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Review

Notch signaling in prostate cancer: refining a therapeutic opportunity

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Summary. Notch is an evolutionarily conserved signaling pathway that plays a critical role in specifying cell fate and regulating tissue homeostasis and carcinogenesis. Studies using organ cultures and genetically engineered mouse models have demonstrated that Notch signaling regulates prostate development and homeostasis. However, the role of the Notch signaling pathway in prostate cancer remains inconclusive. Many published studies have documented consistent deregulation of major Notch signaling components in human prostate cancer cell lines, mouse models for prostate cancers, and human prostate cancer specimens at both the mRNA and the protein levels. However, functional studies in human cancer cells by modulation of Notch pathway elements suggest both tumor suppressive and oncogenic roles of Notch. These controversies may originate from our inadequate understanding of the regulation of Notch signaling under versatile genetic contexts, and reflect the multifaceted and pleiotropic roles of Notch in regulating different aspects of prostate cancer cell biology, such as proliferation, metastasis, and chemo-resistance. Future comprehensive studies using various mouse models for prostate cancer may help clarify the role of Notch signaling in prostate cancer and provide a solid basis for determining whether and how Notch should be employed as a therapeutic target for prostate cancer.

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Introduction

Notch is an evolutionarily conserved signaling transduction pathway. In mammals, this intricate signaling transduction pathway consists of four receptors (Notch1-4), five ligands (Jag1/2, Dll1/3/4) and a plethora of downstream components (Kopan and Ilagan, 2009). Notch receptors are single pass type 1 transmembrane proteins. Notch signaling is usually activated by binding of the ligand expressed on one cell to the receptors expressed on its adjacent cells. The interaction initiates two sequential proteolytic cleavages of the receptors by Tumor necrosis factor-Alpha Converting Enzyme (TACE) and the gamma-secretase complex, leading to the release of the Notch intracellular domain (ICN or NICD). NICD translocates into the nucleus where it converts the CSL [CBF1/Su(H)/Lag-1] transcriptional repressive complex into transcriptional active complex by displacing corepressors such as CtBP, SMRT, SHRP, and recruiting coactivators such as MAML1, and CBP/p300 (Mumm and Kopan, 2000).

Notch regulates various vital biological processes such as organogenesis, cell fate determination, and tissue homeostasis in numerous organ systems (Artavanis-Tsakonas et al., 1999; Chiba, 2006; Kopan and Ilagan, 2009). Deregulation of Notch activity results in various diseases including cancer (Ntziachristos et al., 2014). Many excellent and comprehensive reviews on the topic of the biochemistry and biology of Notch signaling have been published (Bray, 2006; Kopan and Ilagan, 2009; del

Alamo et al., 2011; Ranganathan et al., 2011; Kandachar and Roegiers, 2012; Musse et al., 2012; Takeuchi and Haltiwanger, 2014). The focus of this review is the role of Notch signaling in prostate carcinogenesis based on the search of publications with "Notch" and "prostate" as the two key words. We will first summarize briefly the role of Notch in other tumor models and then focus on the role of Notch signaling in prostate tissue development, homeostasis and carcinogenesis.

Notch signaling in hematopoietic and solid tumors: a coin with two sides

Notch pathway components are widely expressed during organogenesis (Artavanis-Tsakonas et al., 1999). Multiple modes of regulation in the Notch pathway exist, including genetic alteration, epigenetic modification, and posttranslational modification, etc. (Ntziachristos et al., 2014). Aberrant activation or silencing of Notch can manifest as tissue abnormalities and cancers. Evidence from cancer biology studies has suggested both tumor suppressive and oncogenic roles for the Notch signaling pathway.

