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Review article

Tumor biology

Interactions between Notch and matrix metalloproteinases: the role in cancer

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Notch has its importance in the development and maintenance of cells and tissues. Either gain or loss of Notch signalling causes a wide range of abnormalities including cancer. To activate Notch signalling, the notch ligand must be processed by the family of proteases, ADAMs. Until recently, exclusively in a cancer context, a class of proteases, matrix metalloproteinases (MMPs) were known to cleave notch and trigger downstream signalling. Notch was found to regulate the expression of matrix metalloproteinases (through crosstalk. Studies have revealed that interactions between Notch and MMPs are associated with aggressive cancer traits such as invasion, metastasis, angiogenesis, and endothelial mesenchymal transition. In this review, we resummarise the studies which reveal the Notch-MMP interactions that have provided new perceptions into the mechanisms behind Notch-mediated aggressiveness in cancers.

Key words: angiogenesis, epithelial mesenchymal transition, invasion, matrix metalloproteinase, non-canonical Notch signalling

Introduction

The notch signalling pathway is a conserved signalling pathway that regulates normal development and maintains homeostasis by regulating cell fate decisions and cellular processes. It has an oncogenic role and tumour suppressor role depending in a cellular context [1]. Notch is activated *via* canonical and noncanonical ways that lead to the expression of the Notch target genes [2]. Inappropriate activation of Notch causes over-accumulation of the Notch intracellular domain (NICD) thereby activating abnormal cellular transformation and resultant morbid cellular traits. Knockdown of Notch or use of γ-secretase inhibitors reverses such caused morbid traits *in vitro* [3–5]. Matrix metalloproteinases (MMPs) can cleave the notch receptor and activate signalling leading to pathologic outcomes [6].

Matrix metalloproteinases (MMPs) are zinc-dependent proteases which have a role in normal tissue development and maintenance through remodelling an extracellular matrix (ECM) [7]. There are about 23 MMPs known in humans and their expression is stimulated *via* PI3/AKT, MAPK, and ERK signalling pathways, with turnover being regulated by endogenous MMP inhibitors, TIMPs [8]. Dysregulation in MMP turnover has a potential effect on tissue homeostasis and cell signalling dynamics [9–12]. Immunohistochemical (IHC) studies on tumour biopsies show that MMPs are critical role players in the breakage of tumour boundaries leading to tumour cell migration [13].

Role of matrix metalloproteinases in cancer

In general, matrix metalloproteinases contribute to cancer processes *via* migration, EMT, metastasis and angiogenesis. During the migration process, the cell-to-cell and cell-to-matrix adhesion has to be disrupted. MMPs can degrade ECM, and shed the adhesion molecules (cadherins and integrins), making them well-suited for the role during invasion

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and metastasis [14, 15]. MMP3 directly cleave the E-cadherin, an adhesion molecule of the epithelial cell. Loss of E-cadherin mediates the epithelial cell to acquire the mesenchymal phenotype [16]. MMP2, MMP9 and MT1-MMP degrade the basal membrane and interstitium and promote angiogenesis. The MMP knockout mice did not exhibit such a phenotype [17]. Clinical trials involving broad-spectrum MMP inhibitors have been unsuccessful so far. Not least, the MMP-specifically targeted therapeutics have their challenges such as MMP sub-type selectivity, metabolic risks and toxicity [18–20].

The canonical Notch cascade

Notch signalling occurs between the two juxtaposed cells or within the same cell caused by the interaction of the Notch receptor to its ligand. There are four Notch receptors Notch1, Notch2, Notch3, and Notch4 and five canonical ligands containing DSL-motif – DLL1, DLL3, DLL4, Jagged1, Jagged2, and many non-canonical ligands that lack the DSL-motif [21]. On the ligand binding to the Notch receptor, the NRR region of the receptor undergoes a conformational change to expose the S2 site for cleavage recognised by ADAM proteases. The NRR region protects the extracellular Notch S2 site from proteases until the NRR site is physically destabilised by the ligand binding and ligand endocytosis [22, 23]. The S2 cleavage typically requires ADAM10 and ADAM17, a disintegrin and metalloproteinase for Notch signalling, whereas Notch1 ligand-independent signalling requires ADAM17 [24]. The S2 cleavage is an important event for the succeeding S3 cleavage by γ-secretase [25]. The S3 cleavage liberates the NICD, translocates to the nucleus, interacts with the DNA binding proteins CSL/RBPJ and MAML to form a ternary complex [26, 27]. The ternary complex binds to DNA at the super-enhancer region and causes the transcription of target genes [28, 29]. Common targets of Notch signalling are transcription factors of the HES family – Hes1, Hes5, and Hes7 and HEY family – Hey1, Hey2, and HeyL that modulate fundamental cellular processes such as proliferation, stem cell maintenance, and differentiation during embryonic and adult development [2, 30].

