This is a provisional PDF only.

Nowotwory
Journal of Oncology

Interactions between Notch and Matrix metalloproteinases: role in cancer

Authors: Jeeja Hernole, Rajeswari Narayanappa

How to cite:

Hernole J, Narayanappa R. Interactions between Notch and Matrix metalloproteinases: role in cancer. NOWOTWORY J Oncol 2023; 73 (Ahead of print).

Interactions between Notch and Matrix metalloproteinases: role in cancer

Jeeja Hernole[1, 2 0000-0002-1387-508X], Rajeswari Narayanappa[1 0000-0002-4594-0050]

1. *Department of Biotechnology, Dayananda Sagar College of Engineering, Bangalore, India*
2. *Bangalore and Visvesvaraya Technological University, Karnataka, India*

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 the 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 (MMPs) 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 recapitulate the studies which reveal the Notch-MMP interactions that have provided new perception 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 on the 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 gamma-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 and their turnover is 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 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 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

The 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 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 □-secretase [25]. The S3 cleavage liberates the NICD, translocates to the nucleus, it 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 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, Notch 1 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 gamma-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 occurs 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 gamma-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, having 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. And, 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 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-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. But, 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. 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, y-catenin, actin cytoskeleton organisation and gain of vimentin, fibronectin, fibrillar collagen, N-cadherin, and 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-B, Hedgehog, NFkB and Notch signalling which involves crosstalks that lead to dynamic changes in the phenotype of epithelial cell [64] (fig. 4). Reports verify that down-regulating Notch signalling inhibits EMT by downregulating MMPs [65, 66]. 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 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 main role in retaining NF-κB subunits in the nucleus, which leads to uncontrolled expression of target MMPs. Notch inhibition alone may not be not 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, secondly, 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, infections, skin cancer related, 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 worse prognoses to various cancers including 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, reviewed and approved the final version of the manuscript.

Rajeswari Narayanappa – study conception and design, analysis and interpretation of results, draft manuscript preparation, reviewed and approved the final version of the manuscript.

Funding

Jeeja Hernole

Dayananda Sagar College of Engineering

Department of Biotechnology

Shavige Malleshvara Hills

Kumaraswamy Layout

560111 Bangalore, India

e-mail: hernole@gmail.com

References
[1] Lobry C, Oh P, Aifantis I. Oncogenic and tumour suppressor functions of Notch in cancer: it's NOTCH what you think. Journal of Experimental Medicine. 2011 Sep 26;208(10):1931-5.
[2] Borggrefe, T., & Oswald, F. (2009). The Notch signalling pathway: transcriptional regulation at Notch target genes. *Cellular and Molecular Life Sciences*, 66(10), 1631-1646.
[3] Stylianou S, Clarke RB, Brennan K. Aberrant activation of notch signalling in human breast cancer. Cancer research. 2006 Feb 1;66(3):1517-25.

[4] Yu JB, Jiang H, Zhan RY. Aberrant Notch signalling in glioblastoma stem cells contributes to tumour recurrence and invasion. Molecular medicine reports. 2016 Aug 1;14(2):1263-8.

[5] Li L, Tang P, Li S, Qin X, Yang H, Wu C, Liu Y. Notch signalling pathway networks in cancer metastasis: a new target for cancer therapy. Medical oncology. 2017 Oct;34:1-0.

[6] Sawey ET, Crawford HC. Metalloproteinases and cell fate: Notch just ADAMs anymore. Cell Cycle. 2008 Mar 1;7(5):566-9.

[7] Nagase H, Woessner JF. Matrix metalloproteinases. Journal of Biological chemistry. 1999 Jul 30;274(31):21491-4.

[8] Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA, Alvarez-Sánchez ME. Role of matrix metalloproteinases in angiogenesis and cancer. Frontiers in oncology. 2019 Dec 6;9:1370.

[9] Gaffney J, Solomonov I, Zehorai E, Sagi I. Multilevel regulation of matrix metalloproteinases in tissue homeostasis indicates their molecular specificity in vivo. Matrix Biology. 2015 May 1;44:191-9.

[10] Obermajer N, Jevnikar Z, Doljak B, Kos J. Role of cysteine cathepsins in matrix degradation and cell signalling. Connective tissue research. 2008 Jan 1;49(3-4):193-6.

[11] Löffek S, Schilling O, Franzke CW. Biological role of matrix metalloproteinases: a critical balance. European Respiratory Journal. 2011 Jul 1;38(1):191-208.

