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Notch Signaling Pathway in Pancreatic Cancer Progression

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Introduction

Pancreatic cancer (PC) is one of the highly aggressive malignances in the United States, suggesting that novel treatment strategies are required to achieve better treatment outcome in PC patients [1]. To achieve this goal, elucidation of underlying mechanism of development and progression of PC is necessary [1]. Although the molecular causes of PC are largely elusive, many studies have demonstrated that multiple critical genes including K-ras, p53, p16, and other key cellular signaling pathways such as PI3K/Akt, mammalian target of rapamycin (mTOR), nuclear factor-kappa B (NF-κB), epidermal growth factor receptor (EGFR), and sonic hedgehog (SHH) plays important roles in the pancreatic tumorigenesis [2-4].

Mounting evidence from recent studies suggests that Notch signaling pathway contributes to PC development and progression [5,6]. It is known that Notch signaling pathway, a ligand-receptor pathway, is involved in cell proliferation, apoptosis, migration, invasion, metastases, and angiogenesis in a variety of human cancers including PC [7]. Four Notch receptors (Notch-1, 2, 3, 4) and five ligands (Dll-1, 3, 4 and Jagged-1, 2) have been discovered so far [8]. Notch signaling is initiated when Notch ligand binds to its receptor between adjacent cells [9]. Upon activation, Notch is cleaved and released the Notch intracellular domain (NICD) via a cascade of proteolytic cleavages by the multiple enzymes including γ-secretase [10]. Finally, NICD translocates to the nucleus and activates its target genes such as Hes-1, Hey-1, Bcl-2, Cyclin D1, C-myc, etc [11].

Multiple studies have revealed that Notch plays pivotal role in the PC tumorigenesis among many others [12,13]. The overexpression of Notch signaling pathway has been observed in PC [14]. Specifically, the up-regulation of Notch-1, Notch-2, Jagged-1, Jagged-2 and Notch target genes including Hes-1, Hey-1 was reported in PC [14,15]. Our previous studies also showed that inhibition of Notch-1 using its siRNA or γ-secretase inhibitor (GSI) suppressed cell growth, induced apoptosis, reduced migration, and decreased invasion in PC cells [16-18]. In line with the oncogenic role of Notch pathway, down-regulation of Notch by GSI blocked acinar-to-ductal metaplasia in TGF-α-treated cells [15]. More importantly, GSI completely inhibited tumor development in the genetically engineered model of PC [19], suggesting that Notch signaling is required for PC progression. Interestingly, one study showed that loss of Notch-1 led to increased tumor incidence and progression in a model of K-ras-induced PC, arguing that Notch-1 could be a tumor suppressor in PC [20]. Some of these controversies require further in-depth investigation in order to elucidate the function of Notch in PC progression.

Accumulating evidence has shown that there is a molecular link between Notch and epithelial-to-mesenchymal transition (EMT) in PC [21]. EMT is a unique process by which epithelial cells acquire mesenchymal phenotype. During the EMT process, epithelial cells gain the expression of mesenchymal markers including Vimentin, Slug, Snail, ZEB1 (zinc-finger E-box binding homeobox 1), ZEB2, and fibronectin consistent with the loss of epithelial marker E-cadherin expression [22]. EMT-type cells have increased migratory and invasive capacity, leading to invasion and metastasis [23]. EMT could be induced by many key cellular signaling pathways including Notch signaling pathway [23]. For example, Jagged-1-mediated activation of Notch caused EMT through repression of the E-cadherin in breast cancer cells [24]. Our previous studies have shown that EMT-type PC cells have high expression of Notch genes and ligands, suggesting that Notch pathway could play a role in EMT in PC [25]. In support of this role of Notch pathway in the induction of EMT, Kang et al. found that over-expression of Dll-4 in PC cells up-regulated the expression of Vimentin, ZEB and Snail, leading to EMT phenotype [26]. Moreover, another study demonstrated that mesenchymal stem cells govern EMT and tumor progression of PC cells through activation of Notch signaling pathway [27]. To further support the function of Notch in EMT, it has been reported that Midkine-Notch-2 interaction activated Notch signaling and subsequently induced EMT in PC cells [28]. Recently, our study confirmed the direct link between Notch and EMT in PC [29]. Over-expression of Notch-1 in PC cells induced EMT by activation of ZEB1, leading to increased migration and invasion [29]. These findings provide strong evidence suggesting that the activation of Notch signaling pathway is mechanistically associated with EMT in PC cells.

