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REVIEW

Discoid Domain Receptors Signaling in Macrophages-Mediated Diseases

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Abstract: Macrophages, as a crucial component of the body's immune system, play a vital role in the onset, progression, and outcome of diseases. Discoidin domain receptors (DDRs), important members of the novel receptor tyrosine kinase superfamily, exhibit unique functions in macrophage physiology. Through interactions with the extracellular matrix, DDRs activate signaling pathways such as p38 MAPK and NF-κB, regulating macrophage adhesion, migration, and secretory functions, thereby influencing their behavior in diseases. Recent studies have indicated a direct correlation between DDRs and the progression of various diseases, including inflammation, cancer, and fibrosis. However, there remain numerous knowledge gaps regarding the specific mechanisms by which DDRs function in macrophage-mediated diseases. This article provides an in-depth summary of the regulatory mechanisms of DDRs on macrophages, detailing their modulatory roles in various diseases through macrophages and their underlying mechanisms. The aim is to offer new insights into biomedical therapies targeting DDRs and the development of novel drugs.

Keywords: DDR1, DDR2, macrophages, disease

Introduction

In the early 1990s, a new class of transcripts encoding proteins with a discoidin (DS) I-like N-terminal domain and a catalytic kinase C-terminal domain were reported, exhibiting approximately 45% similarity to the nerve growth factor receptor tyrosine kinase A.[1] Subsequently, due to the homology of their unique extracellular DS domains with the lectin discoidin I secreted by the slime mold Dictyostelium discoideum, these newly discovered proteins were named DS domain receptors 1 and 2 (DDR1 and DDR2). They remained orphan receptors until 1997, when it was discovered that these two receptors bind to different types of collagen as their functional ligands.[2] Indeed, DDRs belong to the receptor tyrosine kinase (RTK) family, which controls numerous critical cellular processes, including cell proliferation, differentiation, survival, migration, and cell cycle regulation.[3] DDR1 and DDR2 exhibit high sequence conservation and are both single-transmembrane proteins homologous to RTKs.[4] Most RTKs are activated within seconds after ligand binding through phosphorylation of tyrosine residues, followed by a rapid decline in activity due to dephosphorylation or internalization and degradation of the receptor/ligand.[5] However, they differ from typical RTKs in that they serve as collagen receptors in the extracellular matrix (ECM). Unlike the signal transduction of other typical RTKs with acute and rapid responses, collagen binding to DDRs is slow and continuous.[5,6] DDRs participate in cell activation, proliferation, migration, adhesion, ECM remodeling, and organismal homeostasis by inducing multiple signaling pathways.[7]

Tissue repair and regeneration are crucial biological processes fundamental to the survival of all organisms.[8] Macrophages are the first responders when tissues are infected or mechanically damaged, capable of detecting tissue damage and pathogen threats.[9,10] In response to these threats, they can clear pathogens through phagocytosis while mediating defense and inflammatory responses. Macrophages engulf and internalize pathogens through endocytosis, followed by fusion of phagosomes with acidic lysosomes to degrade the pathogens.[11] On the other hand, macrophages are activated and polarized into pro-inflammatory macrophages (M1) or anti-inflammatory macrophages (M2) by certain signals, thereby mediating inflammatory responses or producing defensive functions through the regulation of various

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signal transduction pathways.[12,13] They also have a potent sentinel function, capable of summoning and guiding innate and adaptive immune cells. Macrophages initiate and coordinate local or systemic immune activation by secreting cytokines, chemokines, and growth factors, as well as presenting antigens to adaptive immune cells.[14]

Various studies have shown that abnormal activation of DDRs promotes macrophage activation, leading to the onset and progression of multiple diseases. In 2007, Sang-Hyun Kim's research demonstrated that the interaction between DDR1 and collagen induced iNOS expression and increased NO synthesis in the mouse macrophage cell line J774A.1 by activating NF-κB, p38 MAPK, and JNK, thereby exacerbating immune-inflammatory responses.[15] Inhibition of DDR1 effectively suppressed macrophage migration and the production of inflammatory cytokines. LCB-03-0110, a broad-spectrum tyrosine kinase inhibitor, inhibited lipopolysaccharide-induced migration of J774A.1 macrophages and the synthesis of inflammatory cytokines such as NO, iNOS, COX-2, and TNF-α in a dose-dependent manner.[16] Additionally, studies have found that DDR1-selective inhibitor compound 7ae dose-dependently inhibited LPS-induced IL-6 and TNF-α production in mouse primary peritoneal macrophages.[17] Therefore, the unique role of DDRs in macrophages makes them a promising therapeutic target.

However, no drugs targeting DDRs on macrophages have been approved for clinical use. This can be partially attributed to insufficiently comprehensive research on the immune regulatory mechanisms of DDRs in macrophages, leading to a lack of conclusive evidence for their clinical indications. In this review, we introduce the structure, activation, and physiological function characteristics of DDRs and systematically discuss the potential mechanisms of DDRs in macrophages and related diseases, aiming to promote the development of novel immunotherapies targeting DDRs.

