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REVIEW ARTICLE

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The Notch pathway in prostate development and cancer

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Abstract The Notch family of transmembrane receptors are important mediators of cell fate determination. Accordingly, Notch signaling is intimately involved in the development of numerous tissues. Recent findings have highlighted a critical role for Notch signaling in normal prostate development. Notch signaling is required for embryonic and postnatal prostatic growth and development, for proper cell lineage specification within the prostate, as well as for adult prostate maintenance and regeneration following castration and hormone replacement. Evidence for Notch as a regulator of prostate cancer development, progression, and metastasis has also emerged. This review summarizes our current understanding of the role of Notch pathway elements, including members of the Jagged, Delta-like, hairy/enhancer-of-split, and hairy/enhancer-of-split related with YRPW motif families, in prostate development and tumorigenesis. Data supporting Notch pathway elements as oncogenes and tumor suppressors in prostate tumors, as well as data implicating Notch receptors and ligands as potential markers of normal prostate stem/progenitor cells and prostate cancer stem/initiating cells, are also presented.

Key words Notch · Jagged · stem cell · prostate development · prostate cancer

Introduction

The Notch signaling pathway

In mammals, the Notch family of transmembrane receptors consists of four members: Notch1 through Notch4 (Fleming, 1998). Following synthesis, full-length unprocessed Notch proteins are transported to the *trans*-Golgi network where they are cleaved by Furin at a site referred to as the S1 cleavage site, thus generating a mature heterodimeric type I transmembrane receptor (Blaumueller et al., 1997). Mammals also express Notch ligands, of which five members have been identified: Jagged1/2 and Delta-like 1/3/4 (Dll1/3/4) (Fleming, 1998). Notch ligands, similar to Notch receptors, are type I transmembrane proteins. Notch signaling is initiated when Notch ligand binds to an adjacent Notch receptor (Fig. 1). This interaction is thought to induce a conformational change within the Notch receptor, resulting in the exposure of an S2 cleavage site for tumor necrosis factor-α converting enzyme within the Notch extracellular domain (Mumm and Kopan, 2000). Subsequent to S2 cleavage, Notch receptors undergo S3 cleavage mediated by the γ-secretase complex (comprised of presenilin-1/2, nicastrin, Pen-2, and Aph-1) at a site located within the Notch transmembrane domain (Edbauer et al., 2003). The net effect of S3 cleavage is the release of the Notch intracellular domain into the cytoplasm, which can subsequently translocate into the nucleus to effect gene transcription.

Within the nucleus, the Notch intracellular domain binds to CSL (C protein binding factor 1/Suppressor of Hairless/Lag1) and converts it from a transcriptional repressor to a transcriptional activator (Mumm and Kopan, 2000). This process involves the displacement of transcriptional corepressors and/or the recruitment of transcriptional coactivators. Transcriptionally active Notch–CSL complexes direct the expression of numerous downstream target genes, including two families of basic helix-loop-helix transcription factors: the hairy/enhancer-of-split (HES) family and the hairy/enhancer-of-split-related with YRPW motif (HEY) family (Iso et al., 2003). HES and HEY proteins in turn act as transcriptional repressors themselves. Several target genes repressed by HES1 have been reported, including achaete-scute in *Drosophila* (human achaete-scute

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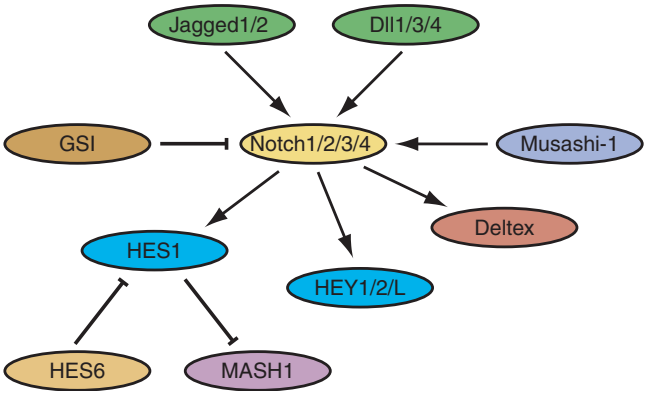

