PAX genes in cancer; friends or foes?

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INTRODUCTION

The PAX/Pax (paired box) gene family is now recognized as potentially playing important roles in cancer progression (reviewed in Robson et al., 2006). The family comprises nine transcription factors in humans (PAX1–PAX9) and mice (Pax1–Pax9) that are often described as cell-lineage-specific regulators of tissues where their expression is normally found. PAX gene family members share highly similar structural motifs, evolutionarily conserved among orthologs present in worms, flies, frogs, fish, and birds (Vorobyov and Horst, 2006). Relationships between PAX genes in terms of their sequence homologies and evolutionary phylogeny are shown in Figure 1. The pivotal roles of Pax during development are further exemplified by loss-of-function Pax mutant mouse models, many of which demonstrate prenatal or early postnatal lethality (reviewed in Wang et al., 2008). The expression and role of Pax genes during embryogenesis and tumorigenesis has previously been reviewed extensively (Chi and Epstein, 2002; Robson et al., 2006; Wang et al., 2008). However, upon completion of organogenesis the expression of most Pax genes attenuates, while in some tissues Pax gene expression either continues into adult-life or re-expression is possible (Table 1). The presence of Pax gene expression in adult tissues is often linked with stem cell-like properties and tissue repair, depending on the tissue context (see below). Although features of Pax expression in adult tissues may potentially confer significant functions on specific cells in these tissues, their specific roles in adult tissue in many cases remain largely unexplored. With their expression profiles often finely tuned both spatially and temporally, one would predict that deregulated Pax gene expression could therefore disrupt tissue homeostasis and contribute to diseases such as cancer (Maulbecker and Gruss, 1993; Muratovska et al., 2003).

Each of the nine PAX family members has been associated with multiple cancer types (Robson et al., 2006). PAX gene expression is often found in cancer types that originate from tissues that require PAX gene expression during development or in homeostasis (see Table 1). Together, these data suggest that PAX gene expression may be deregulated in cancer, but at least in some cases PAX gene expression is a carry-over of normal expression in normal adult tissues. It is now clear that PAX genes can either promote or inhibit tumorigenesis. This minireview will focus on specific examples of the role of PAX gene expression in adult tissues and PAX gene expression in cancer. In addition, we will discuss evidence supporting hypothesized functions of PAX gene expression in cancer.

PAX EXPRESSION IN ADULT TISSUES AND IN CANCER

PAX gene expression is relatively uncommon in adult tissues, and re-expression occurs only under certain circumstances. Pax gene knockout mice generally die either prenatally or soon after birth (Wang et al., 2008), which creates difficulties for investigating Pax gene functions in adult tissues unless conditional or tissue-specific knockouts are available. In some cases (i.e., Pax2, Pax3, and Pax6) Pax genes demonstrate haploinsufficiency (Epstein et al., 1991; Hill et al., 1991; Favor et al., 1996), and research has focused on their functions in adult tissues using heterozygous Pax mouse models (see below). PAX gene expression in adult tissues is often associated with tissue homeostasis. Table 1 summarizes current knowledge of PAX gene expression in adult tissues. There are two main types: (1) continuing expression from organogenesis, and (2) recurring expression under certain physiological conditions. During embryogenesis and in adult tissues a frequent role of PAX gene expression appears to be to maintain stem or progenitor cell state (plasticity) before cells fully commit to their fate, whether this is during organogenesis, or in tissue regeneration. However, the exact role that PAX expression plays in stem cell maintenance is not yet clear, but one possibility that we discuss below is that PAX8 might maintain the capacity of cells to enter the cell cycle, whilst simultaneously inhibiting senescence (Li et al., 2011a).
Table 1 | Continuing and recurring expression of PAX genes in adult tissues.