Structure and Activation of DDRs

The classical structure of transmembrane receptor tyrosine kinases (RTKs) encompasses an extracellular region, a transmembrane (TM) domain, and an intracellular kinase domain. In contrast to members of the RTK family, the extracellular region of discoidin domain receptors (DDRs) comprises a globular discoidin (DS) domain consisting of 155 amino acids, DS-like domains, and an extracellular juxtamembrane (JM) region,[18,19] providing matrix metalloproteinase (MMP) cleavage sites and sites for N- and O-glycosylation. The JM segment is responsible for transmitting extracellular signals to the intracellular kinase domain.[20] The intracellular kinase domain of DDRs consists of the intracellular JM region, a catalytic tyrosine kinase domain (KD), and a C-terminal kinase domain, which regulate ligand-independent dimerization of DDRs and mediate the activation and phosphorylation of downstream signals.[20,21] An amino acid (S175) within the DS domain and two surface-exposed loops (R105-K112 and S52-T57) are responsible for collagen (COL) binding.[22] Upon forming dense clusters, DDR1 undergoes trans-autophosphorylation between adjacent dimers upon binding to triple-helical COL.[23–25] Phosphorylated DDR1 interacts with adapter molecules such as Nck2 and ShcA, triggering cell-specific events such as the activation of p38 mitogen-activated protein kinase (MAPK) or Src pathways, thereby regulating cell differentiation and migration, as well as collagen deposition and MMP expression.[26–29] DDR1 has five isoforms (DDR1a-e) arising from alternative splicing of its intracellular kinase domain, whereas DDR2 has only one isoform[30–33] (Figure 1). DDR1a, DDR1b, and DDR1c contain 876, 913, and 919 amino acids, respectively, with kinase activity in their coding sequences. However, DDR1d, consisting of 508 amino acids, lacks a kinase domain, while DDR1e (767 amino acids) has a non-functional kinase domain.[34,35] DDR2 has 855 amino acids.[33,36] A sixth isoform of DDR1, lacking the extracellular domain, has been identified in rat testes.[37]

Collagen, the primary component of the extracellular matrix, serves as a specific ligand for DDRs. Unlike typical RTKs, the DS domain of DDRs is activated through binding to the microenvironmental COL or its fragments rather than by peptide growth factors.[38] However, only collagen with a native triple-helical structure can bind to DDRs.[39,40] Additionally, DDR1 and DDR2 exhibit differences in specificity towards different collagens. Using a series of overlapping triple-helical peptides, the DS domains of DDR1 and DDR2 were found to specifically recognize the amino acid sequence GVMGFO (O, hydroxyproline) on type I, II, and III collagen fibers.[41,42] However, basement membrane (type IV) collagen only activates DDR1, while type V and X collagens only interact with DDR2.[43–45] Typically, typical RTKs are activated within seconds of ligand binding through phosphorylation,[5] but collagen-DDR binding undergoes a slow and sustained process of autophosphorylation.[2]