Non-canonical processing of Notch by specific MMPs

Typically, Notch1 requires consecutive two cleavage steps post Notch ligand-receptor binding: first at the S2 site by ADAM protease ADAM10 or 17, and second at S3 by γ-secretase, which resultantly releases the Notch intracellular domain (NICD). ADAM 10 and ADAM17 have been regarded as canonical S2 proteases for cleavage at the S2 site on the Notch receptor which is regularly implied in normal development and tissue homeostasis *via* regulation of cell fate decisions and cellular processes occurring in drosophila, mice, and humans [25–31]. Many canonical and non-canonical Notch pathway components have been identified; the non-canonical ligands include DLK1, VE-cadherin, stanniocalcin-1 and the non-canonical proteases MMP7, MMP9, and MT1-MMP are mostly involved in pathogenesis [31–35]. Sawey and colleagues in 2008 found that MMP7 (matrilysin, an MMP) processes Notch1 independent of ADAMs which causes N1-NICD to be released and translocated to the nucleus [6]. On topical addition of recombinant MMP7 to COS-7 cells that are expressing Notch1 with C-terminal V5 tag underwent Notch activation including γ-secretase cleavage, NICD nuclear translocation, and resultant expression of Notch target genes. Moreover, the immunoblots of the Notch-V5 tag showed that cleavage of the Notch extracellular domain particularly occurred at the S2 site [36]. MMP7 is prevalently overexpressed in advanced cancers, with poor overall survival of patients, and is regarded as a prognostic biomarker in invasive and recurrent cancers [37–39]. MMP7 expression is controlled by PI3-K/AKT and/or ERK signalling *via* NF-κB transcription factor, and its loss of control is indicated in pathogenicity [40]. Similarly, like MMP7, the membrane-bound MT1-MMP (MMP14) can activate Notch by processing it independently of ADAMs (fig. 1). Changes in MT1-MMP expression affect the Notch signalling in melanoma cells. In the experiments, MT1-MMP processes the Notch1 actively in a Jagged1 ligand-dependent or independent manner. Moreover, when the full-length MT1-MMP was expressed in WM266-4 melanoma cells, it cleaved the Notch1. In the same experiment, the Notch processing intensity correlated to the expression of MT1-MMP. The resultant stimulation of the Notch target gene, HES, was confirmed by HES-reporter assay and gene expression analysis [41]. Non-canonical Notch processing by MT1-MMP not only affects cancer in the individuals but immunity too. It acts as a switch in normal B cell development in the bone marrow. Ectopic MT1-MMP cleaves the Notch ligand Delta-like 1 (DLL1) in bone marrow stem cells and thereby diminishes the Notch signalling by switching the B cell development [42].

Notch-MMP interactions: implications

Generally, MMPs are expressed at low levels in tissues, and their expression is induced by stimuli when required for ECM remodelling [11]. Matrix metalloproteinase expression demands multilevel regulation of various stimulating factors such as cell-ECM interactions, cell-cell interactions, ECM stimulation and other cellular environmental factors such as pH, ROS, cellular endopeptidases, lipid peroxidation, hyperglycemic, hypoxia, etc. [9]. MMP expression regulation may involve transcriptional regulatory elements, epigenetic regulation, post-transcriptional regulation, or different regulation occurring due to disease conditions involving gene mutations and promoter polymorphisms in MMP [43]. These external stimuli lead to downstream cell signalling; MMP turnovers are majorly regulated by protein kinases PKA, PKB/AKT, and PKC/MAPKs (JNKs, ERKs, and P38) signalling pathways [44]. Downstream of these signalling pathways, there are cell-type specific transcription factors-NF-κB, AP-1 subunits C-jun/C-fos, PEA3, ETS, and STAT that have binding sites on the promoters of specific MMPs. Moreover,