[12] Blicharz-Dorniak, J., Kos-Kudła, B., Foltyn, W., Kajdaniuk, D., Marek, B., Zemczak, A., & Strzelczyk, J. (2012). Is determination of matrix metalloproteinases and their tissue inhibitors serum concentrations useful in patients with gastroenteropancreatic and bronchopulmonary neuroendocrine neoplasms?. Endokrynologia Polska, 63(6), 470-476.

[13] Alaseem A, Alhazzani K, Dondapati P, Alobid S, Bishayee A, Rathinavelu A. Matrix Metalloproteinases: A challenging paradigm of cancer management. InSeminars in cancer biology 2019 Jun 1 (Vol. 56, pp. 100-115). Academic Press.

[14] Webb, A. H., Gao, B. T., Goldsmith, Z. K., Irvine, A. S., Saleh, N., Lee, R. P., ... & Morales-Tirado, V. M. (2017). Inhibition of MMP-2 and MMP-9 decreases cellular migration, and angiogenesis in in vitro models of retinoblastoma. BMC cancer, 17(1), 1-11.

[15] Itoh, Y. (2006). MT1-MMP: A key regulator of cell migration in tissue. IUBMB life, 58(10), 589-596.

[16] Zheng, G., Lyons, J. G., Tan, T. K., Wang, Y., Hsu, T. T., Min, D., ... & Harris, D. C. (2009). Disruption of E-cadherin by matrix metalloproteinase directly mediates epithelial-mesenchymal transition downstream of transforming growth factor-β1 in renal tubular epithelial cells. The American journal of pathology, 175(2), 580-591.

[17] Jackson, C. (2002). Matrix metalloproteinases and angiogenesis. Current opinion in nephrology and hypertension, 11(3), 295-299.

[18] Fisher, J. F., & Mobashery, S. (2006). Recent advances in MMP inhibitor design. Cancer and Metastasis Reviews, 25, 115-136.

[19] Lenci, E., Cosottini, L., & Trabocchi, A. (2021). Novel matrix metalloproteinase inhibitors: an updated patent review (2014-2020). Expert Opinion on Therapeutic Patents, 31(6), 509-523.

[20] Wróbel-Roztropiński, A., Zielińska-Kaźmierska, B., Roztropiński, H., Lucas-Grzelczyk, W., Szemraj, J., & Józefowicz-Korczyńska, M. (2021). Expression of matrix metalloproteinases (MMPs) and their inhibitor (TIMP) genes on mRNA and protein levels in oral squamous cell carcinoma. Biuletyn Polskiego Towarzystwa Onkologicznego Nowotwory, 6(1), 1-8.

[21] D'Souza B, Meloty-Kapella L, Weinmaster G. Canonical and non-canonical Notch ligands. Current topics in developmental biology. 2010 Jan 1;92:73-129.

[22] Lanning DB, Nicholas T. Constant-life diagram modified for notch plasticity. International journal of fatigue. 2007 Dec 1;29(12):2163-9.

[23] Gordon WR, Vardar-Ulu D, L'Heureux S, Ashworth T, Malecki MJ, Sanchez-Irizarry C, McArthur DG, Histen G, Mitchell JL, Aster JC, Blacklow SC. Effects of S1 cleavage on the structure, surface export, and signalling activity of human Notch1 and Notch2. PloS one. 2009 Aug 24;4(8):e6613.

[24] Bozkulak EC. Characterization of roles for the disintegrin and metalloproteases, kuzbanian and tumour necrosis factor-alpha converting enzymes, in mammalian Notch signalling. University of California, Los Angeles; 2009.

[25] Lieber T, Kidd S, Young MW. kuzbanian-mediated cleavage of Drosophila Notch. Genes & development. 2002 Jan 15;16(2):209-21.

[26] De Strooper B, Annaert W, Cupers P, Saftig P, Craessaerts K, Mumm JS, Schroeter EH, Schrijvers V, Wolfe MS, Ray WJ, Goate A. A presenilin-1-dependent γ-secretase-like protease mediates release of Notch intracellular domain. Nature. 1999 Apr 8;398(6727):518-22.

[27] Nam Y, Weng AP, Aster JC, Blacklow SC. Structural requirements for assembly of the CSL· intracellular Notch1· Mastermind-like 1 transcriptional activation complex. Journal of Biological Chemistry. 2003 Jun 6;278(23):21232-9.

