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REVIEW ARTICLE

Oncogenic Role of Neurogenic Locus Notch Homolog 4 (Notch4) in Breast Cancer

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ABSTRACT

The regulation of mammary gland development depends on a variety of signaling pathways, that are concerned with cell differentiation decisions and cell fate. The Neurogenic Locus Notch Homolog 4 (Notch4) pathway masters and preserves a balance among cellular multiplication, differentiation and cell death through its crucial role in stem cells regulation. Notch4 receptor is a member of the Notch family which is expressed in mammary epithelium and endothelial cells of vessels. Abnormal expression of Notch4 receptor has been detected in different types of neoplastic and preneoplastic lesions, suggesting that Notch4 may act as a proto-oncogene. Overexpression or genetic mutations of Notch4 receptor and its ligands may induce breast cancer by activating target genes, cross-talking with other pathways and giving the spark for stem cell deregulation, causing tumor initiation, maintenance, progression, treatment resistance and relapse. Notch4 Overexpression in breast cancer has been documented as a prognostic marker, and is related to the development of aggressive clinico-pathological and biological phenotypes of breast cancer.

Keywords: Notch4; breast cancer; stem cells.

INTRODUCTION

According to the latest report of The International Agency for Research on Cancer (IARC), breast cancer (BC) is by far the most frequent cancer in females worldwide and occupies the second rank among all cancer types. About 2.1 million BC cases have been diagnosed in 2018, accounting for about 11.6% of the total cancer incidence and 6.6% of all cancer death [1].In Egypt, BC is the most prevalent cancer among females, representing about 35.1% of all female cancers. The BC pattern in lower, middle and upper Egypt is dominated by its high frequency (33.8, 26.8 and 38.7% respectively), with a high mortality rate (23.8%) [2]. Breast cancer is characterized by its marked heterogeneity. Depending on gene expression profiles, there are 4 BC molecular subtypes; Luminal A [ER+ (estrogen receptor positive), PR+ (progesterone receptor positive), Her2/Neu - (human epidermal growth factor receptor 2 negative), low Ki67], Luminal B (ER+, PR+, Her2/Neu - or +, high Ki67), Her2-enriched (ER-, PR-, Her2/Neu +, high Ki67), and triple negative breast cancer (TNBC) (ER-, PR-, Her2/Neu -, high Ki67). Both TN and Her2 over-expressing BCs display the worst subtypes [3]. In the mammary tissue development, both division and differentiation are controlled by asymmetric divisions, where the mammary stem cells (MaSCs) divide into basal and luminal cells and then give myoepithelial or ductal cells respectively. The control of this process relies on several specific pathways of differentiation, including Notch4 pathway [4].Neurogenic Locus Notch Homolog 4 protein (Notch4) is a member of the Notch family, that is encoded by the Notch4 gene, located on chromosome 6 p21.32 in humans and shares the same structure of other Notch family members [5]. Notch4 mutation in mammary epithelium induces tumorigenesis by stimulating cellular hyperplasia, increasing mitotic rate, decreasing apoptosis and acquiring epithelial mesenchymal transition (EMT) [6].Although many beneficial reviews have focused on Notch signaling in a variety of cancers, including breast cancer [7-11]. In our review, we will focus on and summarize the specific molecular aspects of aberrant Notch4 signaling in breast cancer including its potential role in deregulation of breast cancer stem cells, tumor angiogenesis, invasion and metastasis, in addition to its crosstalk with other oncogenic signaling pathways.

Historical Brief: The first discovery of Notch arises from genetic studies on mutant Drosophila melanogaster, the fruit fly, where notched wings were observed in 1914 by John Dexter and three years later by Thomas Morgan [12,13]. In the 1980s, both Spyros Artavanis-Tsakonas and Michael Young independently

studied Notch sequencing and its molecular analysis [14]. Notch was known as a "neurogenic" gene, because Notch mutants exhibit a nervous tissue hyperplasia [15]. Whereas Drosophila has only a single Notch protein and two ligands, human and other mammals such as mice possess four Notch proteins and five ligands [16].