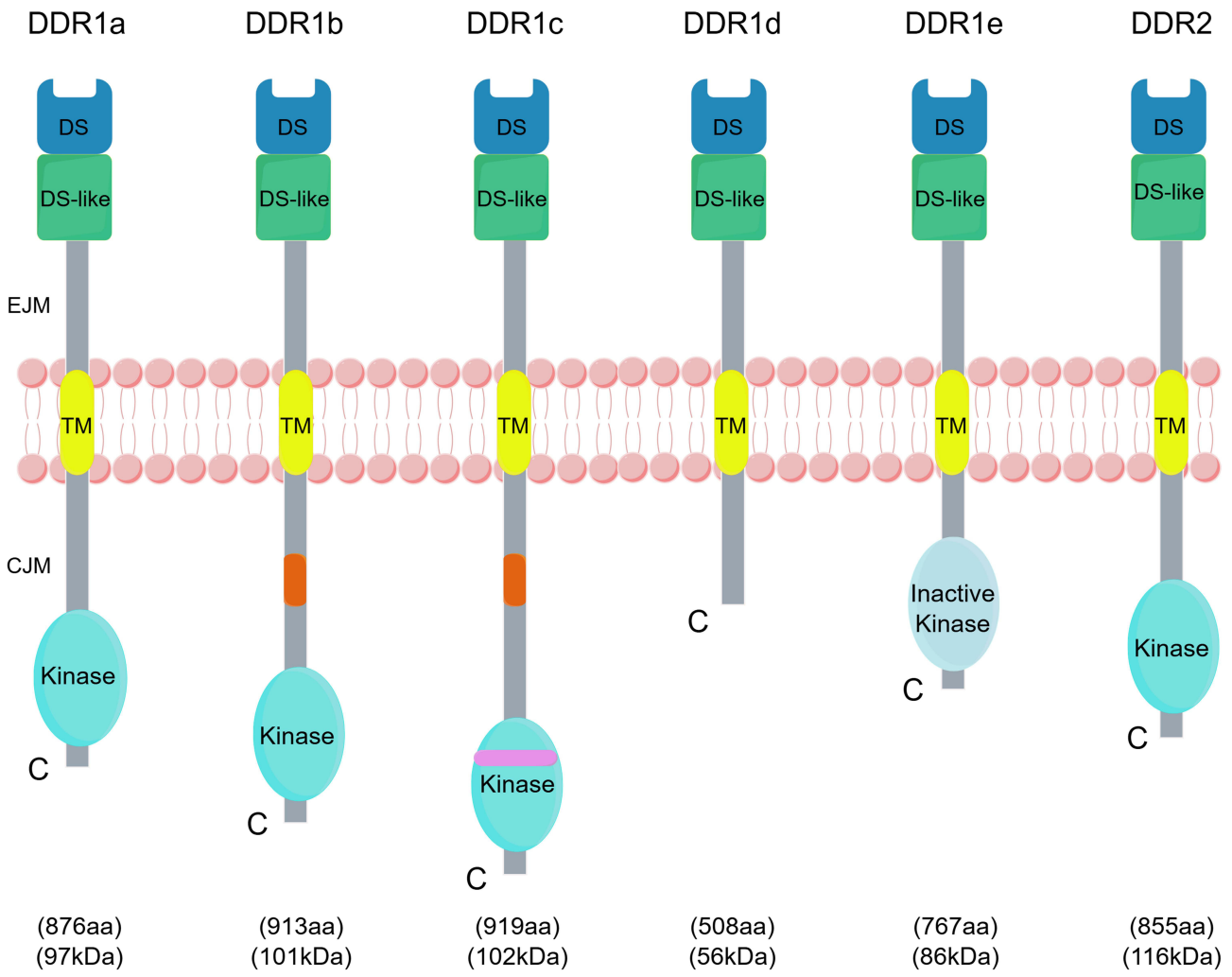

Figure 1 Schematic structural representation of the five DDR1 isoforms and a single DDR2 isoform. DDR1a, DDR1b, DDR1c and DDR2 are enzymatically active tyrosine kinase receptors. While DDR1d lacks a kinase domain, DDR1e has a non-functional or inactive kinase domain and their functions are unknown.
Abbreviations: DDR, discoidin domain receptor; DS, discoidin domain; EJM, extracellular juxtamembrane; TM, transmembrane domain; CJM, intracellular juxtamembrane; aa, amino acid.

Although a single DS domain contains sites for collagen binding, DDRs require dimerization of the DS domains to bind collagen with high affinity.[39] Surprisingly, DDRs form independent and stable dimers mediated by a leucine sequence motif in the transmembrane domain in the absence of ligand recognition, distinguishing them from other RTKs.[23] Furthermore, mutations in cysteine residues within the extracellular JM region of DDRs result in the formation of independent and covalent dimers during biosynthesis.[46] The collagen-binding region, composed of charged residues surrounded by hydrophobic layers within three surface-exposed loops of the DS domain, becomes activated upon collagen binding by forming lateral clusters.[22,39] In other words, the activation of DDRs and the lateral clustering of DDR proteins are mutually causal. Lateral clustering enhances DDR binding to collagen and induces DDR activation, while the lateral clusters that result in transphosphorylation between dimers are a consequence of collagen binding.[23,47] DDRs regulate adhesion and traction forces on collagen by binding to myosin IIA, which condenses collagen fibrils into a denser arrangement.[48,49] Activation of the DDR kinase domain enhances the binding of the kinase domain to myosin IIA filaments, optimizing the transmission of myosin-dependent contractile forces to collagen fibrils.[47] The degree of DDR activation is proportional to the contractile force of collagen.[47] Upon DDR binding to collagen, tyrosine residues in the intracellular JM region and the intracellular kinase domain of DDRs undergo autophosphorylation.[5] This phosphorylation recruits intracellular signaling protein complexes, such as Src Homology-2/3 (SH2/3) and Phosphotyrosine

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Binding (PTB) domains, for the assembly and transmission of receptor signals that function in cell signal transduction.[39] Additionally, an atypical but functional crosstalk exists between the insulin/insulin-like growth factor system (IIGFS) and DDRs, recently discovered and unrelated to typical collagen-dependent DDR activation. Interestingly, DDR1 exhibits better functional interaction with IIGFS than DDR2.[50] As a complex network, IIGFS consists of transmembrane receptors, corresponding ligands, and binding proteins.[50] Insulin-like growth factor 1 receptor (IGF1R) and insulin receptor (IR)-A belong to the transmembrane receptors of IIGFS, with common ligands including insulin-like growth factors (IGF1 and IGF2) and insulin, participating in crosstalk with DDR1.[50] Upon stimulation by homologous ligands, IGF1R or IR-A physically interact with DDR1, inducing rapid and sustained phosphorylation of DDR1 independently of its binding ability to collagen.[51] IIGFS not only stimulates DDR1 phosphorylation but also upregulates DDR1 protein levels to some extent by activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) cascade and further inhibiting the downstream miR-199a-5p, a negative regulator of DDR1.[52]

Physiological Role of DDRs

The expression of Discoidin Domain Receptors (DDRs) varies across different tissues during early embryonic development in both humans and mice. DDR1 is broadly expressed in various tissues, including vascular smooth muscle, mesangial cells, renal epithelial cells, and macrophages.[53–55] In contrast, DDR2 is predominantly expressed in mesenchymal-derived tissues such as connective tissue, muscle, and bone.[31] The molecular mechanisms of DDR1 and DDR2 exhibit tissue specificity. DDR1 primarily regulates cell adhesion, proliferation, and migration through binding to type I and IV collagens.[56] In comparison, DDR2 mainly binds to type I and III collagens, modulating the differentiation and maturation of osteoblasts and chondrocytes.[57]