[28] Wilson JJ, Kovall RA. Crystal structure of the CSL-Notch-Mastermind ternary complex bound to DNA. Cell. 2006 Mar 10;124(5):985-96.

[29] Wang W, Struhl G. Drosophila Epsin mediates a select endocytic pathway that DSL ligands must enter to activate Notch. 2004; 5367-5380

[30] Fischer A, Steidl C, Wagner TU, Lang E, Jakob PM, Friedl P, Knobeloch KP, Gessler M. Combined loss of Hey1 and HeyL causes congenital heart defects because of impaired epithelial to mesenchymal transition. Circulation research. 2007 Mar 30;100(6):856-63.

[31] Christian J. A tale of two receptors: Bmp heterodimers recruit two type I receptors but use the kinase activity of only one. Proceedings of the National Academy of Sciences. 2021 May 11;118(19):e2104745118.

[32] Garg P, Jeppsson S, Yang VW, Gewirtz AT, Merlin D, Sitaraman SV. MMP-9 mediates colitis associated cancer in mice through Notch-1 via p53 activation: O-21. Inflammatory Bowel Diseases. 2011 Dec 1;17(Suppl_2):S9-.

[33] Rodríguez P, Higueras MA, Gonzalez-Rajal A, Alfranca A, Fierro-Fernandez M, García-Fernández RA, Ruiz-Hidalgo MJ, Monsalve M, Rodríguez-Pascual F, Redondo JM, de la Pompa JL. The non-canonical NOTCH ligand DLK1 exhibits a novel vascular role as a strong inhibitor of angiogenesis. Cardiovascular research. 2012 Feb 1;93(2):232-41.

[34] Fischer A, Braga VM. Vascular permeability: Flow-mediated, non-canonical notch signalling promotes barrier integrity. Current Biology. 2018 Feb 5;28(3):R119-21.

[35] Li Y, He ZC, Zhang XN, Liu Q, Chen C, Zhu Z, Chen Q, Shi Y, Yao XH, Cui YH, Zhang X. Stanniocalcin-1 augments stem-like traits of glioblastoma cells through binding and activating NOTCH1. Cancer letters. 2018 Mar 1;416:66-74.

[36] Sawey ET, Johnson JA, Crawford HC. Matrix metalloproteinase 7 controls pancreatic acinar cell transdifferentiation by activating the Notch signalling pathway. Proceedings of the National Academy of Sciences. 2007 Dec 4;104(49):19327-32.

[37] Polistena A, Cucina A, Dinicola S, Stene C, Cavallaro G, Ciardi A, Orlando G, Arena R, D'ERMO GI, Cavallaro A, Johnson LB. MMP7 expression in colorectal tumours of different stages. In vivo. 2014 Jan 1;28(1):105-10.

[38] Klupp F, Neumann L, Kahlert C, Diers J, Halama N, Franz C, Schmidt T, Koch M, Weitz J, Schneider M, Ulrich A. Serum MMP7, MMP10 and MMP12 level as negative prognostic markers in colon cancer patients. BMC cancer. 2016 Dec;16(1):1-9.

[39] Chen L, Ke X. MMP7 as a potential biomarker of colon cancer and its prognostic value by bioinformatics analysis. Medicine. 2021 Mar 3;100(9).

[40] Guan PP, Yu X, Guo JJ, Wang Y, Wang T, Li JY, Konstantopoulos K, Wang ZY, Wang P. By activating matrix metalloproteinase-7, shear stress promotes chondrosarcoma cell motility, invasion and lung colonisation. Oncotarget. 2015 Apr 4;6(11):9140.

[41] Ma J, Tang X, Wong P, Jacobs B, Borden EC, Bedogni B. Non Canonical activation of Notch1 protein by membrane type 1 matrix metalloproteinase (MT1-MMP) controls melanoma cell proliferation. Journal of Biological Chemistry. 2014 Mar 14;289(12):8442-9.

[42] Jin G, Zhang F, Chan KM, Xavier Wong HL, Liu B, Cheah KS, Liu X, Mauch C, Liu D, Zhou Z. MT1-MMP cleaves Dll1 to negatively regulate Notch signalling to maintain normal B-cell development. The EMBO journal. 2011 Jun 1;30(11):2281-93.

[43] Fanjul-Fernández M, Folgueras AR, Cabrera S, López-Otín C. Matrix metalloproteinases: evolution, gene regulation and functional analysis in mouse models. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2010 Jan 1;1803(1):3-19.