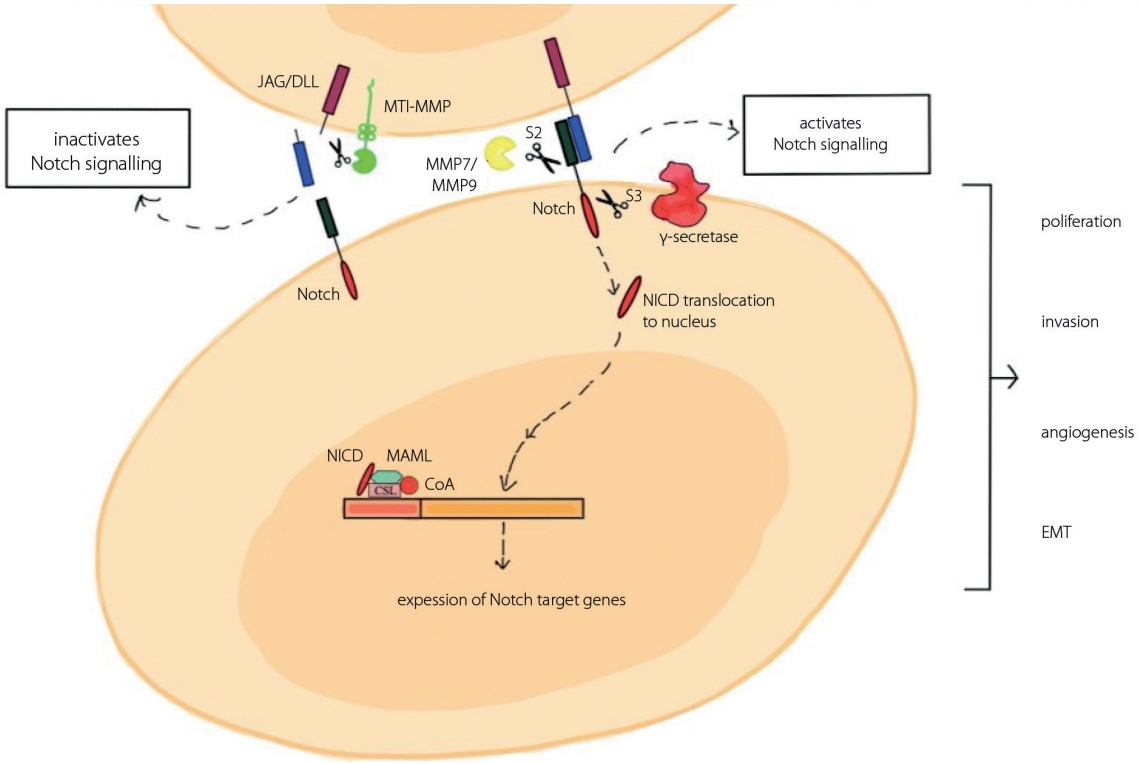

Figure 1. A diagram of the non-canonical Notch signalling pathway. This schematic shows a simplified overview of the main components of MMP-activated Notch signalling. Upon Notch ligand binding, a two-step proteolysis cleavage process i.e. S2 (small scissors within the juxtamembrane region, and the transmembrane domain of the Notch receptor is catalysed by members of the metalloproteases (MMP) family and the γ-secretase containing complex i.e. S3, respectively, then the Notch intracellular domain (NICD) is released from the membrane and translocates to the nucleus, where it forms a transcriptional activation complex with CSL and coactivators (CoA), thereby inducing the transcription of target genes causing proliferation, invasion, angiogenesis, and EMT in cancer

these transcription factors either upregulate or downregulate the expression of MMPs. Functional collaboration of more than one transcription factor may be required to regulate the gene--specific MMP expression. For example, regulatory interactions between AP-1 and cis-acting ETS elements on the MMP1 promoter are required to induce its expression [45].

