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Review article

# Delta- like ligand 4- expressing macrophages and human diseases: Insights into pathophysiology and therapeutic opportunities

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ABSTRACT

Macrophages are key players in the immune response and have been implicated in various human diseases, including atherosclerosis, cancer, and chronic inflammatory disorders. While numerous studies have delved into the nuances of macrophage behavior in these conditions, there remains a gap in understanding the specific role of Delta-like ligand 4 (Dll4)-expressing macrophages and their overarching implications across these diseases. Among the plethora of factors expressed by macrophages, Dll4 has emerged as a molecule of particular interest. Recent studies have highlighted its unique role in modulating macrophage functions and its potential implications in various diseases. This review seeks to consolidate existing knowledge, address this gap, and present a comprehensive overview of Dll4-expressing macrophages in the context of these disorders and highlight their potential as therapeutic targets. We examined the involvement of Dll4-expressing macrophages in multiple human diseases such as atherosclerosis, cancer and chronic inflammatory diseases, emphasizing their influence on disease progression. We also discussed the challenges, limitations, and emerging research areas in targeting Dll4-expressing macrophages and provide an outlook on potential therapeutic strategies for the treatment of these diseases. By addressing the previously existing research gap, we've provided a roadmap that brings together fragmented insights, paving the way for more holistic research and potentially more effective therapeutic strategies centered on Dll4-expressing macrophages.

## 1. Introduction

Macrophages are versatile immune cells that play critical roles in both the innate and adaptive immune responses [1]. As the primary phagocytic cells, macrophages are responsible for the clearance of pathogens, apoptotic cells, and cellular debris, as well as the modulation of tissue repair and remodeling processes [2]. These functions are essential for maintaining homeostasis and defending the host against a wide range of infectious and non-infectious threats [3].

Increasing evidence suggests that the polarization of macrophages into distinct functional phenotypes is a crucial determinant of

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**Table 1**
Types and subtypes of macrophages.

| Subtype | Activation signals | Function/characteristics | Markers |
|---|---|---|---|
| M1 [22] | IFNγ, LPS | 1) Pro- inflammatory responses<br>2) Effective against intracellular pathogens<br>3) Production of pro-inflammatory cytokines, reactive oxygen species, and nitric oxide | Nitric oxide synthase (NOS) |
| M2a [22] | IL-4, IL-13 | 1) Involved in tissue repair and wound healing<br>2) Allergic responses<br>3) Produce extracellular matrix components and anti-inflammatory cytokines | 1) CD206 (Mannose receptor)<br>2) Arginase-1 (Arg-1)<br>3) Ym1 (Chitinase-like protein)<br>4) FIZZ1 (Found in inflammatory zone 1) |
| M2b [23] | Immune complexes, LPS | 1) Immune regulation<br>2) Production of both pro-inflammatory and anti-inflammatory cytokines<br>3) Regulation of adaptive immunity | 1) CD86<br>2) IL-1 receptor antagonist (IL-1ra)<br>3) IL-10 |
| M2c [24] | IL-10, glucocorticoids | 1) Anti-inflammatory<br>2) Tissue remodeling<br>3) Phagocytosis of apoptotic cells<br>4) Immune regulation | 1) CD163<br>2) CD206 (Mannose receptor)<br>3) TGF-β (Transforming growth factor-beta) |
| M2d [25] | Adenosine, IL-6 | 1) Promote angiogenesis<br>2) Tissue remodeling<br>3) Tumor progression | 1) VEGF (Vascular endothelial growth factor)<br>2) IL-10 |

their roles in various human diseases [4–8]. Classically activated M1 macrophages are characterized by their pro-inflammatory and antimicrobial functions, while alternatively activated M2 macrophages exhibit immunoregulatory and tissue repair properties [9]. The balance between M1 and M2 polarization states is essential for maintaining immune homeostasis, and its dysregulation has been implicated in the pathogenesis of numerous pathological conditions, including atherosclerosis, cancer, and chronic inflammatory diseases [10,11].

Delta-like ligand 4 (Dll4), a transmembrane protein, is a crucial ligand in the Notch signaling pathway [12]. Dll4-Notch signaling has been shown to regulate a variety of cellular processes, including cell differentiation, proliferation, and survival, as well as angiogenesis and vascular development [13]. Recent studies implemented by our team and others have revealed that Dll4's vital roles in modulating macrophage polarization, function and mediating behaviors of other cells upon cell-to-cell communications [14–18].