[44] Reuben PM, Cheung HS. Regulation of matrix metalloproteinase (MMP) gene expression by protein kinases. Frontiers in Bioscience-Landmark. 2006 May 1;11(2):1199-215.

[45] White LA, Brinckerhoff CE. Two activator protein-1 elements in the matrix metalloproteinase-1 promoter have differential effects on transcription and bind Jun D, c-Fos, and Fra-2. Matrix biology. 1995 Dec 1;14(9):715-25.

[46] Sahlgren C, Gustafsson MV, Jin S, Poellinger L, Lendahl U. Notch signalling mediates hypoxia-induced tumour cell migration and invasion. Proceedings of the National Academy of Sciences. 2008 Apr 29;105(17):6392-7.

[47] De La O JP, Murtaugh LC. Notch signalling: where pancreatic cancer and differentiation meet?. Gastroenterology. 2009 May 1;136(5):1499-502.

[48] Fukusumi T, Guo TW, Sakai A, Ando M, Ren S, Haft S, Liu C, Amornphimoltham P, Gutkind JS, Califano JA. The NOTCH4–HEY1 Pathway Induces Epithelial–Mesenchymal Transition in Head and Neck Squamous Cell CarcinomaNOTCH4–HEY1 Induces EMT in HNSCC. Clinical Cancer Research. 2018 Feb 1;24(3):619-33.

[49] Wang Z, Li Y, Banerjee S, Kong D, Ahmad A, Nogueira V, Hay N, Sarkar FH. Down-regulation of Notch-1 and Jagged-1 inhibits prostate cancer cell growth, migration and invasion, and induces apoptosis via inactivation of Akt, mTOR, and NF-κB signalling pathways. Journal of cellular biochemistry. 2010 Mar 1;109(4):726-36.

[50] Venkatesan B, Valente AJ, Prabhu SD, Shanmugam P, Delafontaine P, Chandrasekar B. EMMPRIN activates multiple transcription factors in cardiomyocytes, and induces interleukin-18 expression via Rac1-dependent PI3K/Akt/IKK/NF-κB andMKK7/JNK/AP-1 signalling. Journal of molecular and cellular cardiology. 2010 Oct 1;49(4):655-63.

[51] Li L, Zhao F, Lu J, Li T, Yang H, Wu C, Liu Y. Notch-1 signalling promotes the malignant features of human breast cancer through NF-κB activation. PloS one. 2014 Apr 23;9(4):e95912.

[52] Rajasinghe LD, Pindiprolu RH, Gupta SV. Delta-tocotrienol inhibits non-small-cell lung cancer cell invasion via the inhibition of NF-κB, uPA activator, and MMP-9. OncoTargets and therapy. 2018 Jul 24:4301-14.

[53] Li L, Zhang J, Xiong N, Li S, Chen Y, Yang H, Wu C, Zeng H, Liu Y. Notch-1 signalling activates NF-κB in human breast carcinoma MDA-MB-231 cells via PP2A-dependent AKT pathway. Medical Oncology. 2016 Apr;33:1-1.

[54] Jang MS, Miao H, Carlesso N, Shelly L, Zlobin A, Darack N, Qin JZ, Nickoloff BJ, Miele L. Notch-1 regulates cell death independently of differentiation in murine erythroleukemia cells through multiple apoptosis and cell cycle pathways. Journal of cellular physiology. 2004 Jun;199(3):418-33.

[55] Shin HM, Minter LM, Cho OH, Gottipati S, Fauq AH, Golde TE, Sonenshein GE, Osborne BA. Notch1 augments NF-κB activity by facilitating its nuclear retention. The EMBO journal. 2006 Jan 11;25(1):129-38.

[56] López-López S, Monsalve EM, Romero de Ávila MJ, González-Gómez J, Hernández de León N, Ruiz-Marcos F, Baladrón V, Nueda ML, García-León MJ, Screpanti I, Felli MP. NOTCH3 signalling is essential for NF-κB activation in TLR-activated macrophages. Scientific Reports. 2020 Sep 9;10(1):1-6.

[57] Liu Y, Su C, Shan Y, Yang S, Ma G. Targeting Notch1 inhibits invasion and angiogenesis of human breast cancer cells via inhibition nuclear factor-κB signalling. American journal of translational research. 2016;8(6):2681.

[58] Lee YH, Seo EK, Lee ST. Skullcapflavone II inhibits degradation of type I collagen by suppressing MMP-1 transcription in human skin fibroblasts. International journal of molecular sciences. 2019 Jun 4;20(11):2734.

