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Gene Section
Review

PAX2 (Paired box gene 2)

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Abstract

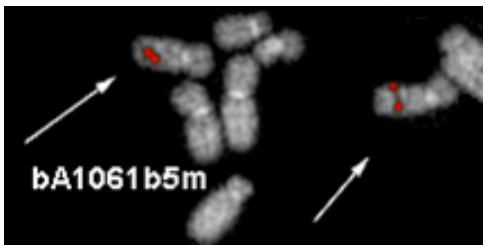
PAX2 is the second member of the nine-member PAX gene family. PAX2's role begins as a developmental gene in late primitive streak stage embryos (Dressler et al., 1990). If PAX2 becomes expressed out of its normal context, its powerful functions as a transcription factor and epigenetic regulator (reviewed in Robson et al., 2006) can be recruited to the advantage of cancer cells (Robson et al., 2006; Li and Eccles, 2012). Normally PAX2 has key roles during embryogenesis, particularly in epithelial cell differentiation from mesenchyme (Rothenpieler and Dressler, 1993), such as in kidney development, and in mammary gland ductal morphogenesis (Silberstein et al., 2002). There is a requirement for the attenuation of PAX2 expression during development, particularly for the terminal differentiation of nephrogenic precursors (Dressler et al., 1993). Following the completion of development, PAX2 is capable of being re-expressed, such as in instances of nephrotoxicity or in other kidney damage (Cohen et al., 2007). In adult tissues, PAX2 is normally expressed in the pancreas (Zaiko et al., 2004), and also in subpopulations of nodal lymphocytes (Gilmore and Dewar, 2011). When expressed out of its normal context, expression of PAX2 is frequently observed in several cancer types (Robson et al., 2006). Expression of PAX2 has been linked with cell survival (Torban et al., 2000; Muratovska et al., 2003), cell migration and invasion (Buttiglieri et al., 2004), and mesenchyme-epithelial transition (MET) and epithelial-mesenchyme transition (EMT) (Doberstein et al., 2011).

Identity

Other names: PAPRS

HGNC (Hugo): PAX2

Location: 10q24.31



Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

12 exons, including alternative spliced exons 6 and 10 (Sanyanusin et al., 1996).

Transcription

Several alternatively spliced isoforms of PAX2 have been described involving exon 6, exon 10 (Dressler et al., 1990; Ward et al., 1994), and intron 9 (Busse et al., 2009).

Pseudogene

No

Protein

Note
PAX2 contains a DNA binding paired domain, a truncated homeodomain, an octapeptide region and a carboxyl-terminal transactivation domain (Sanyanusin et al., 1996).
Degradation/destruction of the PAX2 protein in cells is mediated by the prolyl hydroxylase domain protein 3 (PHD3) protein (Yan et al., 2011).
PHD3 is also known to hydroxylate hypoxia inducible factors (HIFα) in the presence of oxygen, and leads to HIFα proteosomal degradation.
In some colorectal cancer cell lines where PAX2 protein is expressed PAX2 expression was found to be elevated due to decreased PHD3 expression (Yan et al., 2011).

Description

416 amino acids; 44.7 kDa.

Expression

PAX2 is expressed in the developing eye, ear, central nervous system (CNS), spinal cord, pancreas and urogenital tract (Eccles et al., 2002).

Localisation

Nuclear.

Function

PAX2 is a transcription factor that regulates the expression of genes involved in mediating cell proliferation and growth, resistance to apoptosis, and cell migration (Dahl et al., 1997).
PAX2 null mutant mice die perinatally with absent cochlea, kidneys, ureters, oviducts, vas deferens and epididymis, and also demonstrate mid- and hindbrain deficiency and defective optic nerves (Torres et al., 1995; Torres et al., 1996).
PAX2's role in normal tissues includes promoting osmotic tolerance in the adult kidney (Cai et al., 2005), determining axon number and axon trajectory in the developing optic nerve (Torres et al., 1996; Alur et al., 2008), and determining nephron number in the kidney (Dziarmaga et al., 2003; Dziarmaga et al., 2006; Clark et al., 2004).
In cancer cells and in tumour endothelial cells the over-expression of PAX2 has been linked to the acquisition of a pro-invasive phenotype (Fonsato et al., 2008), and PAX2 has been suggested as a molecular target in tumour endothelial cells against which to design anti-angiogenic strategies (Bussolati et al., 2010).

Homology

PAX2 shares homology through the conserved paired box domain with several other members of the nine member PAX gene family (Dahl et al., 1997; Robson et al., 2006).

Mutations

Germinal

PAX2 mutations have been reported as associated with renal coloboma syndrome (see below), oligomeganephronia and isolated renal hypoplasia (Bower et al., 2012; Bower et al., 2011). These mutations are collated on the Leiden Open Variant Database platform (www.lovd.nl/PAX2). A PAX2 mutational hotspot and germline mosaiscism for PAX2 mutations have been reported (Amiel et al., 2000).