DDR1 plays a pivotal role in embryonic development, particularly in organ growth. Mice lacking DDR1 exhibit a smaller body size and defects in fibular ossification.[7,58] Female DDR1-deficient mice are infertile due to improper blastocyst implantation into the uterine wall. Additionally, pregnant mice with DDR1 deficiency cannot lactate due to improper alveolar differentiation in the mammary glands.[59] DDR1-defective mice also display structural abnormalities in the inner ear, leading to hearing impairment.[60] DDR1 is crucial for neointimal formation in the aorta and smooth muscle cell migration.[54] Smooth muscle cells lacking DDR1 show decreased proliferation, migration, collagen attachment, and MMP-2/9 secretion compared to normal cells.[61] DDR1 expression is upregulated in skin wound healing.[62] Furthermore, a high incidence of temporomandibular joint osteoarthritis has been observed in DDR1-deficient mice.[63] In the kidney, studies have reported slit diaphragm defects in podocytes of DDR1-defective mice, accompanied by focal subepithelial glomerular basement membrane thickening and proteinuria.[64] However, no loss of nephrons, tubulointerstitial fibrosis, or glomerulosclerosis was detected in these mice.[65]

DDR2 plays a significant role in bone growth. Multiple studies have demonstrated that DDR2 regulates osteoblast differentiation and chondrocyte maturation by activating the Runx2 molecule.[66,67] DDR2-deficient mice exhibit dwarfism, accompanied by shorter long bones and noses.[66–68] Dwarfism caused by DDR2 deficiency has also been observed in humans with DDR2 mutations. DDR2 knockout mice have smaller and malformed hearts, resulting from irregular cross-linking and deposition of collagen fibers in DDR2-defective fibroblasts, leading to defects in cardiomyocyte health.[69] DDR2 expression is essential for the proliferation of skin fibroblasts during wound healing.[68,70] In vascular smooth muscle cells, the absence of DDR2 does not affect cell proliferation, migration, or adhesion.[71] Although the expression of DDR1 and DDR2 overlaps in some tissues (eg, chondrocytes and smooth muscle cells), their roles are distinct. These different molecular mechanisms suggest that the functions of DDR1 and DDR2 in various tissues may be influenced by their specific ligands and downstream signaling pathways, exhibiting tissue specificity.

Despite extensive research exploring the physiological roles of DDR1 and DDR2, several knowledge gaps remain. For instance, the specific mechanism of DDR1 in the kidney is not fully understood. Although studies have found slit diaphragm defects and proteinuria in DDR1-defective mice, its role in glomerulosclerosis and tubulointerstitial fibrosis requires further investigation.[64] Additionally, the mechanism of DDR2 in the heart is controversial. While DDR2-deficient mice exhibit smaller and malformed hearts, the specific impact on cardiomyocyte health and collagen fiber cross-linking needs further exploration.[69] These knowledge gaps highlight the need for more research to comprehensively understand the physiological roles of DDRs in different tissues.

DDR1 and DDR2 play crucial roles in embryonic development and tissue repair, but their specific mechanisms and functions differ significantly across tissues. DDR1 is essential for organ growth, wound healing, and blood vessel formation, whereas DDR2 plays a key role in bone growth and chondrocyte maturation.[6,38] However, existing research also reveals the complexity and diversity of DDRs' functions, suggesting the need for further investigation into their specific mechanisms in different pathophysiological processes. Future research should focus on the molecular mechanisms of DDRs in different tissues and their potential therapeutic applications in diseases, aiming to fill current knowledge gaps and provide new strategies for the treatment of related conditions.

Regulation of DDRs on Immune Cells

DDR1 can regulate certain characteristics of immune cells. Studies have found that the extracellular domain (ECD) of DDR1 enhances the arrangement of collagen fibers and prevents immune cell infiltration by binding to collagen.[72] Similarly, the expression of DDR1 is negatively correlated with intratumoral T-cell abundance in triple-negative breast cancer.[73] DDR2 is also implicated in immune regulation. Dang et al reported that DDR2 acts as a co-stimulatory receptor for T-cell activation, inducing T-cell differentiation, intracellular calcium mobilization, and proliferation.[74] Mixed lymphocytes exhibited enhanced responses to allogeneic antigens through DDR2-mediated interactions. Meanwhile, DDR2 is also involved in fibrosis regulation, which is closely associated with chronic inflammation. During fibrosis, macrophages undergo significant phenotypic and functional changes.[7]

Macrophages constitute a plastic and multipotent population of immune cells that respond to microenvironmental stimuli and signals.[75,76] Macrophage polarization is characterized by classical activation (also known as M1) or alternative activation (also known as M2).[77] Typically, M1 macrophages are activated by IFN-γ or lipopolysaccharide and are primarily responsible for producing proinflammatory cytokines. Conversely, M2 macrophages can be activated by IL-4 or IL-13 to attenuate inflammatory responses and promote wound healing.[78–80] Macrophages are a crucial component of the innate immune system, participating in almost every biological process, including tissue homeostasis, infection resistance, post-infection repair, metabolism, and inflammation, thereby influencing organismal development and immune responses.[81,82] The expression of DDRs can activate macrophages and promote their migration and secretion.