[59]Aggarwal BB, Van Kuiken ME, Iyer LH, Harikumar KB, Sung B. Molecular targets of nutraceuticals derived from dietary spices: potential role in suppression of inflammation and tumorigenesis. Experimental Biology and Medicine. 2009 Aug;234(8):825-49.

[60] Huang WC, Chan ST, Yang TL, Tzeng CC, Chen CC. Inhibition of ICAM-1 gene expression, monocyte adhesion and cancer cell invasion by targeting IKK complex: molecular and functional study of novel α-methylene-γ-butyrolactone derivatives. Carcinogenesis. 2004 Oct 1;25(10):1925-34.

[61] Hellström M, Phng LK, Gerhardt H. VEGF and Notch signalling: the yin and yang of angiogenic sprouting. Cell adhesion & migration. 2007 Jul 1;1(3):133-6.

[62] Funahashi Y, Hernandez SL, Das I, Ahn A, Huang J, Vorontchikhina M, Sharma A, Kanamaru E, Borisenko V, DeSilva DM, Suzuki A. A notch1 ectodomain construct inhibits endothelial notch signalling, tumour growth, and angiogenesis. Cancer research. 2008 Jun 15;68(12):4727-35.

[63] Teodorczyk M, Dudvarski Stanković N, Bicker F, Schmidt MH. VEGF and Notch signalling in angiogenesis. Endothelial Signalling in Development and Disease. 2015:3-46.

[64] Wang Z, Li Y, Kong D, H Sarkar F. The role of Notch signalling pathway in epithelial-mesenchymal transition (EMT) during development and tumour aggressiveness. Current drug targets. 2010 Jun 1;11(6):745-51

[65] Chen Y, Zheng S, Qi D, Zheng S, Guo J, Zhang S, Weng Z. Inhibition of Notch signalling by a γ-secretase inhibitor attenuates hepatic fibrosis in rats. PLoS ONE 7 2012; 10: e46512.

[66] Peng X, Zhou J, Li B, Zhang T, Zuo Y, Gu X. Notch1 and PI3K/Akt signalling blockers DAPT and LY294002 coordinately inhibit metastasis of gastric cancer through mutual enhancement. Cancer Chemotherapy and Pharmacology. 2020 Feb;85:309-20.

[67] Xie J, Lin LS, Huang XY, Gan RH, Ding LC, Su BH, Zhao Y, Lu YG, Zheng DL. The NOTCH1-HEY1 pathway regulates self-renewal and epithelial-mesenchymal transition of salivary adenoid cystic carcinoma cells. International Journal of Biological Sciences. 2020;16(4):598.

[68] Cheng F, Pekkonen P, Laurinavicius S, Sugiyama N, Henderson S, Günther T, Rantanen V, Kaivanto E, Aavikko M, Sarek G, Hautaniemi S. KSHV-initiated notch activation leads to membrane-type-1 matrix metalloproteinase-dependent lymphatic endothelial-to-mesenchymal transition. Cell host & microbe. 2011 Dec 15;10(6):577-90.

[69] López-Nieva P, González-Sánchez L, Cobos-Fernández MÁ, Córdoba R, Santos J, Fernández-Piqueras J. More Insights on the Use of γ-Secretase Inhibitors in Cancer Treatment. The Oncologist. 2021 Feb;26(2):e298-305.

[70] Peereboom DM, Ye X, Mikkelsen T, Lesser GJ, Lieberman FS, Robins HI, Ahluwalia MS, Sloan AE, Grossman SA. A phase II and pharmacodynamic trial of RO4929097 for patients with recurrent/progressive glioblastoma. Neurosurgery. 2021 Feb;88(2):246-51.

[71] Chen YT, Huang CR, Chang CL, Chiang JY, Luo CW, Chen HH, Yip HK. Jagged2 progressively increased expression from Stage I to III of Bladder Cancer and Melatonin-mediated downregulation of Notch/Jagged2 suppresses the Bladder Tumorigenesis via inhibiting PI3K/AKT/mTOR/MMPs signalling. International Journal of Biological Sciences. 2020;16(14):2648.

[72] Wang J, Fu L, Gu F, Ma Y. Notch1 is involved in migration and invasion of human breast cancer cells. Oncology reports. 2011 Nov 1;26(5):1295-303.