The original evidence suggesting Notch as an oncogene came from T cell acute lymphoblastic leukemia (T-ALL) in which a chromosomal translocation generating a constitutively active form of Notch was identified (Ellisen et al., 1991). Transgenic mice harboring NICD1 develop T cell neoplasms (Pear et al., 1996). Subsequently, the discovery of recurrent activating mutations of Notch1 firmly established the link between Notch signaling and etiology of T-ALL firmly (Weng et al., 2004). In contrast, chromosomal translocation and activating mutations of the Notch signaling components are found at a lower rate in solid tumors such as breast cancer. Insertion of the mouse mammary tumor virus (MMTV) activates int-3 (Notch4) and leads to the formation of mammary tumors (Gallahan and Callahan, 1987; Jhappan et al., 1992). Over-expression of activated Notch1 and Notch3 in transgenic mice induces mammary tumor formation (Hu et al., 2006). Additionally, recurrent chromosomal rearrangements and mutations of Notch signaling components that facilitate receptor activation or inhibit receptor degradation were identified in breast tumor specimens (Robinson et al., 2011; Wang et al., 2015). Besides genomic alteration, aberrant expression of the Notch pathway elements was found to be closely correlated to cancer progression in human tumor specimens (Parr et al., 2004; Zardawi et al., 2010; Han et al., 2011). Functional studies indicate that Notch signaling drives breast cancer progression by interacting with other signaling pathways, including Wnt and Ras pathways (Fitzgerald et al., 2000; Ayyanan et al., 2006) and enables the crosstalk of tumor cells with niche cells through ligand/receptor engagement (Sethi et al., 2011). Other than breast cancer, Notch signaling also exhibits oncogenic properties in other solid tumors such as colorectal cancer, cervical cancer, and ovarian cancer (Maliekal et al., 2008; Qiao and Wong, 2009; Rose et al., 2010; Ntziachristos et al., 2014). Therefore, it has long been proposed that Notch signaling may serve as both a prognostic marker and a therapeutic target.

On the contrary, Notch signaling displays tumor suppressive features in some malignancies. For example, loss of Notch1 expression in epidermal keratinocytes promotes tumorigenesis. Mechanistically, loss of Notch activity impairs skin-barrier integrity and induces a wound-like microenvironment that in turn promotes epidermal transformation (Demehri et al., 2009). Notch signaling was also shown recently as a tumor suppressor in myeloid leukemia (Klinakis et al., 2011) and bladder cancer (Maraver et al., 2015).

To make the matter more complicated, the functions of Notch signaling can be different in distinct tumor subtypes. For example, Notch signaling imposes an oncogenic effect in lung adenocarcinoma and its activity correlates significantly with poor survival (Ntziachristos et al., 2014). In contrast, Notch signaling appears to be tumor suppressive in squamous cell lung carcinoma (Wang et al., 2011b). In addition, different Notch receptors are capable of playing opposite roles in cancer progression. Notch4 activation augments breast cancer stem cell activity (Harrison et al., 2010) while Notch3 activation leads to cellular senescence and p21 expression (Cui et al., 2013). Finally, temporal activation of Notch signaling also influences the biological outcomes. For example, Notch plays a tumor suppressive role in the early stage of hepatocellular carcinoma but an oncogenic role in the late stage (Ntziachristos et al., 2014).

In summary, Notch signaling can be tumor suppressive and oncogenic. Unique transcriptome and pathological outputs in Notch signaling may result from a heterogeneous population of cancer cells and exposure to different oncogenic stress, growth stimuli, and survival signaling. This may explain why Notch signaling mediates distinct biology in different biological contexts (Ranganathan et al., 2011).

Role of Notch signaling in prostate development and homeostasis

Notch signaling components are expressed in prostate epithelia, suggesting that Notch plays a role in prostate development and homeostasis (Leong and Gao, 2008). We showed that Notch receptors are widely expressed in both the luminal and basal cell compartments of adult murine prostates while Notch ligands are mainly expressed in the basal cells (Valdez et al., 2012). Major Notch downstream target genes and regulatory components of the Notch pathway are also widely expressed in prostate epithelial cells (Valdez et al., 2012). Suppressing Notch signaling in *ex vivo* cultured rat ventral prostates with gamma-secretase inhibitors, inhibits branching morphogenesis (Wang et al., 2006). Interestingly, inhibiting Notch signaling in *ex vivo* cultured rat prostates also leads to loss of stromal

tissues (Orr et al., 2009), suggesting a role of Notch signaling in prostate stromal homeostasis. A prostate sphere assay has been utilized to understand molecular mechanisms regulating the capacity of prostate progenitor/stem cells for self-renewal (Xin et al., 2007). Induction of Notch signaling in the progenitor cells impairs their capacity to form spheres while suppressing Notch signaling by DAPT (a gamma-secretase inhibitor) inhibits basal epithelial stem cell differentiation and induces their proliferation in the prostate sphere assay (Shahi et al., 2011; Valdez et al., 2012).