Implicated in

Endometrial carcinoma

Note
PAX2 is activated by oestrogen and tamoxifen in endometrial carcinomas, but not in the normal endometrium, and this activation is associated with cancer-linked hypomethylation of the PAX2 promoter (Wu et al., 2005; reviewed in Shang, 2006).
In the progression from normal to endometrial precancer to cancer, the expression of both PAX2 and PTEN is progressively lost (Monte et al., 2010; Allison et al., 2012).
Nevertheless, inhibition of PAX2 or silencing of PAX2 by RNAi inhibits the growth of transplanted human endometrial cancer cells in nude mice (Zhang et al., 2011).

Breast cancer

Note
PAX2 is expressed in breast cancer cell lines and tissues (Silberstein et al., 2002). A role for PAX2 in the crosstalk between estrogen receptor (ER) and ERBB2/HER-2 pathways is suggested by the observation that PAX2 is an important mediator of ER-associated repression of ERBB2 following tamoxifen treatment (Hurtado et al., 2008). PAX2 and the ER co-activator AIB-1/SRC-3 were found to compete for binding and regulation of ERBB2 transcription. Competition for binding, and dependence of the effect of tamoxifen on PAX2 is responsible for tamoxifen-responsiveness in breast cancer cells, and might suggest potential mechanisms for tamoxifen-resistance in breast cancer. PAX2 expression is negatively correlated with the recurrence of breast cancer (Liu et al., 2009), and expression of PAX2 is selectively achieved in breast cancer cells of the luminal subtype via ERα (Beauchemin et al., 2011).
PAX2 has a role in maintaining a low invasive

behavior in luminal breast cancer cells upon exposure to estradiol. However, in contrast to PAX2, GPR30 expression is correlated with ER expression and showed significant association with ERBB2 expression and also association with a tendency for tumour recurrence (Liu et al., 2009).
An MCF-7 cell line that was selected for tamoxifen resistance resulted in several outgrowing sublines that acquired PAX2 expression, accompanied by loss of phosphorylated ERBB2, and rapamycin resistance (Leung et al., 2010).

Ovarian carcinoma

Note
PAX2 is expressed in carcinomas of the ovary (Schaner et al., 2003; Muratovska et al., 2003; Tong et al., 2007). As compared with high-grade serous ovarian carcinomas, low-grade serous carcinomas are characterized by a greater expression of PAX2 (Tung et al., 2009; Roh et al., 2010; reviewed in Gershenson, 2013). PAX2 expression was reduced in secretory cell outgrowths (SCOUTS), which are associated with serous ovarian cancer (Chen EY et al., 2010), and PAX2 expression has also been associated with SCOUTS and serous borderline tumours occurring in the fallopian tube (Laury et al., 2011). A relationship between discrete PAX2 gene dysregulation in the oviduct and both increasing age and, more significantly, the presence of co-existing serous cancer has been suggested (Quick et al., 2012). PAX2 appears to have both oncogenic and tumour suppressor gene roles in ovarian cancer cells, depending on the cellular context (Song et al., 2013). In chemoresistant epithelial ovarian cancer cell lines PAX2 expression was down regulated (Ju et al., 2009). In ovarian cancer cell lines inhibition of PAX2 led to reduced cell proliferation and apoptosis.

Renal cell carcinoma

Note
Renal cell carcinomas (RCC) cells express PAX2 (Gnarra and Dressler, 1995; Daniel et al., 2001; Igarashi et al., 2001) as a result of loss of the von-Hippel Lindau (VHL) tumour suppressor gene and hypoxia (Luu et al., 2009; reviewed in Kuroda et al., 2013). PAX2 promotes cell survival in renal cell carcinoma cells (Hueber et al., 2006). PAX2 expression correlates with proliferation index in the majority of kidney tumour subtypes, and expression levels are significantly higher as compared to primary RCCs in patients presenting with metastatic disease (Pan et al., 2013). PAX2 may therefore provide a useful prognostic marker for determining the severity of kidney cancers (Kuroda et al., 2013). PAX2 has been shown to regulate ADAM10, which is a metalloproteinase expressed in RCC cells. PAX2 has been validated in vivo as a therapeutic target for the treatment of renal cell carcinoma cells (Hueber et al., 2008). Immunogenic HLA-A*0201-binding T-cell epitopes of PAX2 have been identified, which were able to generate a T-cell response to at least 1 of 6 PAX2 peptide pools in patients with renal cell carcinoma, colorectal cancer, or lymphoma (Asemissen et al., 2009).