[65]Wang Z, Banerjee S, Li Y, Rahman KW, Zhang Y, Sarkar FH. Down-regulation of Notch-1 inhibits invasion by inactivation of nuclear factor-κB, vascular endothelial growth factor, and matrix metalloproteinase-9 in pancreatic cancer cells. Cancer research. 2006 Mar 1;66(5):2778-84.

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 (NSCLC)	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 (LEC)	[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 (PDA)	human primary acinar cell line and C57BL/6J mice	[36]
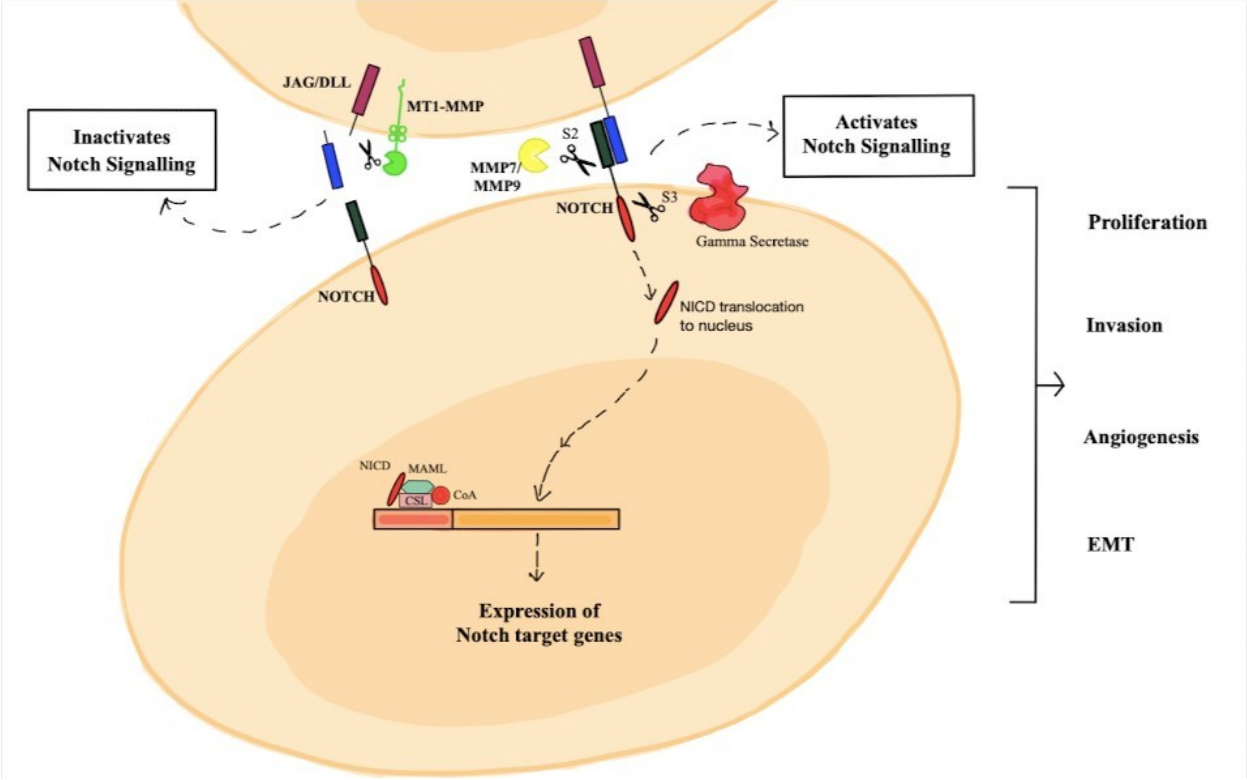