Notch-NF-κB-MMP axis: invasion and migration

The notch signalling pathway critically participates in cell proliferation, apoptosis, cell invasion, and metastasis; studies show that notch pathway members are overexpressed [46–48]. Notch inhibition by downregulating Notch1 decreased invasion in prostate cancer [49]. The proliferation and invasion of cancer cells require remodelling of the extracellular matrix surrounding it through the action of MMPs. Studies show Notch controls the expression of ECM component-specific matrix metalloproteinases to bring about the rearrangements in the tumour environment through cross-talks with the NF-κB pathway [50–52]. NF-κB expression is driven by Notch. Also, the ectopic feeding of NICD, usually the nuclear-translocated part of Notch to the breast cancer cells, causes the cells to lose cell to cell adhesion and promotes migration and invasion [51, 53]. Notch1 is an upstream regulator of the NF-κB pathway where Notch1 and Notch3 induce transcription of NF-κB and its various subunits [54], moreover, NICD1 and NF-κB interaction leads to its NF-κB retention in the nucleus and enhances binding to the promoter of its target MMP genes [55, 56] (fig. 2). However, it is not clear whether in addition to retention of NF-κB, NICD1 and NF-κB complexed together is required for its transcriptional activity. That said, Notch1 downregulation leads to inhibition of NF-κB binding activity thereby inhibiting the expression of MMPs [53, 57]. NF-κB has a binding site on promoters of MMP1, MMP2, MMP7, and MMP9 to drive their expression [43, 52, 58]. Apart from MMPs, NF-κB drives the activity of cell adhesion molecules of ICAM, VCAM-1, and ECAM-1 which are essential for the cell migration process [59, 60].

Notch-VEGF and MMP axis: angiogenesis

Studies at the molecular level enable us to understand that Notch plays a pivotal role in sprouting angiogenesis; it maintains the functional integrity of leading apical endothelial cells and growing basal cells. Particularly, the VEGF--Notch axis allows the extravasation of MMPs that degrade the basal membrane and facilitate angiogenic sprouting. In the process, the apical endothelial cell (EC) maintains low--notch signalling and high VEGFR2 expression to preserve the sprouting phenotype. VEGFR2 helps the apical cell to migrate towards the VEGF-transmitting angiogenic centre.

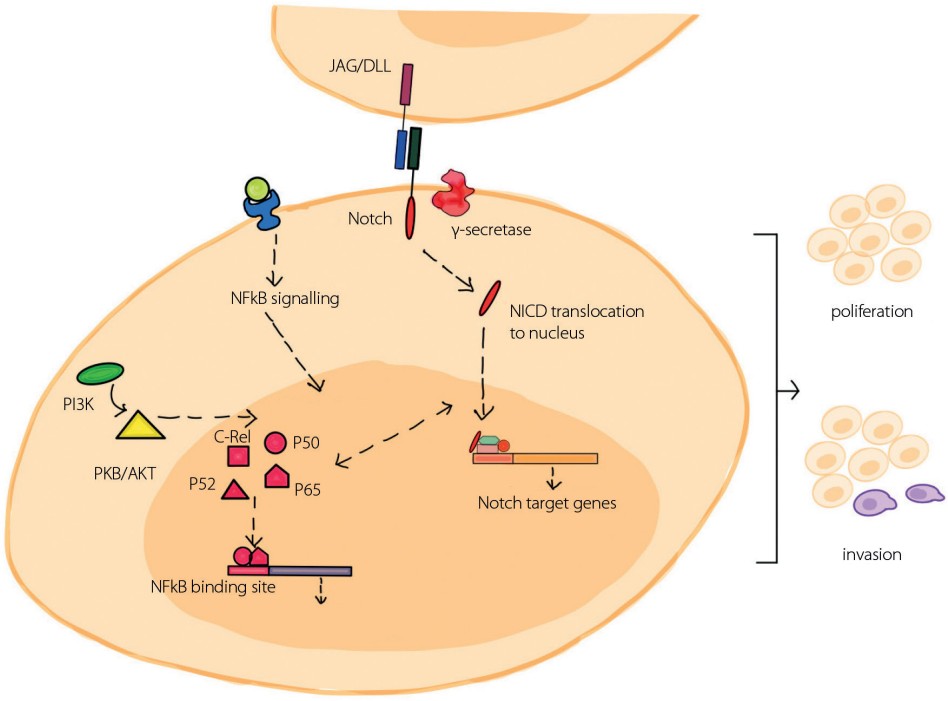

Figure 2. Schematic illustration of Notch signalling pathway to regulate MMP gene expression. This model summarises, through a literature survey, that Notch activation promotes malignant features such as proliferation and invasion in cancer *via* cross-talking the NF-κB signal pathway