Fig. 1 The Notch signaling pathway. Notch signaling is initiated when Notch ligands (Jagged1/2, Dll1/3/4) bind to Notch receptors (Notch1/2/3/4) expressed on adjacent cells. Ligand binding triggers proteolytic cleavage of the Notch receptor to release the Notch intracellular domain into the cytoplasm, which subsequently migrates into the nucleus to regulate gene transcription. Within the cytoplasm, the Notch intracellular domain may transduce Notch signals in a CSL-independent manner via the E3 ubiquitin ligase Deltex. Within the nucleus, the Notch intracellular domain binds to the transcription factor CSL and initiates gene transcription. Primary target genes of the Notch pathway include basic helix-loop-helix proteins belonging to the hairy/enhancer-of-split (HES) (e.g., HES1) and hairy/enhancer-of-split related with YRPW motif (HEY) (e.g., HEY1/2/L) families. HES1 in turn functions as a transcriptional repressor of mammalian achaete-scute homolog 1 (MASH1). HES6 functions as an antagonist of HES1, thus blocking the ability of HES1 to repress MASH1 transcription. Inhibition of the Notch pathway can also be achieved via gamma secretase inhibitors (GSIs), which block the proteolytic cleavage of full-length Notch receptors at the cell surface. In contrast, the RNA-binding protein Musashi-1 functions as a positive regulator of Notch signaling.

homolog 1 [HASH1] in humans; mammalian achaete-scute homolog 1 [MASH1] in mouse) (Axelson, 2004). The Notch pathway has been shown to regulate numerous cellular processes essential for proper tissue growth and development, including cell proliferation, survival, and differentiation.

Notch and tissue development

It is well established that Notch signaling regulates cell fate in numerous cell lineages (Ohishi et al., 2003; Lai, 2004). In addition to maintaining cells in an undifferentiated state to permit inductive cues to drive cellular diversification (Artavanis-Tsakonas et al., 1995), Notch signaling can also direct cells to adopt alternate differentiation fates (Wang and Barres, 2000). This ability of Notch to regulate cellular differentiation has led to the identification of Notch as a key regulator of tissue development in multicellular organisms. In mammals, Notch pathway elements are widely expressed during organogenesis (Artavanis-Tsakonas et al., 1999). Moreover, Notch signaling has been shown to regulate the development of tissues from all three primary germ layers (Milner and Bigas, 1999; Callahan and Egan, 2004; Yoon and Gaiano, 2005). Postnatal tissue development and adult tissue maturation are also regulated by Notch signaling (Artavanis-Tsakonas et al., 1999). Hence Notch signaling must be precisely controlled for proper tissue development to occur. Accordingly, perturbation of Notch signaling can manifest as tissue abnormalities and facilitate cancer development. This review focuses on the Notch pathway as a regulator of normal prostate development and prostate tumorigenesis.

Notch and normal prostate development

The prostate gland is a complex branched ductal organ. During embryogenesis, the prostate develops from the primitive urogenital sinus due to interactions between the urogenital sinus epithelium and the urogenital sinus mesenchyme (Cunha et al., 2002). Around day 17.5 of gestation in the mouse, prostatic epithelial buds first emerge from the urogenital sinus and begin to proliferate and extend through the urogenital sinus mesenchyme (Abate-Shen and Shen, 2000; Marker et al., 2003). At this stage, the fetal urogenital sinus is enriched in prostate stem cells, with the majority of cells in the urogenital sinus epithelium co-expressing basal and luminal cell markers (Wang et al., 2001). Epithelial cells continue to co-express basal and luminal markers, a progenitor cell phenotype, until postnatal day 5, after which distinct populations of basal and luminal cells differentiate (Hayward et al., 1996; Wang et al., 2001). The prostate continues to undergo active branching morphogenesis for several weeks postnatally (Sugimura et al., 1986), during which prostatic lobes grow in size, canalize, and undergo lobe-specific branching (Abate-Shen and Shen, 2000; Marker et al., 2003). Hence formation of a mature prostate gland is only achieved postnatally. The mature mouse prostate is comprised of four distinct lobes: dorsal, lateral, ventral, and anterior (Sugimura et al., 1986). Although prostate morphogenesis in humans follows a similar androgen-dependent developmental process, the human prostate does not exhibit a lobular architecture. Rather, the human prostate develops as an acorn-shaped structure that can be divided into three morphological regions: peripheral, transitional, and central zones (McNeal, 1988). Numerous signaling pathways have been shown to regulate prostate morphogenesis, including sonic hedgehog (Freestone et al., 2003; Wang et al., 2003; Berman et al., 2004), fibroblast growth factor 10 (Nakano et al., 1999; Donjacour et al., 2003), and bone morphogenic protein 4 (BMP4) (Lamm et al., 2001). Recent studies have now implicated the Notch pathway as an important regulator of normal prostate development.