DDRs and Macrophages

In 2001, Kamohara H et al utilized in situ hybridization to discover the expression of DDR1 on human macrophages (Mφ).[83] In 2007, KIM et al further demonstrated the expression of DDR1 in the murine macrophage cell line J774A. Binding of collagen to DDR1 induced the expression of inducible nitric oxide synthase (iNOS) and the synthesis of nitric oxide (NO) in the macrophage cell line J774A.1, thereby exacerbating immune-inflammatory responses.[15] Additionally, DDR1 binding to collagen in the extracellular matrix promoted the differentiation of monocytes into macrophages and facilitated the secretion of IL-8, macrophage inflammatory protein-1α (MIP-1α), and monocyte chemoattractant protein-1 (MCP-1) by human macrophages (Mφ) through signaling pathways involving p38 mitogen-activated protein kinase (p38 MAPK) and NF-κB.[53] This promoted the migration and chemotaxis of macrophages.[53,83,84] p38 MAPK was crucial for the increase in NF-κB transcriptional activity mediated by DDR1b but was not necessary for IκB degradation or NF-κB nuclear translocation.[53] Intriguingly, DDR1b activation-induced IκB degradation was regulated by the recruitment of adapter protein Shc to the LXNPXY motif of the receptor and was modulated by downstream TNFR-associated factor 6/NF-κB activator 1 (TRAF-6 and NF-κB Act-1) signaling cascades.[15,53] In vitro studies revealed that under the influence of MCP-1, Mφ from $Ddr1^{-/-}$ mice exhibited decreased adhesion and chemotactic invasion capabilities towards type IV collagen.[85] DDR1 could also promote cell motility independently[86] or without relying on collagen binding. This role has been previously reported in tumors[87] and inflammatory cells (macrophages and T cells).[85,88,89]

After exploring the role of DDR1 in macrophages, we turn our attention to DDR2, which differs from DDR1 in its expression profile and function. DDR1 is predominantly expressed in epithelial cells, while DDR2 is mainly expressed in mesenchymal cells.[6] DDR1 and DDR2 play pivotal roles in regulating collagen production and degradation and are abnormally expressed in many malignancies, correlating with tumor progression and poor patient prognosis. The interaction between collagen and DDR2 promotes the repolarization of macrophages from the M1 phenotype to the

M2 phenotype and prevents systemic inflammation. Studies have shown that conditional knockout of Ddr2 in myeloid cells results in more severe inflammation in collagen antibody-induced arthritis (CAIA) and high-fat diet (HFD)-induced obesity.[90] Neuropilin-1 myeloid cell-specific conditional knockout (Nrp1 myeloid cKO) mice exhibited exacerbated insulin resistance and enhanced systemic inflammation. Nrp1 regulates the NF-κB signaling pathway, thereby enhancing the priming of Nlrp3 and promoting the assembly of the Nlrp3-ASC inflammasome. HFD leads to a reduction of Nrp1 in macrophages, exacerbating insulin resistance by promoting the priming and activation of the Nlrp3 inflammasome.[91]

In summary, DDRs signaling contributes to the differentiation of macrophages in the tissue microenvironment, suggesting that targeted intervention of DDRs signaling pathways in macrophages could be used to control disease progression. By comparing the mechanisms of action and expression profiles of DDR1 and DDR2, we can gain a deeper understanding of their distinct roles in macrophage physiology, which is of great significance for the development of targeted therapeutic strategies against these receptors.

DDRs Participate in the Regulation of Diseases Through Macrophages

Discoidin Domain Receptors (DDRs) are pivotal factors in regulating macrophage functions, particularly in cell adhesion, migration, and secretion.[7] In diseases such as inflammation, fibrosis, or cancer, the expression levels of DDRs in macrophages are significantly elevated, and DDRs influence the infiltration and secretion of macrophages in inflammatory or tumor microenvironments, participating in disease progression. DDR1 and DDR2, two members of the DDRs family, play roles in various immune cells by specifically binding to collagen and activating downstream signaling pathways.[42] DDR1 and DDR2 are crucial in modulating the inflammatory response and polarization state of macrophages.

The positive roles of DDRs include promoting the differentiation and function of macrophages. They participate in the adhesion, migration, and secretion of immune cells through signaling pathways such as NF-κB, p38 MAPK, JNK, and ERK, thereby regulating the occurrence and development of various diseases, including inflammation, fibrosis, and cancer. For instance, the activation of DDR1 can significantly promote the production of interleukin-8 (IL-8), macrophage inflammatory protein-1α (MIP-1α), and monocyte chemotactic protein-1 (MCP-1) by macrophages during inflammatory responses.[53,83,84] The activation of DDR2, on the other hand, promotes the production of cytokines such as IL-12, tumor necrosis factor-α (TNF-α), and interferon-γ (INF-γ) by human dendritic cells, playing a significant role in inflammatory diseases.[90,92] However, DDRs also have their negative aspects. In the tumor microenvironment, the activation of DDRs may promote the M2 polarization of tumor-associated macrophages (TAMs), which is associated with tumor invasion and metastasis.[93] M2-polarized TAMs can promote angiogenesis, providing sufficient nutrients and oxygen for the rapid growth of tumors, and facilitate the migration of cancer cells from primary tumor tissues by secreting matrix metalloproteinases (MMPs) and cathepsins.[94] Additionally, the activation of DDRs may exacerbate inflammation in idiopathic pulmonary fibrosis (IPF) by regulating NLRP3 inflammasomes and macrophage responses.[95]