| Gene    | Continuing expression | Recurring expression* | Reference                                                                 |
|---------|-----------------------|-----------------------|---------------------------------------------------------------------------|
| PAX1    | Thymus                | –                     | Peters et al. (1995), Wallin et al. (1998)                                |
| PAX2    | Brain, pancreas, eye, female genital tract, breast, lymphocytes | Kidney, prostate     | Stoykova and Gruss (1994), Ritz-Laser et al. (2000), Chu et al. (2001),  |
|         |                       |                       | Silberstein et al. (2002), Tong et al. (2006, 2007), Chen et al. (2010)  |
| PAX3    | Brain, skin, skeletal muscle | –                     | Stoykova and Gruss (1994), Relaix et al. (2006), He et al. (2010)          |
| PAX4    | –                     | Pancreas, eye, pineal gland | Brun et al. (2004), Rath et al. (2009a,b)                                 |
| PAX5    | Brain, B-lymphocytes, lung, testis | –                     | Stoykova and Gruss (1994), Nutt et al. (1997), Adams et al. (1992)        |
| PAX6    | Brain, pancreas       | Eye, brain (olfactory) | Stoykova and Gruss (1994), Sikov et al. (2000), Guo et al. (2010)         |
| PAX7    | Brain, skeletal muscle | –                     | Stoykova and Gruss (1994), Relaix et al. (2006)                           |
| PAX8    | Thyroid, kidney, placenta, female genital tract, lymphocytes | Pancreas             | Zannini et al. (1992), Ferretti et al. (2005), Rieck et al. (2009), Tong et al. (2009), Ozcan et al. (2011) |
| PAX9    | Thymus, esophagus     | –                     | Peters et al. (1995)                                                     |

*Recurring expression includes minimally detected expression.

**PAX1**

PAX1 is expressed in a small fraction of cortical cells in the adult thymus (Peters et al., 1995; Wallin et al., 1996), where it is required for the maturation of thymocytes. Expression of PAX1 in adult thymus epithelium promotes the thymus microenvironment required for normal T cell maturation.

In cervical cancer tissues PAX1 was one of six genes that were shown to be hypermethylated (Lai et al., 2008). Moreover, parallel testing for human papillomavirus (HPV) and PAX1 methylation status in cervical swabs conferred an improved sensitivity than HPV testing alone.

**PAX2**

PAX2 is expressed in the medullary regions of adult kidneys, and in the transitional urothelium of the ureter and bladder wall (Tong et al., 2006). PAX2 is also expressed in the epithelial lining of the fallopian tube in females (Tong et al., 2007) and in the epithelium of the male genital tract from the Rete testis to the ejaculatory duct (Tong et al., 2011). In female mice, Pax2 is expressed during puberty in the mammary tubular epithelium (Silberstein et al., 2002), and is required for progesterone-dependent mammary development (Silberstein et al., 2002). PAX2 participates as part of a complex with estrogen receptor to regulate the ERBB2 promoter (Hurtado et al., 2008).

In addition, PAX2 is expressed in the glucagon-expressing cells of the pancreas (Ritz-Laser et al., 2000), and Pax2 expression has been demonstrated in the optic tectum in mice (Nakamura, 2001). Recurring Pax gene expression is important for tissue repair and regeneration. While embryonic Pax2 gene expression has already largely attenuated in the adult kidney cortex, four independent groups have demonstrated that upon kidney injury, Pax2 expression re-emerges at the initial stage of tubular regeneration, in a transient and temporally restricted pattern. The recurring expression is also proposed to confer a protective function, preventing tubular cells from apoptosis in the initial stage of regeneration (Imgrund et al., 1999; Maeshima et al., 2002; Cohen et al., 2007; Huang et al., 2011). Chen et al. (2010) have also shown that androgen-dependent re-expression of Pax2 occurs after castration in male mice.

PAX2 is expressed in ovarian cancers, in renal cell carcinomas (RCC), and in some bladder carcinomas (Muratovska et al., 2003; Tong et al., 2007; Herlitz et al., 2008). In these cell types it appears to be important for tumor cell survival (Muratovska et al., 2003; Hueber et al., 2006), which has recently been shown to be because PAX2 regulates ADAM10 (Doberstein et al., 2011), and in RCC PAX2 expression is promoted by the loss of VHL and hypoxia (Luu et al., 2009).

