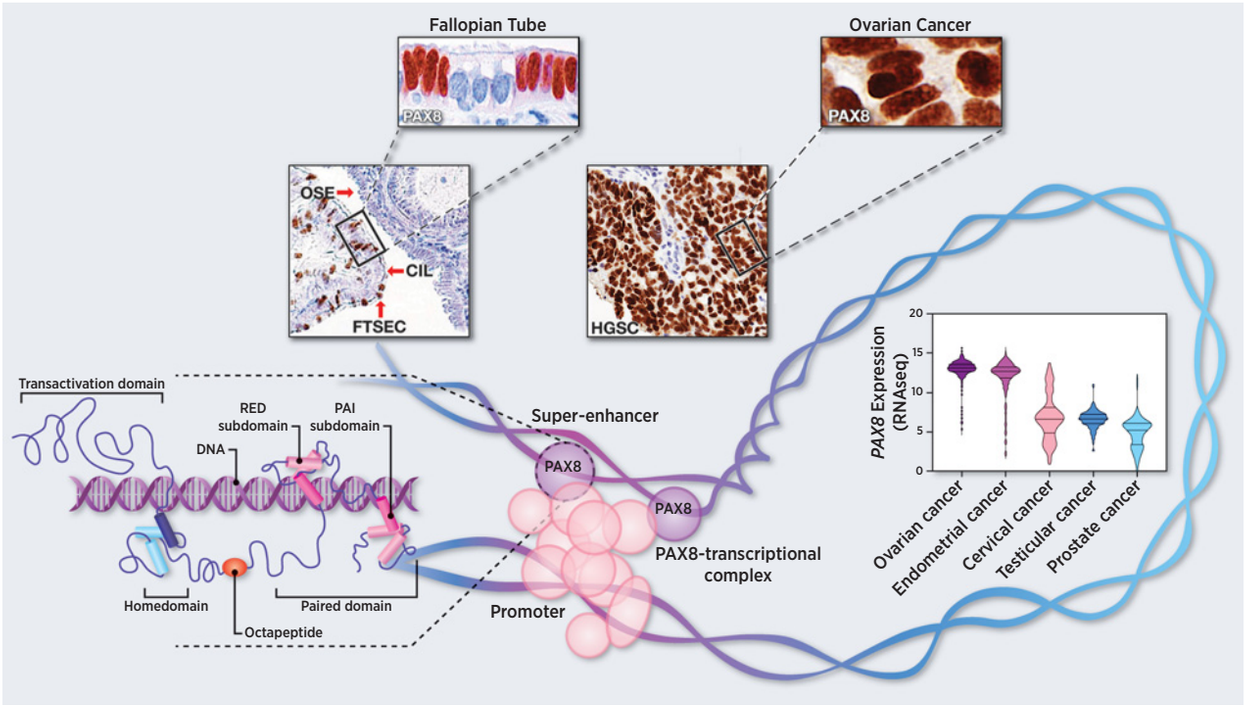

Figure 1.
Unraveling the mysteries of PAX8. Top, representative images of PAX8 immunostaining of normal fallopian tube epithelium (FTSEC, fallopian tube secretory epithelial cells; CIL, ciliated cells) normal ovary (OSE, ovarian surface epithelial cells), and invasive high-grade serous carcinoma (HGSC). Bottom, PAX8 transcript expression levels across different reproductive tract cancers (The Cancer Genome Atlas data set). Insertion, graphic representation of PAX8-transcriptional complex highlighting the PAX8 structural domains.

analysis revealed a negligible impact of PAX8 knockdown on the transcriptomes of immortalized fallopian tube secretory epithelial cell lines (FTSEC) with very few transcripts significantly affected by PAX8 loss. Moreover, PAX8 knockdown had negligible effect on viability or cellular proliferation, consistent with results in murine FTSECs (28). This was not due to functional redundancy between PAX8 and other PAX family members because PAX8 was the only PAX gene significantly expressed in these cells. In contrast, PAX8 loss in ovarian cancer cell lines had a marked impact on the transcriptional profile of the cells, with PAX8 target genes enriched in cell proliferation, angiogenesis, and cell adhesion pathways, processes that are crucial for tumor progression (12).

To determine whether there were differences in how PAX8 interacts with chromatin between the benign and malignant state, ChIP-seq analyses were performed showing that PAX8 binding sites are redistributed in the genome of cancer cells (12). Notably, only a small percentage of peaks (~6%) were near promoter regions. The vast majority of binding peaks were located in either intronic or intergenic regions, including super-enhancers. Corroboration of this finding was observed after the discovery that PAX8, SOX17, and MECOM are tumor-driving master transcription factors required for cell viability and lied proximal to super-enhancers in HGSOC cells. ChIP-seq analyses also revealed that these factors co-occupy HGSOC regulatory elements globally and cobind at critical target genes (13).