Prostate cancer

Note
PAX2 is expressed in prostate cancer cell lines and in some prostate cancer tissues (Khoubehi et al., 2001; Quick et al., 2010). During embryonic development in mice Pax2 mRNA levels are higher in the early stages of development than in postpubertal prostates (Chen Q et al., 2010). PAX2 may regulate the early, androgen-independent stages of prostate development, and expression is associated with a dorsally localized epithelial cell population retaining proliferative and differentiation potential, which may represent a subset of stem-like cells with characteristics of castrate-resistant prostate cancer cells (Chen Q et al., 2010). Angiotensin II up-regulates the expression of PAX2 in prostate cancer cells via the angiotensin II type I receptor (Bose et al., 2009b). Inhibition of PAX2 expression leads to cell death in prostate cancer cells, independently of p53 (Gibson et al., 2007). In addition, PAX2 expression represses the expression of human beta defensin-1 (hBD1) in prostate cancer cells, which may be a mechanism by which PAX2 helps to facilitate evasion of cancer cells from the immune system (Bose et al., 2009a). Human beta defensin is a component of the immune system linking innate and adaptive immune responses. Furthermore, PAX2 over-expression promotes the development of a metastatic state in prostate cancer cells, presumably through upregulating the expression of cell membrane proteins (Ueda et al., 2013).

Nephrogenic adenoma

Note
Nephrogenic adenoma is a benign lesion of the urinary tract, particularly of the urinary bladder. Immunostaining for PAX2 and PAX8 is useful in the detection of nephrogenic adenomas and particularly unveils those nephrogenic adenomas that have a flat pattern (Piña-Oviedo et al., 2013). PAX2 is expressed in bladder cancer cells, and inhibition of PAX2 expression in bladder cancer cell lines induces cell death, indicating a role for PAX2 in tumour cell survival (Muratovska et al., 2003).

Wilms tumor

Note
PAX2, as well as its closely related family member, PAX8, is expressed in Wilms tumor (Dressler and Douglass, 1992; Eccles et al., 1992), but neither PAX2 nor PAX8 is mutated in Wilms tumor (Tamimi et al., 2006). The gene encoding the

calcineurin a-binding protein (CnABP) was identified as a novel target gene, which is up regulated by PAX2 (Nguyen et al., 2009), and is over-expressed in >70% of Wilms tumor samples analysed. CnABP was shown to promote cell proliferation and migration in cell culture experiments (Nguyen et al., 2009).

Melanoma

Note

PAX2 protein was expressed weakly in keratinocytes and melanocytes (Lee et al., 2011). Increased levels of PAX2 protein, as compared to melanocytes, were observed in some melanoma cell lines, and in some melanoma tissues, which strongly correlated with nuclear atypia and prominent nucleoli (i.e a more atypical cellular phenotype). PAX2 was found to regulate ADAM10 expression, which is a metalloproteinase with an important role in melanoma, and the silencing of PAX2 expression in melanoma cells abrogated chemoresistance, and anchorage-independent growth as well as decreasing migratory and invasive capacity of melanoma cells (Lee et al., 2011).

Medulloblastoma

Note

PAX2 is expressed in the majority of medulloblastomas, and its expression correlates with a less differentiated histology. Inhibition of PAX2 expression leads to apoptosis of medulloblastoma cells (Burger et al., 2012).

Colorectal cancer

Note

In colorectal cancers PAX2 protein is elevated due to decreased PHD3 expression (Yan et al., 2011). Silencing of PAX2 in colorectal cancer cells inhibits the activity of AP-1, a transcription factor that induces cyclin D1 expression (Zhang et al., 2012). PAX2 protein expression in colorectal cancer cells prevents JUNB from binding to c-jun and enhances phosphorylation of c-Jun (Zhang et al., 2012).

Kaposi's sarcoma

Note

PAX2 is expressed in Kaposi's sarcomas (Buttiglieri et al., 2004), where it induces apoptosis resistance and a proinvasive phenotype.

Renal coloboma syndrome (RCS)

Note

RCS is associated with heterozygous PAX2 mutations (Sanyanusin et al., 1995). RCS is characterised by end-stage renal failure and blindness (Eccles and Schimmenti, 1999; Bower et al., 2011). Increased apoptosis arises as a result of impaired PAX2 function, and is believed to be responsible for disrupted nephron formation (Porteous et al., 2000). Optic nerve defects are also observed in patients with RCS, and these lead to visual impairment (Eccles and Schimmenti, 1999). There are no reported instances of cancer in patients with renal-coloboma syndrome.

Polycystic kidney disease

Note

An aberrant persistent expression of PAX2 is implicated in autosomal dominant polycystic kidney disease, and cystogenesis is inhibited when Pax2 gene dosage is reduced in mice with ADPKD (Stayner et al., 2006; Eccles and Stayner, 2014). Similarly, in Cpk mice with recessive polycystic kidney disease, reduced dosage of the Pax2 gene was able to reduce cystogenesis, and also enhances apoptosis in fetal kidney cells (Ostrom et al., 2000).

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