Oncogenic role of Notch4 was first discovered by integration of a mouse mammary tumor virus (MMTV) into the Notch4 locus, forming a truncated protein with sustained Notch4 activation, that in turn leads to mammary epithelial dysplasia, impaired differentiation and then mammary tumorigenesis in mice [17].

Notch receptor and ligands: The mammalian Notch family is formed of four receptors (Notch 1-4), that interacts with five ligands (Delta-like (DLL)1,3,4 and Jagged 1,2). Notch family members, share the same structure including an extracellular domain, trans-membrane domain and an intracellular domain [16].The extracellular domain (ECD) has N-terminal region where multiple epidermal growth factor (EGF)-like repeats bind to ligands and begin the signal**.** It is followed by C-terminal region where three cysteine-rich Lin-12/Notch Repeats (LNR) combine with a heterodimerization (HD) domain to compose the negative regulatory region that works as a switch of activation**.** The number of EGF-like repeats and C-terminal sequences differ among Notch family members. EGF-like repeats of Notch4 include about 29 amino acids (Figure 1) [18].The intracellular domain (ICD) consists of several different domain types and acts as a transcriptional activator that is released after ligand binding. In the nucleus, it interacts with transcriptional regulators and then forms a transcriptional activation complex [19].

Ligands, which are single-pass, type-1 transmembrane proteins, are formed of an extracellular domain and intracellular tail. They have a module at the N-terminus, followed by a Delta-Serrate-Lag-2 domain and variable numbers of EGF-like repeats [16].

Notch4 signaling pathway and its target genes: The Notch4 pathway describes the interaction among two adjacent cells, the first is a ligand carrying cell and the second is a receptor carrying cell which is adjusted to interact with the ligand [20].The Notch4 pathway is summarized in (Figure 2). Maturation of Notch4 receptor occurs via multiple steps, starting from its processing in the Golgi apparatus and endoplasmic reticulum, then its cleavage by a furin-like convertase with the production of the mature heterodimers that finally trafficking to the plasma membrane for engagement with its ligands [18].Upon ligand binding, Notch4 signaling is activated and Notch receptors are cleaved by proteases such as a disintegrin and metalloproteinase (ADAM) and γ-secretase. As a result, the Notch4 Intracellular Domain (NICD) is released and then translocates into the nucleus [18].In the nucleus, Notch-C protein binding factor 1/Suppressor of Hairless/Lag-1 (Notch–CSL) complex is produced by binding of NICD with CSL. Notch–CSL complex inducts several transcriptional regulators to form "Notch transcriptional complex" that induces transcription of multiple key genes like Hes (hairy and enhancer of split) and Hey (Hairy/enhancer-of-split related with YRPW motif protein-1) [21]. Other Notch4 target genes also include cyclin-D1, c-Myc (c-myelocytomatosis oncogene product), Akt (protein Kinase-B), mTOR (mammalian target of rapamycin), NF-κB (nuclear factor-kappa B), VEGF (vascular endothelial growth factor), Survivin, GAS-1(Growth Arrest-specific Protein-1), Slug, Her2, and ER. All of which have been well documented for their roles in tumor development and progression (Figure 3) [7,20].

The intimate contact between Notch signaling and carcinogenesis, as well as its crosstalk with many oncogenic signaling pathways suggest that Notch inhibitors at multiple steps of Notch pathway, may be an effective strategy to develop a targeted therapy [4,8,11,20].

Notch stability is regulated by components of post-translational modifications pathway including cyclin-dependent kinase-8 (CDK8), FBW7 (F-box and WD40 domain-containing protein7), Itch (itchy E3 ubiquitin protein ligase), b-arrestin, Fe65 (a transcription coregulator adapter protein) and Numb [22]. Loss of FBW7 and Numb, can induce Notch4 signaling activation [4].