We conducted a comprehensive literature search using databases such as PubMed, Scopus, and Web of Science. The main search terms included "Delta-Like Ligand 4″, "Macrophages", "Inflammation", "Polarization", "Atherosclerosis", "Notch", "Tumor" and "Targeted therapy". These terms were used in various combinations using Boolean operators to identify relevant articles. In this review, we aim to examine the role of Dll4-expressing macrophages in various human diseases, highlighting their involvement in the pathophysiology of these conditions and exploring the therapeutic opportunities that arise from understanding the complex interplay between Dll4, macrophage polarization, and disease progression.

## 2. Macrophage polarization and Dll4 expression

Macrophages are highly plastic cells, capable of adopting distinct functional phenotypes in response to various environmental cues [19]. Classically activated M1 macrophages are induced by pro-inflammatory stimuli, such as interferon-gamma (IFN-γ) and lipopolysaccharide (LPS), and produce pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6) [20]. M1 macrophages are crucial for host defense against intracellular pathogens and contribute to tissue damage in inflammatory diseases. In contrast, M2 macrophages are polarized by anti-inflammatory cytokines, such as interleukin-4 (IL-4) and interleukin-13 (IL-13), and exhibit immunoregulatory and tissue repair properties [21]. M2 macrophages can be further subdivided into M2a, M2b, M2c, and M2d subtypes, each with distinct functional characteristics [3]. Characteristics of these macrophage subtypes were listed in Table 1.

Macrophage polarization is regulated by a complex interplay of cytokines, chemokines, and signaling pathways. Transcription factors, such as signal transducer and activator of transcription (STAT) proteins and nuclear factor kappa B (NF-κB), play essential roles in orchestrating M1/M2 polarization [26]. In addition to cytokine-mediated signaling, cell-cell interactions, extracellular matrix components, and metabolic cues also contribute to shaping macrophage phenotype and function [27,28].

Recent studies have revealed that Dll4 is preferentially expressed in M1 macrophages [17,29]. Dll4 expression is upregulated by pro-inflammatory stimuli, such as LPS and IFN-γ, and is further enhanced by the activation of the Toll-like receptor (TLR) signaling pathway and NF-κB [30]. Dll4 expression has been found to be positively correlated with the expression of M1-associated markers, such as inducible nitric oxide synthase (iNOS) and IL-6 [31].

Dll4 plays a critical role in modulating macrophage function through its involvement in the Notch signaling pathway. Upon binding to its cognate Notch receptors, Dll4 triggers the proteolytic cleavage and nuclear translocation of the Notch intracellular domain (NICD), leading to the activation of downstream target genes [32]. In macrophages, Dll4-Notch signaling has been shown to promote M1 polarization and enhance pro-inflammatory cytokine production, while suppressing M2-associated gene expression [18]. Furthermore, Dll4-Notch signaling is implicated in modulating macrophage-mediated angiogenesis and tissue remodeling processes [33,34]. The features of M1/M2 macrophages are demonstrated in Table 2 and Dll4's unique roles in M1 macrophages were showed in Fig. 1.

**Table 2**
Macrophage polarization and Dll4 expression.

| Features | M1 macrophages | M2 macrophages |
|---|---|---|
| General Functions [35,36] | Pro-inflammatory, anti-tumor, antimicrobial | Anti-inflammatory, pro-tumor, tissue repair and remodeling |
| Markers | CD80, CD86, MHC-II | CD163, CD206 |
| Cytokines/chemokines [36] | IL-1β, IL-6, IL-12, IL-23, TNF-α | IL-4, IL-10, IL-13, TGF-β |
| Polarizing factors [36] | IFN-γ, LPS, GM-CSF | IL-4, IL-13, M-CSF |
| Key transcription factors [36] | IRF5, STAT1 | IRF4, STAT6, PPARγ |
| Dll4 expression [37] | Higher expression | Lower or absent expression |
| Role of Dll4-expressing macrophages [37,38] | Modulation of inflammatory response, cancer, regulation of vascular function and plaque stability | Not well-defined |