In summary, DDRs and diseases interactively regulate each other through macrophages, and their expression and activity in macrophages have a significant impact on disease progression. Therefore, it is necessary to study DDRs in macrophage-related/mediated diseases, as they not only participate in various biological processes of macrophages but may also serve as potential targets for the treatment of inflammation, fibrosis, and cancer. Majo S and Auguste P also discussed the dual roles of DDRs in tumor growth and metastasis development in their research,[96] further emphasizing the importance of conducting in-depth studies on DDRs.

DDR1 is Involved in the Regulation of Disease (Figure 2)

Atherosclerosis

Atherosclerosis is a fibroinflammatory disease of the arterial wall characterized by the accumulation of lipids, inflammatory cells, smooth muscle cells (SMCs), and extracellular matrix within the artery wall.[97] Studies have shown that DDR1 is a critical regulator in the formation of atherosclerosis.[98] DDR1 expressed on macrophages plays an independent role in promoting the development of atherosclerotic plaques by modulating macrophage infiltration and accumulation within the plaques.[85] Compared to mice lacking only the LDL receptor ($Ddr1^{+/+}$; $Ldlr^{-/-}$), mice lacking both DDR1 and LDLR ($Ddr1^{-/-}$; $Ldlr^{-/-}$) developed smaller atherosclerotic plaques with substantial changes in plaque composition,