Genetically engineered mouse models were generated to investigate the role of Notch signaling in prostate homeostasis. Inducible deletion of Notch1 in whole prostate tissues (including both epithelial and stromal cells) caused increased proliferation, expansion of progenitor cells expressing both basal and luminal cell markers, and a reduction of lumen secretion (Wang et al., 2006). Subsequently, Notch activity was specifically altered in prostate epithelial cells using improved mouse models. Wu et al. ablated Notch signaling in prostate epithelial cells at the early developmental stage by disrupting Rbp-J using an Nkx3.1-Cre model. Ablating Notch signaling resulted in decreased epithelial cell proliferation and loss of epithelial progenitor cells (Wu et al., 2011). We recently disrupted Notch signaling in adult murine prostate epithelial cells using a Probasin-Cre model. Interestingly, Notch signaling appears to be dispensable for adult murine prostate epithelial homeostasis. However, Notch signaling functions downstream of TGFβ signaling to maintain basal epithelial stem cells in dormancy (Valdez et al., 2012). In addition, enhanced Notch1 activation in adult murine prostate epithelial cells inhibits the growth of basal cells but promotes luminal cell proliferation (Valdez et al., 2012). Recently, we further showed that Notch signaling is able to suppress anoikis of prostate luminal cells by augmenting NF-kB activity (Kwon et al., 2014). Taken together, these reports suggest that key elements of the Notch pathway are present in murine prostate epithelia and that Notch signaling functionally regulates cellular differentiation and controls cell growth distinctively in different cell lineages and at various developmental stages. The underlying mechanisms are not fully determined, but it is likely due to the interactions and crosstalk of NICD with other lineage specific transcription factors (Wang et al., 2011a).

Cellular biological studies suggest a controversial role of Notch signaling in prostate cancer cell biology

Major Notch pathway elements were detectable in immortalized human primary prostate cells. In immortalized human prostate basal-like epithelial PrEC cells, Notch signaling is required for survival (Dalrymple et al., 2005). Notch1 receptor is also expressed by other immortalized epithelial cells such as BPH-1, PNT2 and RWPE cells, however, its role in these cells is not clearly defined (Leong and Gao, 2008). Notch signaling components are also widely expressed by frequently used human prostate cancer cell lines such as LNCaP, VCaP, CWR22Rv1, C4-2B, DU145, and PC3 (Shou et al., 2001; Zayzafoon et al., 2004; Dalrymple et al., 2005; Litvinov et al., 2006; Scorey et al., 2006; Zhang et al., 2006; Wang et al., 2011c; Hahm et al., 2012; Kashat et al., 2012; Zhang et al., 2014). Notch1 is expressed in all these cell lines. Notch2, Notch3, Notch4 and Jag1 are expressed in LNCaP, C4-2B, DU145, and PC3. The components of the Notch pathway are differentially expressed in these cell lines. For example, the expression of Jag1 in the PC3 cell line is much higher than that in DU145 cells (Zhang et al., 2006). Differential expression of the Notch pathway components in normal and cancerous prostate cells suggest that Notch signaling plays a role in prostate tumorigenesis.