PAX2 is also expressed in breast cancer (Silberstein et al., 2002), where it is important for maintaining the estrogen receptor responsiveness of breast cancer. In breast cancer cells an estrogen receptor–PAX2 complex regulates ERBB2, and determines response to tamoxifen (Hurtado et al., 2008). In addition, PAX2 expression is required for tamoxifen-induced endometrial carcinogenesis (Wu et al., 2005), and loss of PAX2 expression enhances endometrial cancer malignancy (Monte et al., 2010; Roh et al., 2010). Aberrant expression of PAX2 has also been observed in...
prostate cancer (Khoubehi et al., 2001). In addition, PAX2 expression is associated with resistance to apoptosis in Kaposi’s sarcoma cells (Buttiglieri et al., 2004).

**PAX3**

PAX3 is expressed in a pool of stem cells in adult muscle, called satellite cells (reviewed in Buckingham and Relaix, 2007). The PAX3 gene is also expressed in melanocyte stem cells (melanoblasts) localized in the bulge region of hair follicles in adult skin (Lang et al., 2005). In this location PAX3 is involved in a transcriptional regulatory network to maintain the undifferentiated state of the melanocyte stem cells (Lang et al., 2005). Interestingly, PAX3 is also expressed in adult human epidermal melanocytes (He et al., 2010; Medic and Ziman, 2010), but in this location it appears PAX3 has retained only some of its developmental roles.

PAX3 undergoes chromosome rearrangement with FOXO1 in the majority of alveolar rhabdomyosarcomas (Galili et al., 1993; Bennicelli et al., 1999). In addition, PAX3 is persistently expressed in embryonal rhabdomyosarcomas (Frascella et al., 1998). PAX3 expression has been reported to be regulated by oestrogens (Scholl et al., 2001; He et al., 2010), where it was initially thought that PAX3 expression is required for the regulation of MITF gene expression, as in the developing neural crest (reviewed in Kubic et al., 2008). MITF is a dominant regulator in the maintenance of plasticity during differentiation in both eye and melanoblast development (Jackson and Raymond, 1994). In both eye and melanocyte precursors Pax2, Pax3, and Pax6 have been shown to transcriptionally activate the Mitf promoter activity (Watanabe et al., 1998; Baumer et al., 2003). Indeed, Pax3–Mitf genetic interactions were shown to act as a nodal point for maintaining embryonic and adult stem cell plasticity (Lang et al., 2005). However, the silencing of PAX3 expression in metastatic melanoma cells had unexpectedly little or no effect on MITF mRNA and protein expression (He et al., 2011), and indeed PAX3 was only minimally bound to the MITF promoter in melanoma cells (Medic and Ziman, 2010).

**PAX4**

Although there has been a lack of studies relating to the association of PAX4 in both adult and cancer tissues, two independent studies have reported that Pax4 re-expression confers a protective function in pancreatic β-cells (Brun et al., 2004; Lu et al., 2007). The mitogen induced Pax4 expression not only increased β-cell replicative potential, it also protects cells from apoptosis, through transcriptionally activating both the oncogene c-myc and the anti-apoptotic gene Bcl-xl expression, respectively (Brun et al., 2004).

PAX4 expression was shown to be upregulated in human insulinomas (Miyamoto et al., 2001), and was proposed to be a survival factor in rat insulinoma cells, through upregulating Bcl-xl expression (Brun et al., 2007). In contrast, ectopic PAX4 expression in melanoma reduced cell growth, which suggested a possible tumor suppressor role in melanoma (Hata et al., 2008).

**PAX5**

PAX5 is expressed during B lymphopoiesis, and plays an essential role in early B, pre-B and pro-B lymphocyte development, particularly in the developmental pathway controlling V-to-DJ recombination (Nutt et al., 1997; Sanz et al., 2003). Interestingly, re-programming of mature B-cells to pluripotency requires PAX5 knockdown in addition to expression of Oct4, Sox2, Klf4, and c-Myc (Hanna et al., 2008).