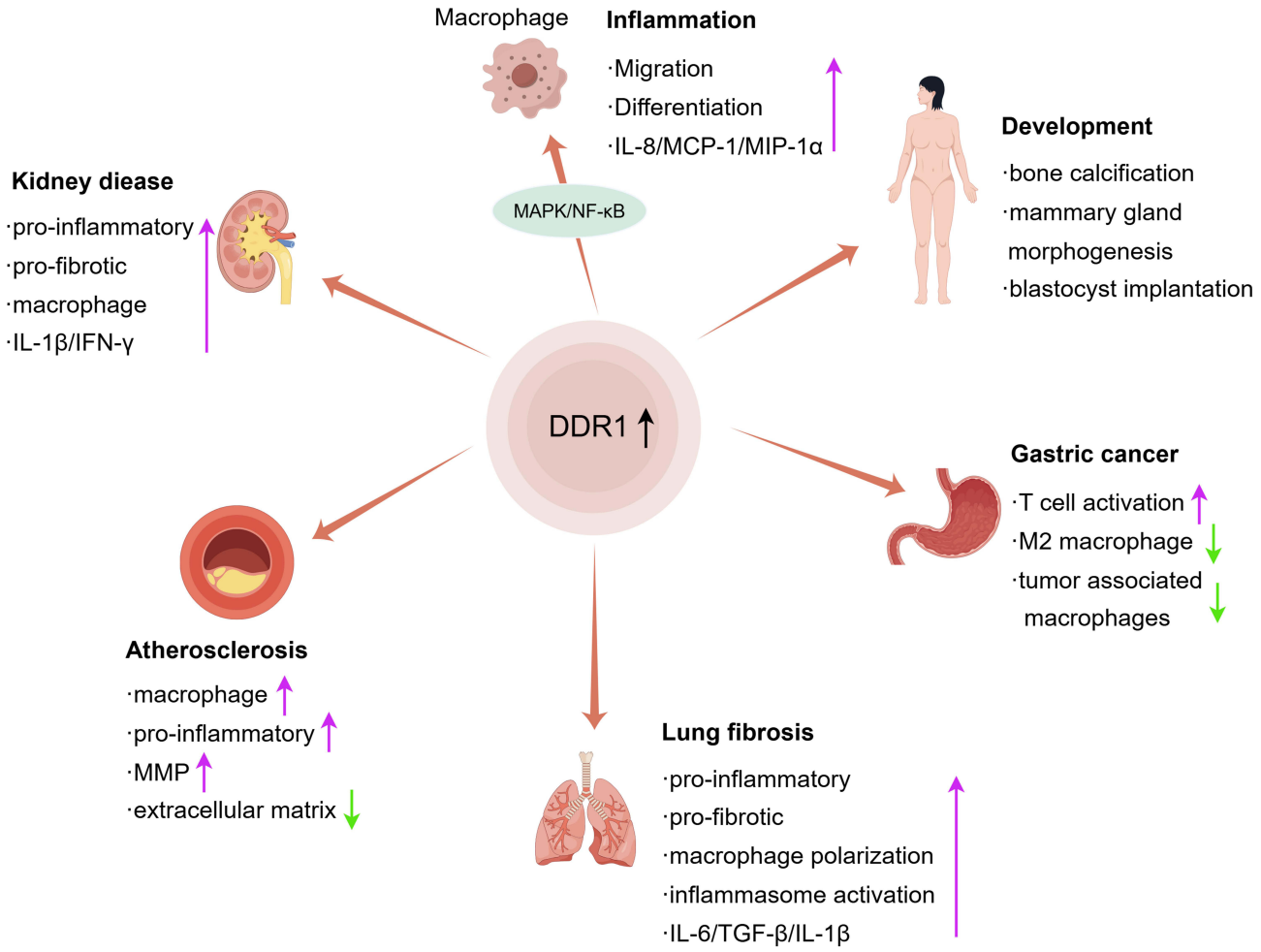

Figure 2 DDR1 expression and/or activation play a role in physiological (eg developmental) and pathological (eg inflammation, fibrosis, cancer) conditions by controlling key cellular processes, including macrophage recruitment, cytokine secretion, protease production, cell migration and matrix production.
Abbreviations: DDR1, discoidin domain receptor 1; IL-8, interleukin-8; IL-6, interleukin-6; IL-1β, interleukin-1β; MCP-1, monocyte chemoattractant protein-1; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; MIP-1α, macrophage inflammatory protein-1α; TGF-β, transforming growth factor-β; IFN-γ, Interferon γ.

including an early increase in extracellular matrix content and a reduction in macrophage accumulation. Additionally, the mRNA expression of monocyte chemotactic protein-1 and vascular cell adhesion molecule-1 was decreased in vivo, and Ddr1$^{-/-}$; Ldlr$^{-/-}$ macrophages exhibited impaired matrix metalloproteinase expression in vitro.[98] DDR1 also mediates SMC-induced calcification of atherosclerotic plaques, which is a long-term complication of atherosclerosis.[99] Studies have demonstrated that DDR1 expressed on bone marrow-derived macrophages promotes the accumulation and invasion of macrophages in the arterial intima through interaction with the endothelial basement membrane rich in type IV collagen and contributes to disease progression at multiple stages.[85] Deletion of DDR1 in bone marrow-derived cells of Ldlr$^{-/-}$ mice results in decreased MMP expression, preventing macrophages from penetrating the endothelial basement membrane, which leads to reduced plaque macrophage infiltration and a significant reduction in lesion size, thereby decreasing intimal inflammation and alleviating atherosclerosis.[85] However, systemic knockout of the DDR1 gene in Ldlr$^{-/-}$ mice enhances matrix accumulation in atherosclerotic plaques. This enhanced matrix accumulation results in a decreased proportion of the plaque area occupied by cells, which is associated with a shift in lesion cellular composition. Compared to bone marrow-derived macrophages, the number of smooth muscle cells derived from the vascular wall increases.[100] Furthermore, DDR1-dependent macrophage accumulation is crucial for the formation of fatty streaks.[85] Research has found that DDR2 is also expressed in human atherosclerotic plaques, primarily distributed around the fatty core, and is involved in the expression and activity of MMP-2.[101] This discovery expands our understanding of the role

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of the DDRs family in atherosclerosis, suggesting that DDR2 may influence plaque stability and progression by regulating MMP-2. Overall, these studies indicate that DDRs contribute to atherosclerosis by increasing the number of macrophages and reducing extracellular matrix deposition. Therefore, targeting DDRs may be beneficial for the treatment of atherosclerosis.

However, these studies have certain limitations. Firstly, animal models, while providing valuable insights, may not fully mimic the complexity of human atherosclerosis. Secondly, studies often focus on specific molecular and cellular pathways, potentially overlooking other factors that may influence the progression of atherosclerosis. Additionally, many studies rely on in vitro experiments and short-term animal models, which may not accurately predict long-term disease progression and treatment outcomes. Finally, the number of human sample studies is limited, and more clinical data are needed to validate the results observed in animal models and determine the specific roles of DDR1 and DDR2 in human atherosclerosis.

Lung Inflammation and Fibrosis

Studies have shown that DDR1-deficient mice are resistant to bleomycin-induced lung injury.[102] Compared to wild-type mice, DDR1-deficient mice exhibited reduced numbers of macrophages and lymphocytes in tissues and bronchoalveolar lavage (BAL) fluid, as well as decreased IL-6 concentrations in BAL supernatants, indicating reduced inflammation in DDR1-deficient mice. Collagen 1 can directly activate DDR1 in macrophages, mediating macrophage polarization and inflammasome activation.[95] Furthermore, the p38 MAPK signaling pathway was not activated by bleomycin in DDR1-deficient mice, whereas it was activated in wild-type mice, revealing the crucial role of DDR1 in lung inflammatory responses. Stimulation of alveolar macrophages expressing DDR1 from the BAL of patients with idiopathic pulmonary fibrosis (IPF) with a DDR1 agonistic antibody led to p38 phosphorylation.[103] Additionally, nuclear factor-κB (NF-κB) has been found to be involved in bleomycin-induced lung injury and is also a target for DDR1 activation.[53,104] Similarly, studies have shown that activated DDR1 in macrophages regulates NLRP3 inflammasome activation through the NF-κB signaling pathway, thereby promoting IL-1β secretion and the progression of IPF.[95] A high proportion of lavage cells expressing DDR1 is important for the effective tissue infiltration of macrophages through collagen-rich basement membranes.[105] However, the lack of inflammatory responses in these animals may be due to lower levels of recruited immune cells, as both $CD3^+$ and $F4/80^+$ reactive cell numbers in the BAL and lung parenchyma were significantly reduced in DDR1-deficient mice compared to wild-type mice.