Notch activity has been shown to promote prostate cancer cell proliferation and survival. Knock-down of Jag1 and Notch1 expression in PC3, DU145, LNCaP, and C4-2B by siRNA significantly reduces cellular growth (Zhang et al., 2006; Wang et al., 2010;). Mechanistically, S phase arrest in mitosis is triggered by Jag1 and Notch1 down-regulation in PC3 cells (Zhang et al., 2006). In addition to the cell cycle regulators, Akt and FoxM1 were reduced upon Notch1 knock-down, accompanied by cell growth inhibition and apoptosis induction (Wang et al., 2011c). Another functional study demonstrated that siRNA-mediated Notch1 silencing inhibits proliferation and induces apoptosis through Bcl-2 and Bax in PC3 cells (Ye et al., 2012). Therefore, these data suggest that Notch signaling affects prostate cancer cell proliferation by multiple downstream pathways. Subcutaneous injection of PC3 cells overexpressing Dll4 displays increased tumor growth as compared to control PC3 cells (Li et al., 2007). The increased cell growth is attributed to an increase in vessel lumen size (Li et al., 2007), highlighting a non-epithelial cell autonomous action of Notch signaling. Of note, inhibiting Notch activity by different strategies could lead to distinct biological outcomes. For instance, down-regulation of Rbp-J by lentivirus-mediated shRNA inhibits proliferation of PC3 cells. However, suppressing Notch receptor activation by gamma-secretase inhibitors causes a minimal growth inhibitory effect (Yong et al., 2011).

Notch activity also promotes prostate cancer cell migration and invasion. The migratory capabilities of the PC3 and CWR22Rv1 cells were dramatically reduced by Notch1 siRNA treatment (Bin Hafeez et al., 2009). Mechanistically, Notch1 down-regulation leads to significant reduction of expression of uPA and MMP9 (Bin Hafeez et al., 2009). Motility of LNCaP and PC3 cells is also attenuated by DAPT treatment. Furthermore, Hes1 is upregulated in highly metastatic PC3 and PC3M cells (Scorey et al., 2006).

Finally, Notch activity also augments aggressiveness of prostate cancer cells. Pre-miR-34a has been shown to suppress proliferation and self-renewal capacity of C4-

2B and CWR22Rv1 cells partially by downregulating Notch1 (Kashat et al., 2012). Notch and ERK activation are essential for Runx2 to bind DNA and expression of Osteocalcin in C4-2B cells while Notch inhibitor treatment impairs C4-2B mineralization. This suggests that Notch activity promotes an osteomimetic property of prostate cancer cells (Zayzafoon et al., 2004). Docetaxel-resistant prostate cancer cells in hormone refractory prostate cancer (HRPC) possess higher Notch and Hedgehog signaling. Combined inhibition of Notch (by DBZ) and Hedgehog (by Cyc) signaling depletes docetaxel-resistant DU145 and CWR22Rv1 cancer cells through inhibition of Akt and Bcl-2 (Domingo-Domenech et al., 2012).

However, a tumor suppressive role of Notch signaling is suggested as well in the literature. Expression of a constitutively active form of Notch1 (ICN) in DU145, PC3, and LNCaP cells suppressed their proliferation significantly (Shou et al., 2001). Prostate Tumor OVerexpressed-1 (PTOV1) which down-regulates Notch target genes Hes1 and Hey1 promotes invasion and anchorage independent growth of PC3 cells and also enhances tumor growth and metastasis *in vivo* (Alana et al., 2014). Additionally, Notch downstream targets Hey1/2 and HeyL have also been shown to act as androgen receptor corepressors (Belandia et al., 2005; Lavery et al., 2011). Finally, prostate cancers often undergo neuroendocrine differentiation and become more aggressive. Notch signaling elements are decreased during hypoxia-induced neuroendocrine differentiation of LNCaP cells (Danza et al., 2012). Expression of the proneurogenic transcription factor Ngn3, CGA and the neuroendocrine markers NSE, GCA, b3-tubulin are increased following the transfection of a dominant negative form of Hes1 into LNCaP cells (Danza et al., 2012), which suggests that Notch activation inhibits neuroendocrine differentiation of human prostate cancer cells *in vitro*.

A potential mechanism that accounts for these controversies is the dosage of Notch signaling. Notch has been shown to function in a dose-dependent manner in mammary gland epithelial cells. Lower levels of Notch activity promoted proliferation of MCF-10A cells in a 3D culture while higher levels of Notch activity suppressed their growth (Mazzone et al., 2010).