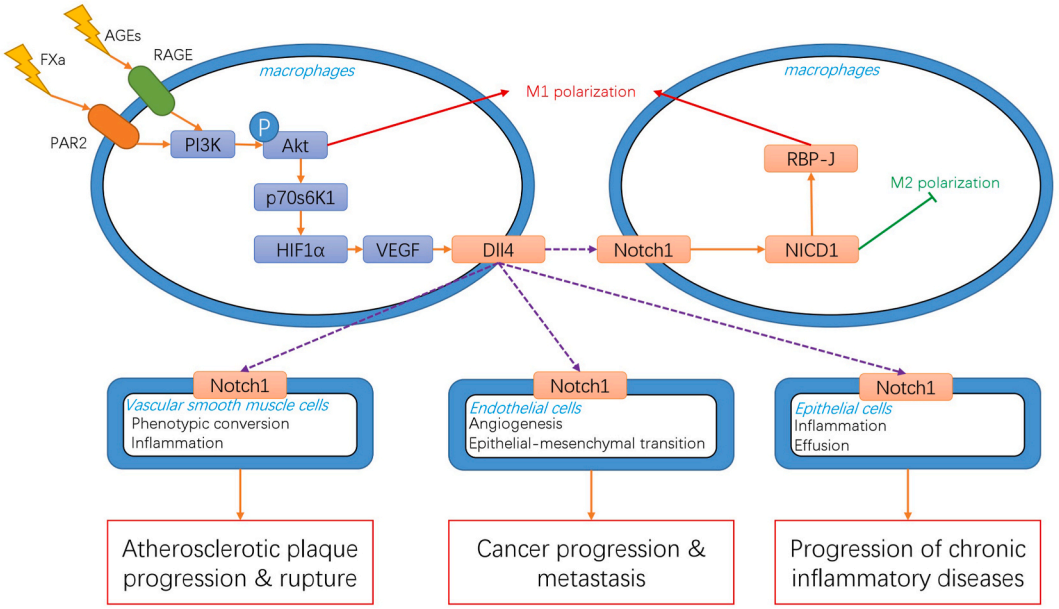


**Fig. 1.** Schematic Overview of Dll4-Mediated Signaling in Macrophages and its Implications in Human Diseases
Dll4 plays a pivotal role in macrophage functions and is implicated in various human diseases. When macrophages are exposed to pathological stimuli, such as AGEs (advanced glycation end products) and Factor Xa, they activate their respective receptors, RAGE (receptor for advanced glycation end products) and protease-activated receptor 2 (PAR2). This activation triggers intracellular pathways, notably the phosphoinositide 3-kinase (PI3K)/Akt pathway, promoting the M1 polarization of macrophages. Concurrently, the PI3K/Akt pathway also induces the hypoxia inducible factor 1 (HIF1)α/vascular endothelial growth factor (VEGF) cascade, leading to an upregulation of Dll4 expression in macrophages. When macrophages expressing Dll4 come into contact with neighboring macrophages, it instigates the activation of the Notch signaling pathway in these neighboring cells. This promotes further M1 polarization while concurrently inhibiting M2 polarization. Moreover, when Dll4-mediated Notch pathway activation occurs in vascular smooth muscle cells (VSMCs), endothelial cells, and epithelial cells, it contributes to the progression of various diseases, including atherosclerosis, cancer, and chronic inflammatory conditions.

## 3. Dll4-expressing macrophages in human diseases and potential therapeutic approaches

### *3.1. Atherosclerosis*

Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids, immune cells, and extracellular matrix components within the arterial wall, leading to the formation of plaques [39]. Macrophages play a central role in atherosclerosis development and progression, through the uptake of modified lipoproteins, such as oxidized low-density lipoprotein (oxLDL), resulting in the formation of foam cells [40]. Additionally, macrophages secrete various pro-inflammatory cytokines and matrix metalloproteinases (MMPs), contributing to plaque inflammation, matrix degradation, and eventual plaque rupture [41].

Our recent studies have demonstrated the presence of Dll4-expressing macrophages within atherosclerotic plaques [14]. Dll4 expression is predominantly localized to the plaque shoulder regions and areas of neovascularization, where it promotes endothelial cell activation and angiogenesis [32]. Activation of the Dll4-Notch signaling pathway in plaque macrophages has been associated with increased expression of pro-inflammatory cytokines, chemokines, and MMPs, exacerbating plaque inflammation and instability [42].

Dll4-expressing macrophages contribute to plaque instability by promoting a pro-inflammatory M1 phenotype and suppressing the

anti-inflammatory M2 phenotype [43]. Dll4-Notch signaling has also been implicated in the regulation of vascular smooth muscle cell (VSMC) function within the plaque. Activation of Notch signaling in VSMCs by Dll4-expressing macrophages induces VSMC senescence and apoptosis, weakening the fibrous cap and increasing the risk of plaque rupture [44,45].