In recent years, it has been accepted that cancer stem cells (CSCs) do exist in a wide variety of human cancers including PC [30]. The CSCs have been isolated from multiple tumors via their specific markers [30]. For example, CD44+, CD133+ and ESA+ (EpCAM+) have been used to identify pancreatic CSCs. CSCs have the ability to self-renew and lead to the maintenance of the tumor mass [31]. Moreover, CSCs have been found to be resistant to standard chemotherapy [32]. Several studies have demonstrated that Notch signaling pathway plays a crucial role in controlling CSCs fate. It has been reported that human pancreatic CSCs contain high expression of Notch-1 and Notch-2 [33,34]. Moreover, over-expression of Dll-4 in PC cells simultaneously stimulates the expression of Oct4 and Nanog, resulting in increased numbers of CSCs [9]. Our recent study showed that over-expression of Notch-1 in PC cells enhanced the formation of pancreatospheres consistent with high level of CSC surface markers CD44 and EpCAM

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[29]. Taken together, activation of Notch signaling could contribute to CSC self-renewal capacity.

It has been well documented that Notch signaling pathway could be regulated by microRNAs (miRNAs). Clearly, miRNAs exert their inhibitory effects on gene expression through binding to the 3' untranslated region of target mRNA [35]. Some miRNAs have oncogenic activities due to targeting tumor suppressor genes, while others have tumor suppressor functions via inhibiting oncogene expression [36]. In general, oncogenic miRNAs are increased, whereas tumor suppressor miRNAs are decreased in human cancers [37]. Recently, miRNAs have been found to crosstalk with Notch pathway in PC [34]. Ji et al. reported that miR-34a governed the expression of Notch-1 and Notch-2, suggesting that Notch-1 and Notch-2 are downstream genes of miR-34 in PC cells [34]. Moreover, this group found that miR-34 was involved in pancreatic CSCs self-renewal via direct modulation of Notch pathway [34]. More recently, it has been revealed that miR-200 members target Notch pathway components, such as Jagged-1 and the mastermind-like co-activators Maml-2 and Maml-3, thereby mediating enhanced Notch activation by ZEB1 in PC cells [38]. Without a doubt, Notch signaling pathway regulates the expression of many miRNAs, and involved in cellular cross-talks. We found that over-expression of Notch-1 up-regulated the expression of miR-21 and down-regulated the expression of miR-200b, miR-200c, and let-7 family in PC cells [29]. Altogether, these results demonstrated the cross-talks between Notch and miRNAs in PC.

Since Notch signaling pathway is involved in EMT, CSCs and drug resistance, targeting Notch pathway to reverse EMT and eliminate CSCs as well as overcoming drug resistance could be a novel strategy for the treatment of PC [39]. Studies have shown that several forms of GSIs could inhibit tumor cell growth, migration and invasion in various human cancers including PC [40]. Moreover, GSI can block EMT, migration and invasion in PC cells, and suppress pancreatic CSCs in a xenograft mouse model [41]. However, GSIs block the cleavage of all four Notch receptors and multiple other γ-secretase substrates. Moreover, GSIs has unwanted cytotoxicity in the gastrointestinal tract [40]. To overcome such limitations, natural agents with non-toxic nature including isoflavone and curcumin have been used to inhibit the Notch signaling pathway. The results from our group have shown that isofalvone and curcumin inhibited the expression of Notch-1 and its target genes including Hes-1, Cyclin D1, Bcl-xL and NF-κB in PC cells [17,42]. Recently, we observed that genistein suppressed cell growth, migration, invasion, EMT phenotype, formation of pancreatospheres through inhibition of Notch-1 expression in PC cells [29]. Very recently, we found that genistein inhibited Notch-1 expression through up-regulation of miR-34a in PC cells [43]. Altogether, these findings suggest that genistein could be a non-toxic inhibitor of Notch-1 in PC cells.

Conclusion

In summary, Notch signaling pathway plays critical roles in the development and progression of PC. Moreover, Notch pathway is involved in the acquisition of EMT phenotype and the formation of CSCs in PC. Furthermore, Notch exerts its oncogenic functions partly through the regulation of multiple miRNAs in PC. Therefore, Notch pathway could be a promising target for achieving effective treatment for PC. More importantly, natural compounds could be useful for the inhibition of Notch pathway, which could lead to the prevention of tumor progression and/or successful treatment of PC in the future.

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