Expression of Notch components is deregulated in transgenic mouse models

A dozen genetically engineered mouse models for prostate cancer have been generated such as TRAMP (Transgenic adenocarcinoma of the prostate), CR2-Tag, Hi-Myc, Pten-null etc. (Greenberg et al., 1995; Masumori et al., 2001; Ellwood-Yen et al., 2003; Wang et al., 2003). The expression of Notch pathway elements are abnormally altered in these mouse models, suggesting an active role of Notch in disease progression. In TRAMP mice (a minimal probasin promoter driving the expression of the SV40 T and t antigens), prostate epithelial cells express much higher levels of Notch1 mRNA than those in control wild type mice. In contrast, expression of Jag1 mRNA is undetectable in the epithelium, but is found in the endothelial cells (Shou et al., 2001). This suggests a potential crosstalk between tumor cells and stromal cells and an involvement of Notch signaling in prostate cancer progression. Notch1 expression is elevated in LADY mice (a larger probasin promoter driving the expression of the SV40 T antigen) at 6 weeks of age, but the expression level is comparable to that of control mice at 16 weeks of age (Gipp et al., 2007). This suggests an active role of Notch in early tumor development. In the CR2-TAg mouse model, in which the SV40 T antigen is driven by the Cryptdin-2 promoter, expression of Hes6, an inhibitor of Hes1, gradually increases over time. Dll1 also increased progressively, probably due to an increase in neuroendocrine cell population (Hu et al., 2002; Leong and Gao, 2008). In conclusion, alterations of the Notch pathway are frequently observed in mouse models for prostate cancer.

Deregulation of the Notch pathway is associated with human prostate cancer progression

A consensus has been reached that Notch signaling is deregulated during prostate cancer initiation and progression based on the data obtained from prostate cancer patient samples. In a gene expression array analysis of human prostate cancer specimens, Jag1 mRNA is found to be significantly upregulated in tumor metastases compared to primary tumors, though the sample size is relatively small (LaTulippe et al., 2002). Another gene expression array analysis using a small number of paraffin embedded tissues reveals that several Notch pathway components are up-regulated in Gleason 8 tumors as compared to Gleason 6 tumors (Ross et al., 2011). Yu et al also corroborated through a large scale tissue microarray analysis that primary prostate cancer samples display significantly higher levels of Jag1than normal prostate tissues while metastatic samples have the highest level of Jag1 (Yu et al., 2014). Expression of Notch3 in prostate tumor specimens is inversely associated with survival (Hudson et al., 2012). These observations support that Notch activity positively correlates with prostate cancer progression.

These changes in expression levels are also validated at the protein level. Santagata et al. showed in a tissue microarray analysis that a higher level of Jag1 expression is associated with prostate cancer metastasis and disease recurrence. (Santagata et al., 2004). Notch1 expression was shown to be statistically significantly higher in bone metastases than in primary tumors (Sethi et al., 2010). A recent study by Zhu et al also concluded that Jag1 and Notch1 expression is elevated in high grade and metastatic prostate cancers (Zhu et al., 2013). Both cytoplasmic and membranous Jag1 levels in metastatic and high grade prostate cancer are significantly higher than those in benign tissues and low

grade prostate cancers. In addition, cytoplasmic staining scores of Notch1 in both high grade and metastatic prostate cancer are also higher than those in benign tissues and low grade prostate cancers (Zhu et al., 2013).

However, other data collected from human specimens suggest that Notch mediates a tumor suppressive role. Data from the Gene Logic database reveals that Notch1 and Hey1 are down-regulated significantly in prostate adenocarcinoma when compared with normal prostate tissue and prostate tissues adjacent to prostate tumors, while other components from the Notch pathway such as Notch2-4, Jag1, and Jag2 are unaltered (Wang et al., 2006). In addition, in a small scale tissue microarray study, cleaved Notch1 and Hey1 levels in tumor specimens are significantly lower than in benign tissues (Whelan et al., 2009). These observations suggest that Notch signaling may suppress prostate cancer progression.