In addition, It has been demonstrated that genetic abnormalities in Notch4 signaling might be induced by loss of ELF5 (E74-like factor 5) and RNF8 (ring finger protein 8), which are differentiation-inducing factors in cells. Normally, Both ELF5 and RNF8 have an important role in regulation of mammary development through the Notch4 pathway. Furthermore, ELF5 inhibits BC metastasis by suppressing Slug, so ELF5-null mammary epithelial cells are considered a fertile soil for tumorigenesis [23]. In addition, RNF8 loss upregulates Notch target genes, expands abnormal luminal progenitor cell and increases risk of mammary tumorigenesis [4].

Subcellular localization of Notch4 in breast cancer: According to Notch pathway, mature, not active Notch4 receptor may be represented by membranous staining, whereas cytoplasmic staining represents the functional or recently synthesized receptor. Nuclear Notch4 staining may represent an activated receptor that is seldomly detected by simple routine immunohistochemical technique

[8,10]. The mechanisms that control nucleo-cytoplasmic shuttling of NICD are not clear. NICD degradation and phosphorylation may be achieved respectively by either direct interaction of Mouse double minute 2 homolog (Mdm2) and p53 [24], or the PI3K-AKT (Phosphatidyl inositol 4,5 biphosphate 3-kinase) pathway and 14-3-3 regulatory proteins [25].

Notch4 expression in breast cancer:

Several studies documented expression of Notch4 in BC. Wang and colleagues found cytoplasmic Notch4 overexpression in 39% of their 98 studied cases, in which TNBCs exhibited the highest levels of Notch4 expression [8]. However, Speiser et al., detected wider Notch4 overexpression (73%) of their 29 studied TNBC cases, with simultaneous cytoplasmic and nuclear expression [9]. In addition, Dickson et al., reported the detection of Jagged-1 and Notch-4 mRNAs in high titers in BC with clinical poor prognosis [26]. Furthermore, Yao et al., demonstrated cytoplasmic and membranous Notch4 expression (71 and 62.1% respectively) mainly in hormonal positive subtypes compared to other subtypes [10]. Moreover, Magnifico et al., found that Notch4 is highly active in Her2-enriched BC cells [27].

Intratumor Notch4 staining heterogeneity has been detected in Notch4+ cells and may be attributed to controversial origin of BC cells [28]. In addition, in many instances Notch4 immunostaining with increasing intensity has been observed near the interface between tumor cells and stroma at invasive edge, reflecting its role in tumor invasion and metastasis [7].

Notch4 and cancer stem cells:

In BC, the bulk tumor cells represent the main cellular burden. Other cell subpopulations with the potency to regenerate bulk tumor cells can also be identified. These cells are defined as cancer stem cells (CSCs) due to similarities with the stem progenitors of normal tissues. They have been described in several cancers and constituted about 1–5% of the tumor size. Self-renewal, proliferation, treatment resistance and cancer relapse are the main characteristics of these CSCs [29]. Genetic mutations in genes encoding proteins that are involved in the signaling pathways of stem cells such as Notch, Hedgehog and Wingless-related integration site (Wnt) pathway, would allow these cells to undergo uncontrolled proliferation and tumorigenesis [23].

Notch4+ stem cell population has been observed to be associated more with CD44+/CD24− population [mesenchymal-like (ML)], compared with the Aldehyde Dehydrogenase (ALDH+) population (epithelial-like). CD44+/CD24− cells have been linked to CSC-like cells exhibiting tumor-initiating features and invasive properties, in contrast to the ALDH+ cells, which is proliferative cells (**Figure 4)**. High level of stemness factors such as, sex determining region Y-box 2 (SOX2), NANOG, octamer-binding transcription factor 4 (OCT4), has been found in Notch4+ cells [7].

It has been documented that TNBCs are highly enriched in ML breast cancer stem cells (bCSCs). Activation of Notch4 in TNBC cells induces chemoresistance by driving ML-bCSCs into a quiescent state through Gas1, and acquires EMT via upregulating Slug, that in turn, eliminates the apoptotic effect of Gas1. Hence, (Notch4-Slug-Gas1) circuit promotes ML-bCSC maintenance by simultaneously inducing EMT and cellular quiescence [7].