Given the pivotal role of Dll4-expressing macrophages in atherosclerosis progression and plaque instability, targeting Dll4 and its associated signaling pathways may represent a promising therapeutic strategy for the treatment of atherosclerosis. Results from an in vitro study suggested Dll4 blockade significantly attenuates the M1 polarizationof macrophages which expressed less proinflammatry mediators such as iNOS and TNF-α [46]. Preclinical studies have shown that blockade of Dll4-Notch signaling by neutralizing anti-Dll4 antibody administration reduced macrophages accumulation and atheroma in mice model of atherosclerosis and vein graft disease [47]. Furthermore, Dll4-Notch signaling suppression increased M2 marcrophages augmentation and reduce the risk of fatal ventricular arrhythmia post myocardial infarction [48].

### 3.2. Cancer

Tumor-associated macrophages (TAMs) are a major component of the tumor microenvironment and play a crucial role in cancer progression [49]. TAMs can exhibit both pro- and anti-tumoral functions, depending on their polarization state. M2-polarized TAMs are generally associated with tumor progression, promoting angiogenesis, immunosuppression, and tissue remodeling, while M1-polarized TAMs exhibit pro-inflammatory and anti-tumoral activities [11].

Dll4 expression has been observed in TAMs within various tumor types, including breast cancer, glioblastoma, and colorectal cancer [50,51]. Dll4-expressing TAMs predominantly exhibit an M2-like phenotype and contribute to the activation of the Notch signaling pathway in the tumor microenvironment, thereby modulating various cellular processes, including angiogenesis, cell proliferation, and migration [52].

Dll4-expressing TAMs play a pivotal role in promoting tumor angiogenesis by activating the Notch signaling pathway in endothelial cells, resulting in the formation of abnormal, leaky blood vessels [53]. This aberrant vascularization leads to an increase in tumor hypoxia, which further drives the recruitment of TAMs, perpetuating a cycle of tumor growth and angiogenesis [54,55]. Additionally, Dll4-expressing TAMs can promote the epithelial-mesenchymal transition (EMT) in tumor cells, enhancing their migratory and invasive capacities, and ultimately facilitating metastasis [56].

Given the crucial role of Dll4-expressing TAMs in tumor progression, angiogenesis, and metastasis, targeting Dll4 may offer a promising therapeutic strategy in cancer treatment. Disrupting Dll4-Notch signaling in TAMs was found to reduce microglia recruitment and results in abnormal angiogenesis [57]. It was reported that an engineered fully human IgG1 mAb named REGN421, which bind human Dll4 with sub-nanomolar affinity, inhibited human ovarian cancer in xenografts models [58]. Using the fusion protein Dll4-Fc as an inhibitor of Dll4-Notch signaling suppressed liver metastasis of small cell lung cancer [59]. Moreover, combining Dll4-targeted therapies with conventional chemotherapy, immunotherapy, or anti-angiogenic agents has shown synergistic effects in preclinical models, highlighting the potential of targeting Dll4 in combination with other therapeutic modalities for improved cancer treatment outcomes [60,61].

### 3.3. Chronic inflammatory diseases

Macrophages are key regulators of chronic inflammation, which is associated with various diseases, such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis [62–64]. Depending on their polarization state, macrophages can either promote or resolve inflammation. M1 macrophages exhibit pro-inflammatory activities, while M2 macrophages are involved in resolving inflammation and promoting tissue repair [20].

Dll4 expression has been detected in macrophages within the inflamed tissues of patients with chronic inflammatory diseases [65,66]. Activation of the Notch signaling pathway, in which Dll4 plays a crucial role, has been implicated in the pathogenesis of various inflammatory diseases by modulating the function and differentiation of immune cells, including macrophages, T cells, and dendritic cells [47,67–69]. Dll4/Notch pathway was found play important roles in inflammatory diseases such as rheumatoid arthritis and Crohn's disease. Increased expressions of Dll4 and NICD were found localized to perivascular/vascular regions in synovial tissue specimens from patients with rheumatoid arthritis [70]. Dll4/Notch pathway activation was suggested to participate in progression of rheumatoid arthritis by regulating inflammation responses through signal transducer and activator of transcription (STAT3) [71]. Notch ligands Jag1 and Dll4 were found high expressed in mucosa of Crohn's disease patients. Jag1 and Dll4-induced M1 macrophages-associated Notch pathway in epithelial cells was related with Crohn's disease [72]. Moreover, sponging miR-30 family-mediated Dll4 expression was found critical in pathogenesis of Crohn's disease [73].