More clinical studies are needed to address this controversy. Given that the cellular localization of Notch pathway components influences the pathway activity, it is crucial to take into the consideration not only the expression levels but also the expression patterns of Notch signaling components. For example, Belandia et al. showed that although the expression level of the Hey1 protein in 24 patient samples are similar, stronger nuclear Hey1 expression was observed in benign prostate specimens as compared to cancerous samples (Belandia et al., 2005).

In summary, data collected from human prostate cancer specimens suggests both tumor suppressive and tumor promoting properties of Notch signaling. We reason that the discrepancy may be caused by the following factors. First, prostate cancer is a heterogeneous and multifocal disease; thus, each focal disease may possess distinct oncogenic signaling, such as the Ets fusion proteins, loss of tumor suppressor Pten and p53 etc. (Boutros et al., 2015). Notch activation may mediate different biological outcomes under distinct genetic contexts. For instance, Notch is capable of suppressing Pten expression through Hes1 (Whelan et al, 2007; Bertrand et al, 2014). Therefore, Notch activation in Pten intact and Pten null prostate cancer cells may lead to distinct cellular outcomes in terms of proliferation and apoptosis (Dail et al., 2014). Second, Notch activation may differentially affect different aspects of tumor cell biology. For example, Notch suppresses neuroendocrine differentiation of prostate cancer cells (Danza et al., 2012), but is essential for the survival of docetaxel-resistant cancer cells (Domingo-Domenech et al., 2012). Third, Notch is a complicated signaling pathway. It has been shown previously that different ligands and receptors may mediate distinct or even opposite biological outcomes. In addition, Notch activity is also well controlled at multiple regulatory levels (Bray, 2006; Kopan and Ilagan, 2009). Over-expression of one ligand or receptor does not necessarily warrant pathway activation. For example, excessive expression of a Notch ligand in cells may prevent rather than promote Notch activation in these cells (del Alamo et al., 2011).

Conclusion and perspectives

The expression of Notch pathway elements in established cancer cell lines, transgenic mouse models and clinical tumor specimens unambiguously demonstrate a deregulation of the Notch signaling pathway in prostate cancer. However, functional studies in human cancer cells by modulation of Notch pathway elements underscore the important roles of Notch signaling and suggest both tumor suppressive and oncogenic roles of Notch. Therefore, the functions of Notch signaling in prostate cancer are still not fully determined. Further studies are needed in order to understand the role of Notch signaling in prostate cancer more comprehensively.

The duality of the role of Notch in prostate cancer is likely due to the heterogeneous nature of prostate cancer and our inadequate understanding of the Notch pathway. In the future, to determine the role of Notch in prostate cancer progression, different mouse models induced by distinct oncogenic signaling, or different mouse models representing distinct subtypes of cancer are needed. Unfortunately, the prostate cancer model repertoire is still small. Complementary approaches such as the prostate regeneration assay (Xin et al., 2003) and the recently established prostate organoid assay (Gao et al., 2014; Karthaus et al., 2014) may be applied to address this question in a relatively middle-throughput, rapid and cost-effective manner. In addition, the advent of CRISPR-Cas9 technology has accelerated generation of novel transgenic mouse models, which will also facilitate our understanding of the pleiotropic role of Notch under various genetic contexts.

Because of the undetermined role of Notch signaling in prostate cancer, inhibitors of the Notch pathway have not been used clinically for prostate cancer (Bertrand et al., 2014). A gamma-secretase inhibitor, RO4929097, was tested in combination with bicalutamide. However, the clinical trial was terminated hence no useful information was obtained. Thus far, no other trial has been documented on www.clinicaltrials.gov. Based on the current knowledge, we reason that caution should be taken when targeting the Notch signaling pathway for prostate cancer treatment as this may lead to unexpected vicious consequences. In the future, a thorough investigation of disease-driving oncogenic signaling and status of Notch activation in individual patient samples will be useful to develop a personalized therapeutic regimen. This will help make decisions whether and how Notch should be employed as a therapeutic target. In addition, it will also help determine whether other therapeutic options such as monoclonal antibodies, RNA interference, and soluble decoy Notch inhibitors other than pan-Notch inhibitors should be used (Villaronga et al., 2008; Kangsamaksin et al., 2015; Sharma et al., 2015).

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