It promotes the expression of MT1-MMP, MMP2 and MMP9 which are prime members that bring about the ECM remodelling for apical cell sprouting and migration. On the other hand, the basal EC maintains high Notch signalling, low VEGFR2, high VEGFR1, and low MMP expression to preserve the non-sprouting phenotype in the basal EC [61–63]. Thus, the positive and negative crosstalks between VEGF-Notch in the apical and basal endothelial cells regulate the expression of MMPs to preserve their functional integrity and promote sprouting angiogenesis (fig. 3).

Notch-HEY-MMP axis: epithelial to mesenchymal transition

Epithelial mesenchymal transition is the most aggressive trait in cancers. Epithelial cells acquire mesenchymal phenotype by undergoing remarkable changes. In the transition process, it loses various epithelial markers and gains mesenchymal markers. The loss of epithelial markers such as E-cadherin, γ-catenin, actin cytoskeleton organisation and the gain of vimentin, fibronectin, fibrillar collagen, N-cadherin, and the increased activity of MMPs (MMP2, MMP2, MMP9). The EMT is a complex process triggered by signalling molecules, proteases, and growth factors (fibroblast growth factor [FGF], platelet-derived growth factor [PDGF], transforming growth factor-β [TGF-β]) that trigger the downstream signalling such as TGF-β, Hedgehog, NF-κB and Notch signalling which involves crosstalks that lead to dynamic changes in the phenotype of the epithelial

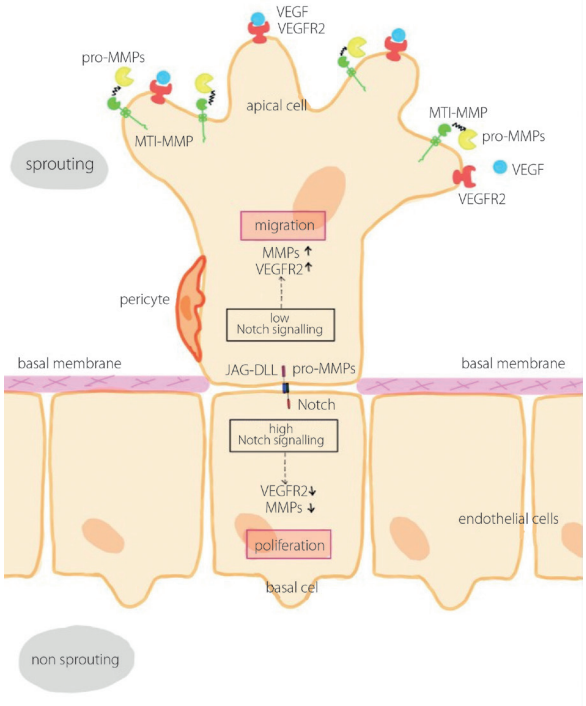

Figure 3. Schematic model of VEGF-Notch and MMP axis in vascular endothelial cell (EC) differentiation. In endothelial tip cells, Low-notch signalling *via* Notch1-DLL4 induces high levels of VEGFR2 and MMPs to promote migration towards the angiogenic centre. In endothelial basal cells, high levels of Notch signalling *via* Notch1-DLL4 suppresses differentiation toward an apical cell phenotype by inducing low expression of VEGFR2 and MMPs