Dll4-expressing macrophages contribute to the progression of chronic inflammatory diseases by promoting the M1 polarization state and enhancing the pro-inflammatory response [74]. In rheumatoid arthritis, for instance, Dll4-expressing macrophages are associated with increased production of pro-inflammatory cytokines, such as TNF-α and IL-6, which promote synovial inflammation and joint destruction [75]. Similarly, in inflammatory bowel disease, Dll4-expressing macrophages contribute to the maintenance of chronic intestinal inflammation through the activation of the Notch signaling pathway [76].

Given the role of Dll4-expressing macrophages in the pathogenesis of chronic inflammatory diseases, targeting Dll4 may represent a promising therapeutic strategy. Blockade of Dll4 suppressed macrophage accumulation and the expression of metaphase chromosome protein 1 (MCP1) in adipose tissue which alleviated non-alcoholic fatty liver disease in mice [47]. Moreover, combining Dll4-targeted therapies with existing immunomodulatory agents may provide synergistic effects and improve treatment outcomes in chronic inflammatory diseases [77].

**Table 3**
Potential therapeutic approaches targeting Dll4 in human diseases.

| Disease | Therapeutic strategy | Mechanism of action |
|---|---|---|
| Atherosclerosis [81] | *Anti*-Dll4 antibodies | Inhibition of M1 macrophage polarization, reduction of inflammation, and promotion of plaque stability |
| Breast cancer [82] | Dll4-targeted therapies | Modulation of tumor-associated macrophages, inhibition of tumor angiogenesis, and suppression of metastasis |
| Rheumatoid arthritis [83] | Dll4 blockade or inhibition | Suppression of M1 macrophage polarization, reduction of inflammation, and attenuation of disease progression |
| Colorectal cancer [84] | Dll4-targeted therapies | Modulation of tumor-associated macrophages, inhibition of tumor angiogenesis, and suppression of metastasis |
| Multiple sclerosis [85] | Dll4 blockade or inhibition | Suppression of M1 macrophage polarization, reduction of inflammation, and attenuation of disease progression |
| Psoriasis [86] | Dll4 blockade or inhibition | Suppression of M1 macrophage polarization, reduction of inflammation, and attenuation of disease progression |

## 4. Future perspectives

Dll4 blockade or silencing would be promising strategy of targeted therapies. In one of our projects, we found that linage knockout of Dll4 in mono-macrophages lead to dramatic alleviation of formation, progression and vulnerability of atherosclerosis. While targeting Dll4-expressing macrophages holds promise for the treatment of various human diseases, there are challenges and limitations to be addressed. One of the main challenges is the potential off-target effects due to the broad involvement of Notch signaling in various cellular processes and tissue homeostasis [78]. Additionally, the complexity of the immune system and the diverse functions of macrophages in health and disease necessitate a thorough understanding of the context-dependent roles of Dll4-expressing macrophages [42].

Emerging research areas and potential new therapeutic strategies are being explored to increase the specificity of targeting. For instance, the development of more selective inhibitors targeting specific Notch ligands or receptors, or modulating specific downstream pathways, may help to overcome off-target effects and improve therapeutic efficacy [79]. Moreover, our team is developing a nanocarrier targeting specific high dll4 expressing- M1 macrophage subgroup. The increased cell targeting would be benefit in decreasing unexpected disruption of immune system function. Additionally, the potential role of Dll4-expressing macrophages in other diseases, such as neurodegenerative disorders, autoimmune diseases, and fibrosis, warrants further investigation [80]. Currently developing Dll4-involved therapeutic strategies in human diseases are demonstrated in Table 3.

The role of Dll4 in disease pathology suggests its potential as a diagnostic or prognostic biomarker. Future research might delve into developing assays or tests that leverage Dll4 levels or activity to predict disease onset or progression. Moreover, understanding how Dll4 interacts with other signaling molecules or pathways can provide a holistic view of its role. This might lead to combined therapeutic strategies that target multiple pathways for enhanced efficacy.

## 5. Conclusion

In conclusion, our review brings together fragmented insights on Dll4-expressing macrophages and offers a fresh perspective on their multifaceted roles in human diseases. The study of in-depth molecular mechanisms has contributed to our understanding of disease progression and provided potential therapeutic opportunities by targeting these Dll4-expressing macrophages. Continued research in this area will be essential to fully elucidate the complex roles of Dll4-expressing macrophages in human diseases and to develop more effective therapeutic strategies.

## Compliance with ethics guidelines

Wenya Yu, Xiqiang Wang, Jing Liu, Zhongwei Liu and Haitao Zhu declare that they have no conflict of interest. This review does not contain any studies with human or animal subjects performed by any of the authors.

## Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

## Data availability statement

Data will be made available on request.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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