Notch4 and angiogenesis:

In the process of angiogenesis, endothelial cells formation is stimulated by Notch ligands, together with VEGF, the strongest mitogenic factor. It has been found that considerable amount of the DLL4 ligand is accumulated on the endothelial tip cells (the ends of vessel sprouts). However, the Jagged-1 protein, another ligand, is found on the stalk cells (the other cells). This specification of endothelial cell, that is important for vascular polarity and could function as a barrier, is regulated by Notch signaling [30].

In BC, the upregulated DLL4 expression in tip cells, by VEGF activation, stimulates the activation of Notch4 signaling in the adjacent stalk cells. This finding may suggest that the Notch4-DLL4 signaling system is a major stimulator of angiogenesis in BC (Figure 5) [4].**Notch4 and invasion** (Figure 6):

During EMT, Notch4 activation stimulates carcinoma cells to shed their epithelial features, with decreased E-cadherin, and acquire mesenchymal traits, including motility and invasiveness with increased Vimentin, N-cadherin, Slug, Snail, Zinc Finger E-Box Binding Homeobox 1 (Zeb1) and β-catenin [6]. Also, Notch pathway activates STAT3 (signal transducer and activator of transcription 3) which is associated with BC aggressive behavior. Furthermore, loss of Numb (Notch antagonist) can activate Notch4 signaling and induce both EMT and CSC-like properties, resulting in early relapse and metastasis [4].

In EMT process, Snail-1, an initiator of EMT, is activated by direct binding of NICD to Snail-1 promoter or by binding of hypoxia-inducing factor-1α to the lysyl oxidase promoter and then secretion of Snail-1 [4].

Both matrix metalloproteinases (MMP-2 and MMP-9) and Urokinase-type plasminogen activator (uPA), that are mostly promoted by Notch4 activation, work together for erosion of microvasculature and degradation of extracellular matrix (ECM) related molecules, including laminin

and fibronectin, to facilitate metastasis [31].

Notch4 and intravasation:

The adhesion of tumor cells and neutrophils to endothelial cells is facilitated by vascular cell adhesion molecule-1 (VCAM-1) that is subverted by Notch4 activation [23]. In addition, the cooperation between Notch4 and β1 integrin affinity promotes the trans-endothelial migration of BC cells [32].

Notch4 and Survival of disseminated cancer cells in the blood stream

In Notch4 activation, survival of tumor cells in the blood stream may occur by either anti-apoptotic mechanism or chemoresistance [23].

Anti-apoptotic function of Notch4 may depend on activator protein1 (AP1), a transcription factor complex, which works on death receptor (DR 4,5). Notch4 is also involved in the sensitization of BC cells to TRAIL (tumor necrosis factor related apoptosis inducing ligand) inducing apoptosis [33]. Furthermore, Notch4 activation induces survival of tumor cells by increasing MMPs, decreasing of apoptosis signal-regulating kinase 1 (ASK1), activation of Survivin and inhibition of p53 by preventing JNK (c-Jun N-terminal kinases) [23,34].Chemoresistance of disseminated tumor cells is acquired by overexpression of VEGFR3, Delta-like3, Notch4 and their downstream targets in tumor endothelial cells during chemotherapy [35].

-Notch4 and secondary colonization

Activation of Notch4 compete with both KiSS1 (Kisspeptin) and Nm23 (Nucleoside diphosphate kinase A), the metastasis suppressor genes, resulting in their down regulation in metastasis [36].

Notch4 and immune system:

In the basal-like BC model, it has been demonstrated that Notch4 activation motivate tumor cells to secrete CCL2 [chemokine (C-C motif) ligand 2] and IL-1β (Interleukin-1 beta) cytokines, which in turn work to recruit monocytes. Also, tumor-associated macrophages promote Jagged-1 ligand expression that induces a feedback loop for amplifying cytokines secretion via Transforming growth factor beta (TGF-β). Arginase 1, an arginine-degrading enzyme produced by tumor associated macrophage, can suppress Cytotoxic T lymphocytes (CTL) activity [37]. Myeloid-derived suppressor cells in BC can activate Notch signaling in cancer cells and promote CSC capacity through IL6/STAT3 and Nitric Oxide/Notch cross talk signaling [23] (Figure 7).