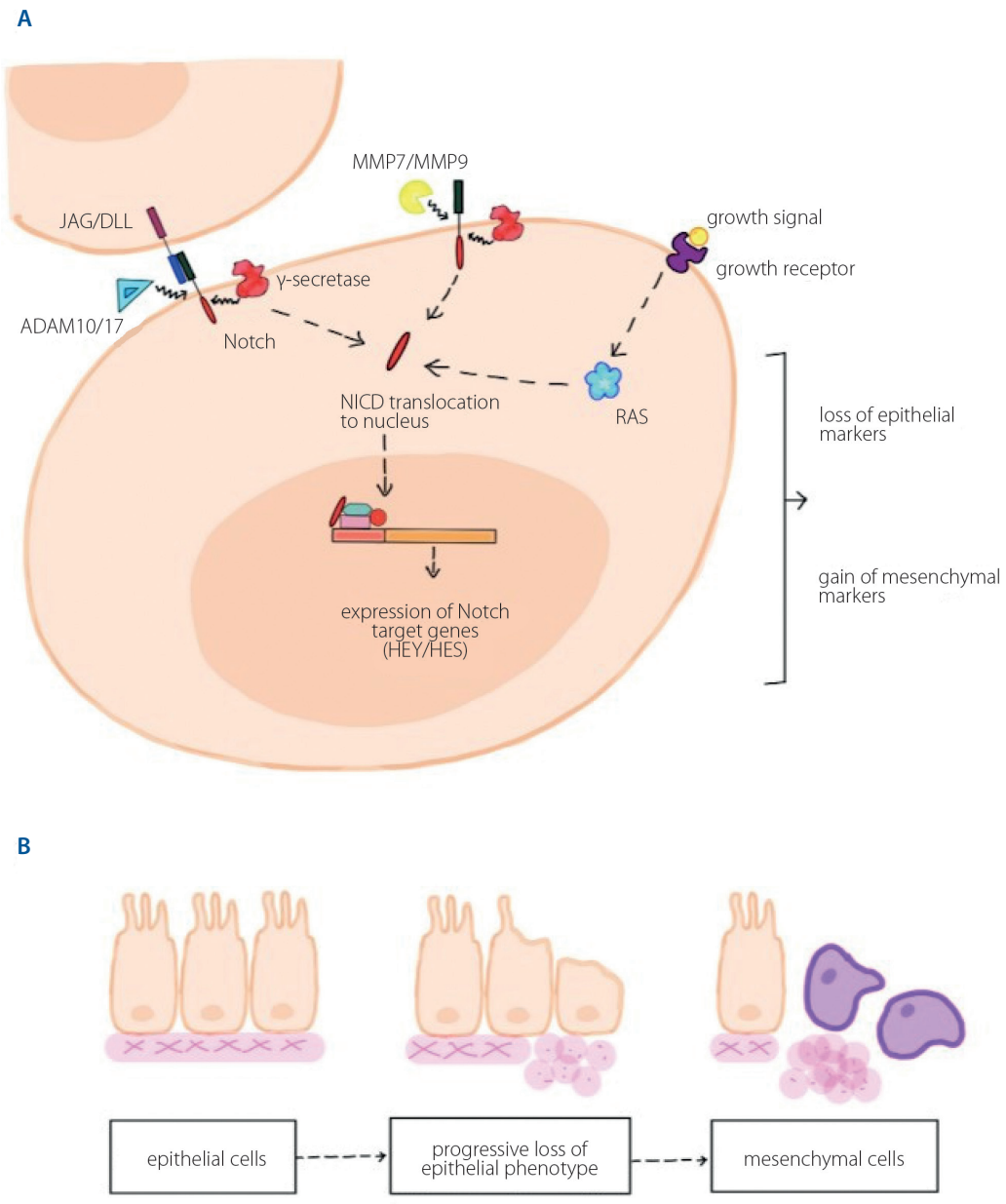

Figure 4. Notch-mediated epithelial-mesenchymal transition (EMT) cross-talk during carcinogenesis: **A.** The above diagram summarises the probable cross-talks between three ways that could drive EMT during carcinogenesis; viz., the canonical Notch signalling, the MMP-Notch-HEY/HES axis and the Growth Factor stimulation that induces notch signalling and translocation of NICD to the nucleus, where it forms a transcriptional activation complex with CSL and coactivators (CoA), thereby inducing the transcription of target genes HES/HEY. HES/HEY expression causes loss of epithelial markers and gain of mesenchymal markers in the epithelial cells leading to EMT. **B.** The EMT process primarily involves progressive loss of epithelial markers and gain of mesenchymal markers. Once the cells acquire a mesenchymal phenotype, they first intravasate and later extravasate from the blood vessel to establish a distant metastasis

cell [64] (fig. 4). Reports verify that down-regulating Notch signalling inhibits EMT by downregulating MMPs [65, 66]. The Notch target gene, HEY1, controls the expression of MMPs in salivary adenoid cystic carcinoma, on knockdown of HEY1 it suppressed the expression of MMP1, MMP2, MMP3, MMP9, MMP11, and MMP13 which may be involved in driving EMT [30, 67]. Similarly, numerous reports mention MMPs (MMP7, MMP9) having a role in triggering Notch signalling that leads to the induction of the EMT trait [36, 68] (fig. 4).