Figure 1. A diagram of the non-canonical Notch signalling pathway. This schematic shows a simplified overview of the main components of MMP-activated Notch signalling. Upon Notch ligand binding, a two-step proteolysis cleavage process i.e. S2 (small scissors within the juxtamembrane region and transmembrane domain of the Notch receptor is catalysed by members of the metalloproteases (MMP) family and the γ-secretase containing complex ie. 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
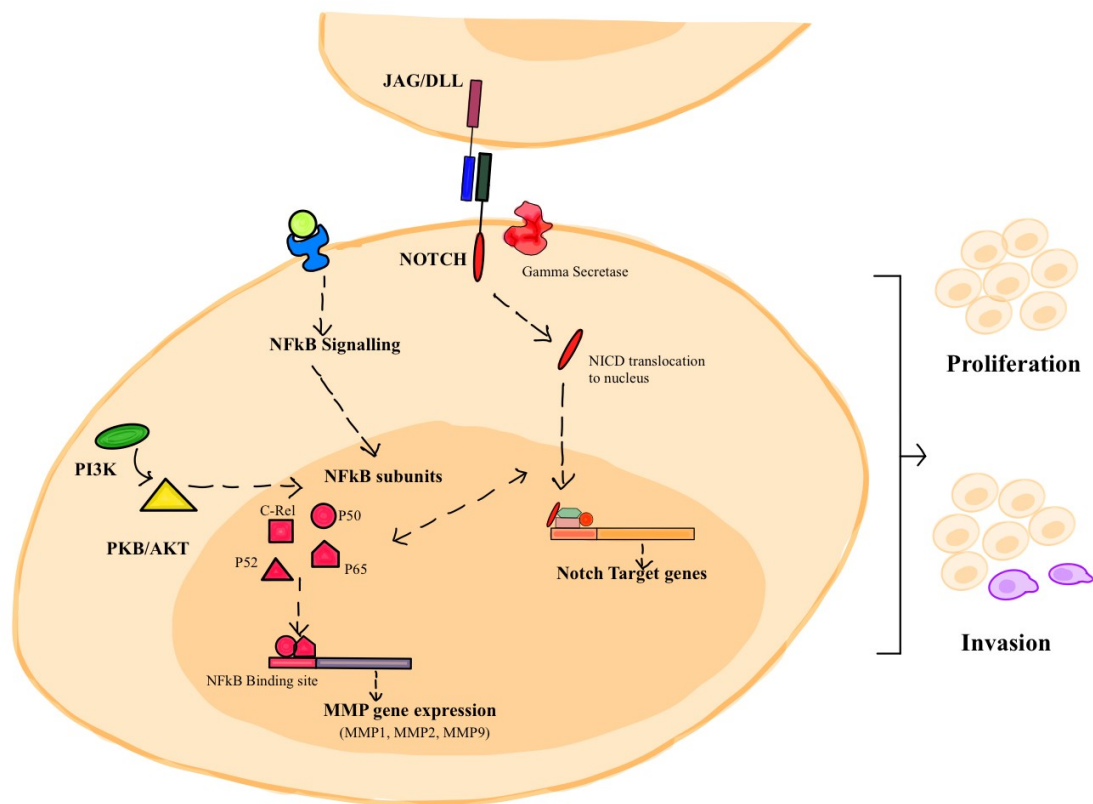