PAX8 redistribution in cancer cells was shown to be in part due to changes in the PAX8 network. Interestingly, purification of the PAX8 protein complex from ovarian cancer cells revealed that PAX8 is part of a 600 kilodalton chromatin-remodeling complex called NurD. Among the protein partners that PAX8 associates with is SOX17, another master transcription factor that helps to orchestrate ovarian cancer angiogenesis and progression (29).

PAX8 is highly expressed in fallopian tube epithelia, a precursor of HGSOC and is commonly amplified in ovarian cancer, emphasizing its essential role in tumor development (30). The PAX8 super-enhancer was detected in all ovarian cancers histotypes and was most active in serous and endometrioid ovarian cancers. Moreover, 90% of ovarian cancers harbor an alteration in the PAX8 pathway, either by somatic amplification of the *PAX8* locus, mutation of enhancers upstream of *PAX8*, or somatic mutations in PAX8 or TEAD binding sites, all of which can lead to the deregulation of PAX8 and its gene targets (31).

Although our understanding of the molecular functions of PAX8 is still evolving, recent studies indicate that PAX8 governs transcriptional programs involved in the regulation of tumor–stromal interactions, cell adhesion, proliferation, survival, and metastasis (25, 32–34). PAX8, as a master transcription factor, has a complex oncogenic mechanism that depends on cell type identity. Adding further complexity, Kozmik and colleagues showed the expression of six different isoforms of PAX8 that are usually coexpressed with PAX2, and their expression levels change during neoplasia (35). The exact roles of the various isoforms during transformation are not completely understood at this time. In addition, a chromosomal translocation between chromosomes 2 and 13 that results in a PAX8–PPARG fusion protein that affects PAX8 transcriptional regulation has been reported in thyroid cancer, but is not common in other cancers (36).

Experimental evidence suggests both a direct and an indirect role for PAX8 in tumorigenesis. PAX8 functions as a transcription factor that

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drives activation of specific target genes and also associates with different interacting partners that regulate cell fate and identity.

Implications for Drug Targeting

Targeting PAX transcription factors as a strategy to inhibit cancer growth could prove highly useful for treating specific subsets of PAX-driven malignancies. Because PAX factors are tissue-specific, this therapeutic strategy is expected to have lower levels of toxicity than approaches that perturb targets with pervasive expression. In addition, while a number of normal tissues express some levels of PAX8 (such as the kidney and the thyroid gland) there is evidence that cancers that overexpress PAX8 become "addicted" to its activity, while normal tissues do not appear to exhibit the same dependency (12, 28, 30, 32, 37–40). This dependency may be related to the specific set of interactions observed in cancer (described above). Importantly, this strong dependency may help mitigate the issue of intratumoral heterogeneity of PAX8 expression, as even cells with low expression would be expected to be dependent on its activity. These issues are currently under investigation.

Strategies to inhibit PAX8 can be grouped in three main categories: (i) those that reduce PAX8 levels, (ii) those that inhibit its DNA-binding activity, and (iii) those that inhibit its binding to crucial interacting protein(s). As a proof of concept, Hardy and colleagues showed that reducing PAX8 levels, either genetically or by treatment with the thiostrepton, a natural cyclic oligopeptide antibiotic, leads to a reduction in tumor burden (34). Moreover, Shi and colleagues demonstrated that blockade of HDAC1, a PAX8-interacting partner, perturbed the super-enhancer topology associated with PAX8 gene locus, resulting in epigenetic downregulation of PAX8 transcripts and related targets, efficaciously suppressing ovarian cancer growth (39).

Interestingly, the targeting of the paired domain has been shown to inhibit DNA-binding activity. For this purpose, Grimley and colleagues identified a small molecule, EG1, that was able to abrogate the transcription factor DNA-binding activity and also slowed the growth of ovarian cancer cells (41). As an example of targeting protein–protein interaction, disrupting super-enhancers as therapeutic strategy could complement traditional approaches and/or lead to new drug discovery. Pharmacologic inhibition of CDK7 impairs phosphorylation of RNA polymerase II and results in preferential downregulation of super-enhancer–regulated genes (such as PAX8; ref. 42). High-grade serous ovarian cancer models are exquisitely sensitive to pharmacologic inhibition of CDK7 by THZ1. PAX8 and SOX17 levels were particularly sensitive to low doses of THZ1 treatment and are among the 10%-most sensitive protein-coding transcripts. In addition, PAX8 and SOX17 knockdowns both phenocopy effects of low-dose THZ1 treatment, suggesting these factors, at least in part, explain the anticancer effect of this drug in ovarian cancer cells. PAX8 and SOX17 target genes are largely overlapping, with some of the most downregulated genes falling into cell cycle, DNA replication, and DNA division pathways, including cell-cycle regulators in the retinoblastoma pathway such as known ovarian cancer oncogene *CCNE1* (13, 29).

Because of its restricted expression patterns in normal tissues, and the strong dependency of certain cancers to its expression, PAX8 and its interacting partners represent promising targets for cancer therapy. If successful, the current efforts focused at inhibiting PAX8 are expected to have a significant impact on individuals with PAX8-dependent cancers.

Authors' Disclosures

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