PAX5 expression is observed in most B-cell neoplasms, including B-cell lymphoma (Krenacs et al., 1998). In contrast, PAX5 haploinsufficiency synergizes with STAT5 activation to induce acute lymphoblastic leukemia (Heltemes-Harris et al., 2011). In hepatocellular carcinoma PAX5 has been identified as a novel tumor suppressor through interacting with the p53 signaling pathway (Liu et al., 2011). Consistent with this, overexpression of PAX5 induces apoptosis in multiple myeloma cells (Proulx et al., 2010). PAX5 is expressed in medulloblastoma (Kozmik et al., 1995), and in a sub-type of neuroblastoma (Baumann Kubetzko et al., 2004), perhaps reflecting the earlier requirement for PAX5 expression in the mid/hindbrain boundary during embryogenesis (Urbanek et al., 1994). PAX5 expression in breast cancer cells enhances epithelial behavior (Vidal et al., 2010), and has been associated with a significantly better prognosis than breast cancers where PAX5 is not expressed.

**PAX6**

Pax6 is re-expressed in the corneal epithelium during corneal wound repair (Sivak et al., 2000). However deficiency of Pax6 expression during corneal wound repair is correlated with reduced cornea epithelial cell adhesion, elevated cell proliferation, increased stromal cells apoptosis (Ramaesh et al., 2005, 2006; Ou et al., 2010), and defective corneal neuronal migration (Leiper et al., 2009), suggesting that Pax6 suppresses proliferation and enhances differentiation. Similarly, during olfactory epithelial regeneration, Pax6 gene expression is transiently elevated in globose basal cells, which comprise the putative stem cell pool to commit to either neuronal and epithelial cell lineages during regeneration (Guo et al., 2010). Pax6 has been referred to as a neuroectoderm cell fate determinant (Zhang et al., 2010). Interestingly it was shown that Pax6 protein level is essential for controlling the balance between neural stem cell self-renewal and neurogenesis (Sansom et al., 2009).

In the early stages of bladder cancer, and in invasive breast cancer, PAX6-associated CpG islands become progressively hypermethylated, and this is associated with increased PAX6 expression (Salem et al., 2006; Hellwinkel et al., 2008; Moelans et al., 2011). PAX6 expression was shown to suppress the growth of human glioblastoma cells (Zhou et al., 2005), suppressing their invasiveness and expression of matrix-metalloproteinase 2 (Mayes et al., 2006), and increasing glioma cell susceptibility to detachment and oxidative stress (Chang et al., 2007), as well as reducing angiogenesis (Zhou et al., 2010). However, PAX6 was not apparently mutated in gliomas (Pinto et al., 2007). In contrast, Pax6 was expressed in pancreatic adenocarcinoma, downregulated upon terminal differentiation (Lang et al., 2008), and actively participated in cancer progression through activation of the MET tyrosine kinase receptor gene (Mascalz et al., 2009). In addition, endogenous and lentiviral-mediated PAX6 expression promoted cell proliferation and inhibited apoptosis in retinoblastoma cells (Bai et al., 2011; Li et al., 2011b), as well as promoting
breast cancer cell proliferation and tumorigenesis (Zong et al., 2011).

**PAX7**

In adult muscle Pax7 is expressed in the muscle satellite cells, a stem cell pool. The satellite cells are required for tissue repair and regeneration following muscle injury (reviewed in Buckingham and Relaix, 2007), and Pax7 expression is required to maintain survival and proliferation of postnatal satellite cells (Relaix et al., 2006).

PAX7 undergoes chromosome rearrangement with FOXO1 in alveolar rhabdomyosarcomas, in a similar fashion to, although less frequently than PAX3 (Galili et al., 1993; Bennicelli et al., 1999).