Crosstalk among Notch4 signaling and other oncogenic pathways in breast cancer:

Hedgehog-Notch4 crosstalk promotes the survival of stem cells. In BC, deregulated Hedgehog, together with Wnt and Notch4 signals, could regulate differentiation ability and self-renewal of bCSC [29]. Wnt1 expression causes activation of Notch4 signaling in human mammary epithelial cells. Also, Wnt target genes along with Notch4 ligand DLL-3 and DLL-4 are concomitantly upregulated in BC [38]. Both Notch4 and Her2 pathways are involved in the progression of BC and regulation of bCSCs. Notch4 signaling could activate Her2 since the Her2 promoter contains Notch4 binding sequences. Activation of NICD induces the transcription of target genes including Her2 which in turn, activate the PI3K/Akt pathway that drives stem cell self-renewal [27,39].

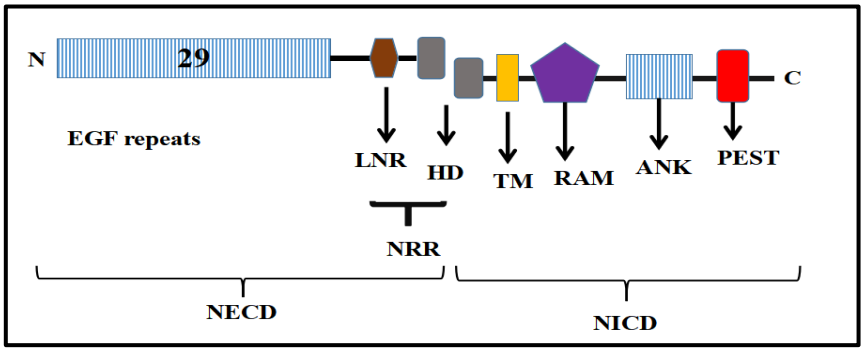
Estradiol either activates Notch4 signaling or decreases Notch4 transcriptional activity in BC cells via ERα. Estradiol and Notch signalings can regulate each other in BC cells. Therefore, combinations of antiestrogens and Notch inhibitors could be more effective in the treatment of ERα+ BCs [11,40]. The angiogenesis-promoting factor, VEGF, increases DLL-4 and activates Notch4 signaling, leading to arterial specification. Notch4 signaling in turn can alter expression levels of VEGFR-2 [29]. Interleukin-1 (IL-1), which is pro-inflammatory and angiogenetic cytokine, can activate Notch4 pathway through NF-κB [19].

CONCLUSIONS

Notch4 signaling is crucial for proper development and function of the mammary gland through regulation of stem cells. So, aberrant Notch4 signaling and its crosstalk with other signaling pathways play a pivotal role in breast cancer stem cell deregulation, tumor initiation, progression and metastasis. Inhibiting survival and differentiation of breast cancer stem cells by blocking of aberrant Notch4 signaling has been considered as a unique strategy for the treatment of breast cancer especially TN subtype.