Conclusions and future perspective

MMP-mediated non-canonical Notch signalling and the involvement of Notch in the regulation of MMPs is associated with aggressive outcome in cancer (tab. I). Though, the MMP expression is majorly driven by NF-κB, MAPK, AKT signalling pathways and TIMPs are regulators of MMPs, it cannot be disregarded that under high Notch signalling, the NICD plays a primary role in retaining NF-κB subunits in the nucleus, which leads to uncontrolled expression of target MMPs.

Table I. Summary of Notch and matrix metalloproteinase interactions in human and mouse cancer models and associated functional phenotypes of those interactions

Matrix metalloproteinase	Axis	Phenotype	Type of cancer	Study model	Reference
MMP2, MMP9	Notch- PI3K/AKT/mTOR-MMP	invasion	bladder cancer	UMUC3 cell line	[71]
MMP2, MMP9	Notch-EMMPRIN-NF-κB/MMP	migration, invasion	human breast adenocarcinoma	MDA-MB-231 cell line	[72]
MMP2, MMP9	Notch-PI3/AKT-NF-κB-MMP	invasion, metastasis, angiogenesis	human breast adenocarcinoma	MDA-MB-231 cell line	[51, 53]
MMP9	Notch-NF-κB/uPA-MMP	invasion, metastasis	non-small-cell lung cancer	A549 and H1299 cell lines	[52]
MMP9	Notch-NF-κB/MMP	invasion	pancreatic cancer	BxPC-3 cell line	[64]
MMP9	Notch-NF-κB/MMP	cell growth, migration, invasion and induction of apoptosis	prostate cancer	PC-3, DU145, LNCaP, and C4-2B cell lines	[65]
MT1-MMP (MMP14)	MMP-Notch	cell growth and proliferation	melanoma cancer	WM115 and WM266-4 primary and metastatic cell lines	[41]
MT1-MMP	Notch-MMP	invasion, EMT	Kaposi sarcoma	lymphatic endothelial cell line	[68]
MMP9	Notch-NF-κB/MMP	invasion, angiogenesis	breast cancer	MDA-MB-231, MCF-7, SKBR-3 and T47D cell lines	[57]
MMP9	Notch-AKT-MMP	migration, metastasis, EMT	gastric cancer	SGC7901 and AGS cell lines; BALB/c mice	[66]
MMP7	Hey1-Notch1	self renewal, EMT, metastasis	salivary adenoid cystic carcinoma	SACC-LM cell line	[67]
MMP7	MMP-Notch1	EMT	pancreatic ductal adenocarcinoma	human primary acinar cell line and C57BL/6J mice	[36]

MMP – matrix metalloproteinase; EMT – epithelial-mesenchymal transition

Notch inhibition alone may not be enough; the negative outcomes of Notch inhibition have been reported in clinical studies which cannot be disregarded, firstly, Notch is a conserved pathway required for normal cell development and homeostasis of tissues by maintaining proliferation and apoptosis balance; due to, low notch activity under Notch inhibitors, the cells may acquire sprouting phenotype leading to angiogenesis. Moreover, several Notch inhibitors under clinical trials have exhibited adverse effects including gastrointestinal issues, infections, skin cancer-related problems, and tumour recurrence [69, 70].

The Notch-MMP axes play important roles in tumour processes like proliferation, migration, EMT, metastasis, and angiogenesis. It has come to our notice that these interactions are lethal impart aggressiveness and have added poorer prognoses to various cancers including those of the brain, breast, and pancreas. Understanding and targeting Notch-MMP interactions may be required to tailor target-specific drugs and combinational therapeutic approaches.

Article information and declarations

Author contributions

Jeeja Hernole – study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation, review and approval of the final version of the manuscript. Rajeswari Narayanappa – study conception and design, analysis and interpretation of results, draft manuscript preparation, review and approval of the final version of the manuscript.

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Conflict of interest

None declared

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