**PAX8**

PAX8 is expressed in the adult thyroid and kidney (Zannini et al., 1992; Tong et al., 2009), and its role in adult thyroid tissue remains the same as in the developing thyroid; regulating Tg (thyroglobulin), Tpo (thyroid peroxidase), and NIS (sodium/iodide symporter) expression, all of which are essential for thyroid hormone synthesis (reviewed in De Felice and Di Lauro, 2011). Interestingly, Oct4 expression, a stem cell marker in adult thyroid, coincides with a subset of Pax8 positive cells, but not Tg positive cells (which represent differentiated cells; Thomas et al., 2006). These observations suggest that Pax8 has a separate role in the maintenance of adult thyroid stem or progenitor cells. Similarly, in adult kidneys Pax8 is expressed in the Bowman’s capsule, and in medullary regions (Tong et al., 2009; Li et al., 2011a), which have been proposed to be sites of renal stem and/or progenitor cells (reviewed in Little and Bertram, 2009), although the functional role of PAX8 in the adult kidney has yet to be explored.

PAX8 undergoes chromosome rearrangement with PPARγ in thyroid adenocarcinomas (Kroll et al., 2000). PAX8 was also identified in a systematic screen as a lineage survival factor for ovarian cancer cells (Hibbs et al., 2004; Bowen et al., 2007; Cheung et al., 2011), possibly relating to its critical role during the development of the fetal Mullerian duct (Mittag et al., 2007). In renal, ovarian and thyroid cancers, we recently showed that PAX8 is required for basal E2F1 transcription and thus the capacity for entry into the cell cycle, and also for maintaining the stability of its transcriptional c-factor, RB (Li et al., 2011a). Either overexpression or loss of E2F1 ultimately results in apoptosis or senescence (Qin et al., 1994; Dimri et al., 2000; Berton et al., 2005; Park et al., 2006), potentially explaining why senescence is observed when PAX8 expression is knocked down using siRNAs in cancer cell lines. Expression of PAX8 has also been shown to regulate telomerase, an important factor in cellular aging and immortalization, in glioblastoma cell lines (Chen et al., 2008).

**PAX9**

Like Pax1, Pax9 is expressed in the adult thymus (Peters et al., 1993), and PAX9 expression is also required for permanent tooth development (Suda et al., 2011). In addition, PAX9 cDNA has been isolated from adult human esophagus (Peters et al., 1997).

PAX9 expression has been shown to mediate oncogene-induced cell survival in oral squamous cell carcinoma (Lee et al., 2008). On the other hand progressive loss of PAX9 expression correlates with increasing malignancy in esophageal cancers (Gerber et al., 2002). PAX9 was shown to be amplified and highly expressed in lung cancer tissues (Kendall et al., 2007), and in addition, pairwise overexpression of genes within the amplified DNA, including PAX9, was synergistic in promoting the proliferation of lung cancer cell lines.

**CONCLUDING REMARKS**

It is widely accepted that tumor formation is an aberrant form of organogenesis in adult tissues. Although PAX expression is relatively rare in adult tissues, evidence suggests this expression may be involved in maintaining pluripotency and survival of stem cell populations. Either continuing or recurring PAX expression is essential to provide pools of progenitor cells for tissue regeneration upon injury. In cancer cells, achieving self-sufficiency in growth signals and unrestricted replicative potential requires that they be able to survive in potentially adverse microenvironments during tumor progression. There are now numerous studies that imply that PAX genes play important roles in conferring growth and survival advantages to cancer cells, and that they regulate cell plasticity.

Conceptually, proliferation and differentiation are placed at opposite ends of the “spectrum” of tumor progression. Yet, PAX genes, such as PAX8, could play key roles in balancing these processes. Clearly, more studies will be required to better understand the role that PAX genes play in adult tissues and in cancer.

**ACKNOWLEDGMENTS**

The authors acknowledge funding from the New Zealand Institute for Cancer Research Trust, the Health Research Council of New Zealand, and the University of Otago Faculty of Medicine Research Trust award.
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any com- mercial or financial relationships that could be construed as a potential con- flict of interest.

Received: 14 October 2011; accepted: 09 January 2012; published online: 31 Janu- ary 2012.

Citation: Li CG and Eccles MR (2012) PAX genes in cancer: friends or foes? Front. Gene. 3:6. doi: 10.3389/fgene.2012.00006

This article was submitted to Frontiers in Cancer Genetics, a specialty of Frontiers in Genetics.

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