Figure 2. Schematic illustration of Notch signalling pathway to regulate MMP gene expression. This model summarises through a literature survey that Notch activation promotes malignant features such as proliferation and invasion in cancer via cross-talking the NF-kB signal pathway
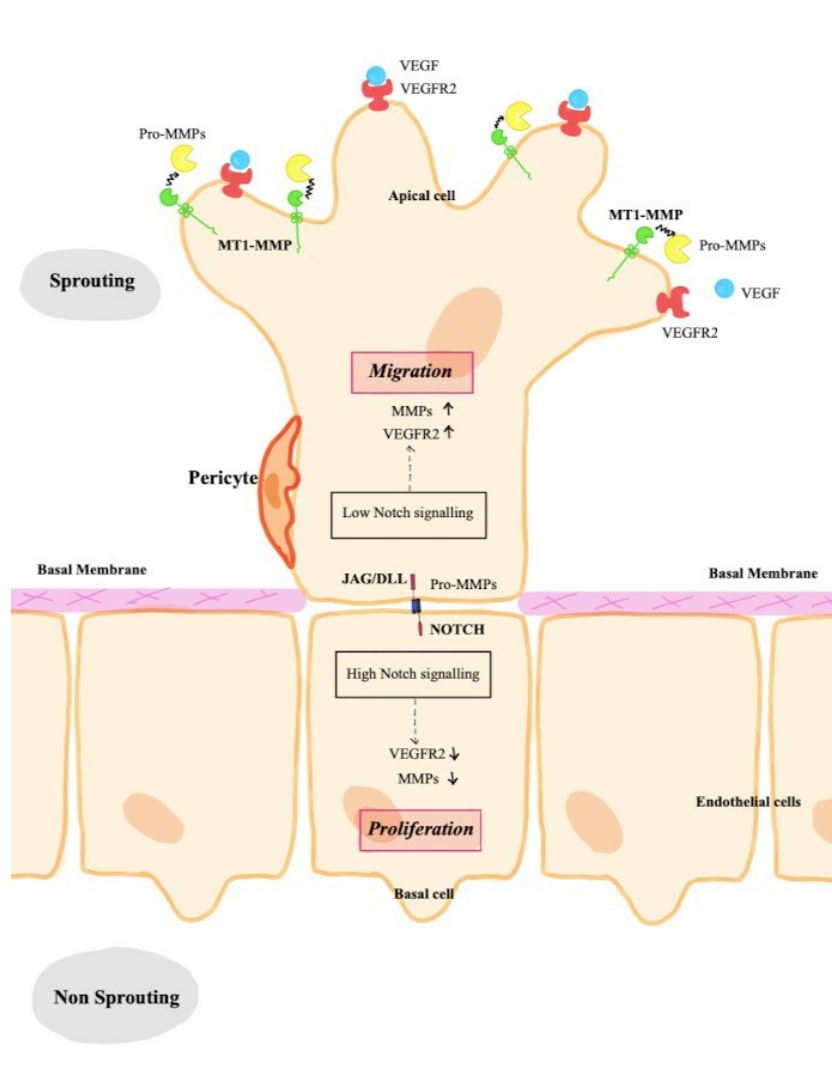
Figure 3. Schematic model of VEGF-Notch and MMP axis in vascular endothelial cell (EC) differentiation. In endothelial tip cells, Low-notch signalling via Notch1-DLL4 induces high levels of VEGFR2 and MMPs to promote migration towards the angiogenic centre. In endothelial Basal cells, high levels of Notch signalling via Notch1-DLL4 suppresses differentiation toward an apical cell phenotype by inducing low expression of VEGFR2 and MMPs
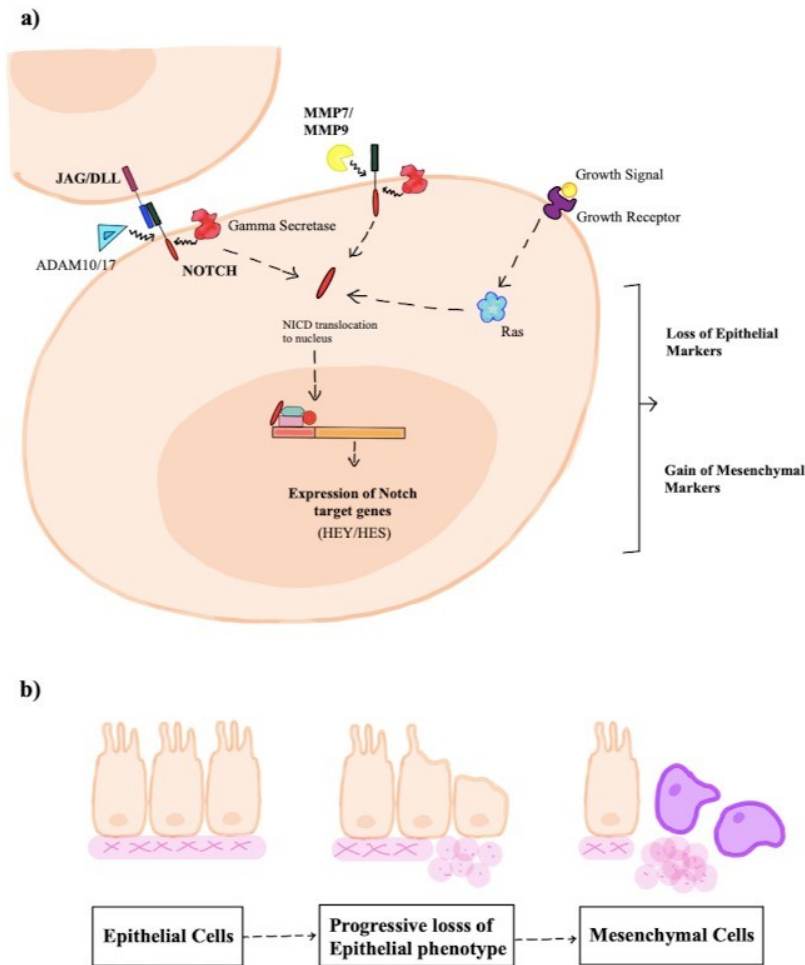
Figure 4. Notch-mediated epithelial-mesenchymal transition (EMT) cross-talk during carcinogenesis: **A.** The above diagram summarises the probable cross-talks between three ways that could drive EMT during carcinogenesis; viz., the Canonical Notch signalling, the MMP-Notch-HEY/HES axis and the Growth 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