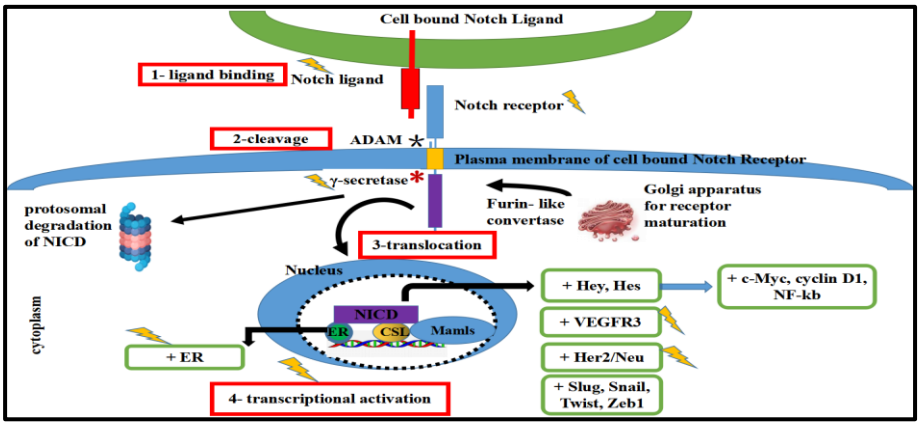
Conflicts of interest: Non

Financial disclosure: Non



ANK, Ankyrin repeats**; LNR,** Lin12-Notch Repeats; **RAM,** RBP-jk

Figure (1): Structure of Notch4



: Represent the target therapy, ligand antibody, receptor antibody, gamma secretase inhibitor (GSI), blocking the transcriptional complex, anti-target genes(ER, HER2,VEGFR)

Figure (2): Notch4 signaling pathway steps

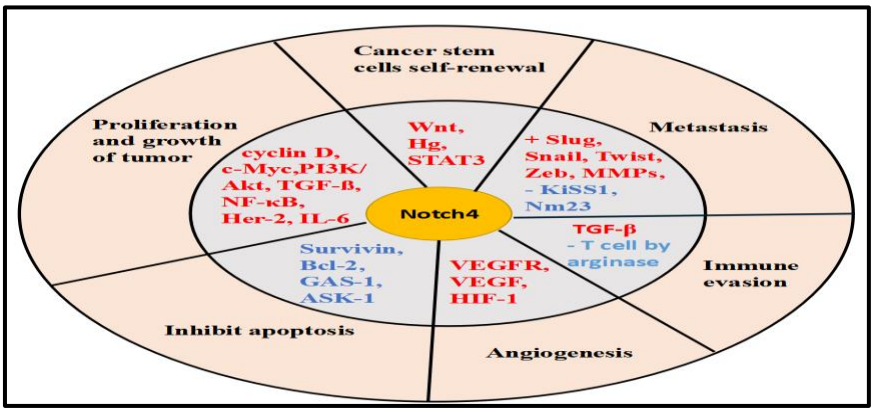


Figure (3): Schematic presentation of target genes of Notch4 activation and their role in carcinogenesis

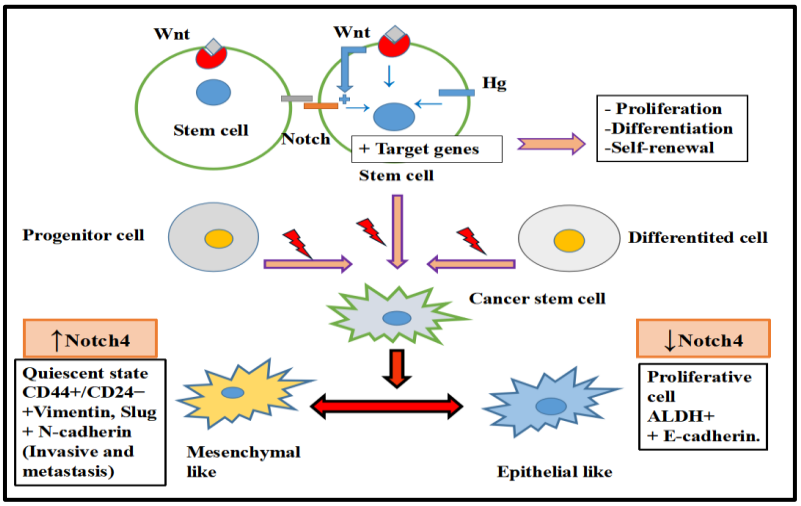


Figure (4): Role of Notch4 in cancer stem cell.

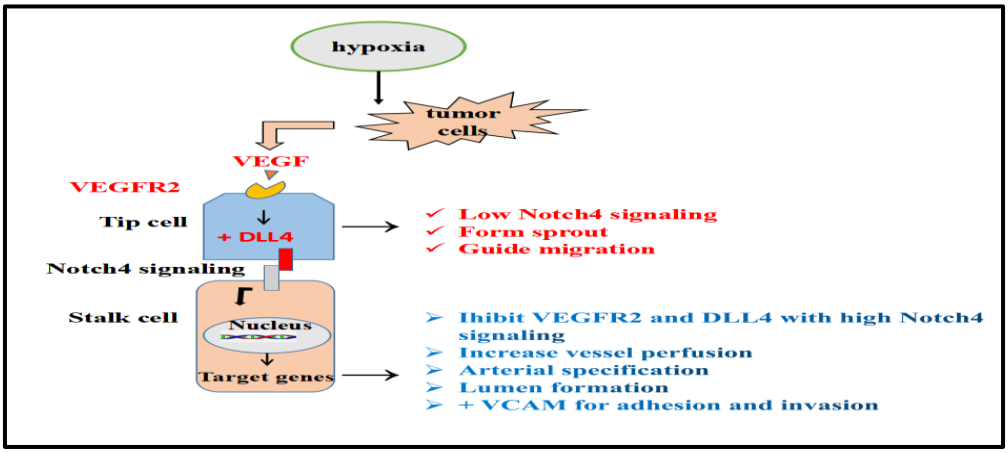


Figure (5): The role of Notch4 in angiognesis

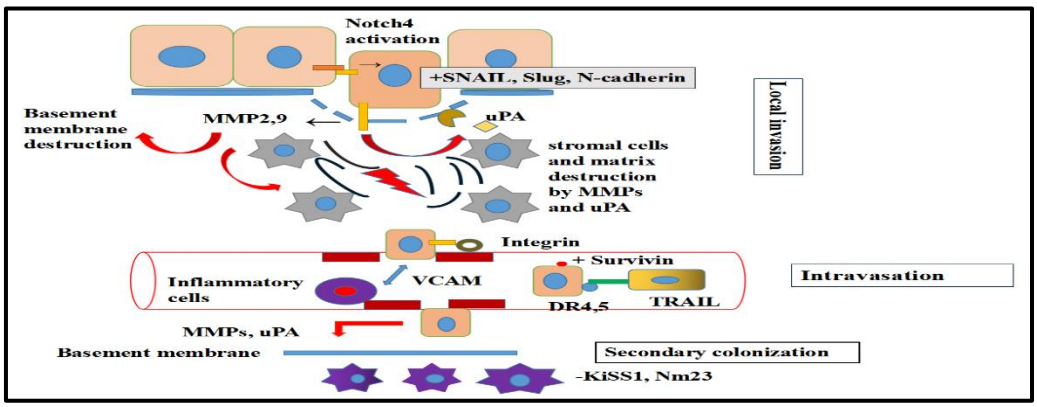


Figure (6): The role of Notch4 in metastasis

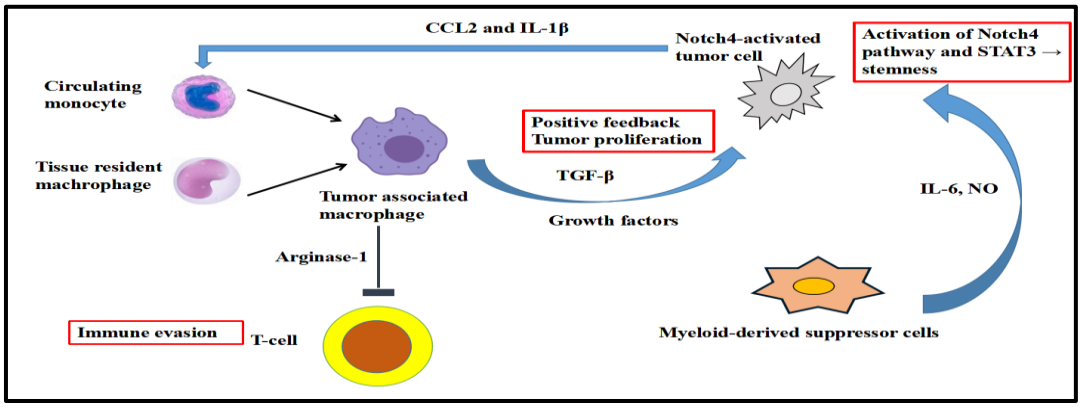


Figure (7): The association between Notch4 and immune system.

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