DDR1-deficient mice are also resistant to bleomycin-induced lung fibrosis. Apoptosis and myofibroblast expansion are key factors associated with lung fibrosis. CCL2 upregulation was detected in fibrotic tissue, recruiting macrophages to exert pro-inflammatory and pro-fibrotic functions.[95] DDR1 is surface-expressed in BAL cells and its expression increases non-collagenous matrix molecule Tenascin-C through bleomycin injury, which may also be important in the development of parenchymal lung fibrosis.[105] In the absence of DDR1, damaged epithelial cells fail to secrete cytokines such as TGF-β, a key molecule for myofibroblast differentiation and survival.[106] Therefore, tissue repair in DDR1-deficient mice is associated with limited myofibroblast expansion, reducing fibrosis and allowing the epithelial compartment to heal and restore normal lung function. Recent studies support this hypothesis, showing that blocking integrin-mediated adhesion responses with protein kinase inhibitors can prevent bleomycin-induced myofibroblast accumulation and fibrosis but not inflammation.[107] Studies by Vogel et al also indicate a protective effect of DDR1 deficiency in lung fibrosis.[108] Elevated DDR1 levels were found in ciliated epithelial cells, alveolar macrophages, and smooth muscle cells in lung samples from patients with lymphangioleiomyomatosis (LAM). LAM patients also exhibited high MMP-2 and MMP-9 activities and elevated MMP-1 levels.[109] Similar to DDR1, DDR2 also plays a crucial role in lung fibrosis. The study by Ling S et al provides evidence for DDR2 in regulating fibroblast activity. DDR2 is a key regulator in the fibrosis process, and its inhibition can reduce fibroblast activation and collagen deposition, thereby alleviating lung fibrosis.[110] Both kinase-dependent and kinase-independent functions of DDR2 have important effects on fibroblast behavior. Studies by Zhao H et al also show that DDR2 can synergize with transforming growth factor (TGF)-β and fibrous collagen to promote the transition of lung fibroblasts to myofibroblasts and the expression of vascular endothelial growth factor (VEGF).[111] Knockout of DDR2 can inhibit the progression of lung fibrosis. These findings not only reveal new mechanisms of DDR2 in the development of lung fibrosis but also provide potential targets for the treatment of IPF.

The role of DDRs in lung inflammation and fibrosis cannot be overlooked. Studies of DDR-deficient mice have shown that DDRs play crucial roles in inflammatory responses and fibrosis development. These findings provide potential targets for the development of new therapeutic strategies. However, we must also recognize the limitations of these studies and further explore the role of DDRs in human lung diseases in future research.

Kidney Disease

In models of glomerulonephritis, the deficiency of DDR1 reduces the number of macrophages within the renal cortex, subsequently decreasing the secretion of inflammatory mediators and effectively mitigating glomerular injury and fibrinogen deposition.[112] As a key pro-inflammatory cytokine, IL-1β exhibits a positive feedback mechanism with DDR1.[113] Studies have revealed that in the unilateral ureteral obstruction (UUO) mouse model, DDR1 gene expression in interstitial infiltrating and activated macrophages plays a pivotal role in the inflammatory response and subsequent progression of renal diseases.[88,114–117] Notably, in the absence of differential CCR2 expression in macrophages, DDR1-deficient mice exhibited similar leukocyte rolling and adhesion after MCP-1 injection compared to wild-type (WT) mice.[88] Additionally, macrophages isolated from DDR1-deficient mice showed a significantly reduced invasion index when migrating through a Boyden chamber coated with type IV collagen.[85] Concurrently, DDR1$^{-/-}$ mice demonstrated defects in macrophage recruitment and migration capabilities.[88] Of particular interest, DDR1-deficient mice showed a marked reduction in IFN-γ expression in obstructed kidneys, a cytokine closely associated with macrophage cytotoxic activity. In T cells, the expression of IFN-γ depends on p38 MAPK, a key pathway for DDR1 activation.[53,118,119] In the process of hypertension-induced renal fibrosis, DDR1-deficient mice exhibited decreased lymphocyte and macrophage infiltration, as well as reduced expression of type I and IV collagen.[120] The absence of DDR1 decreased the number of pro-inflammatory cells (such as F4/80^{+} and CD3^{+}positive cells) and profibrotic cells by affecting TGFβ, CTGF, NF-κB, and IL-6 signaling, also reducing extracellular matrix deposition.[64] DDR1, as a collagen-activated receptor tyrosine kinase, is closely related to renal fibrosis,[121] whereas periostin, a matricellular protein, regulates cell-matrix interactions and promotes inflammation and fibrosis.[122] In nephropathies, the upregulation of DDR1 and periostin may play crucial roles in renal injury and fibrosis progression.

In the UUO model, DDR1 expression significantly increased in the injured kidney, particularly in macrophages, suggesting DDR1's involvement in macrophage activation. DDR1 knockout (KO) mice exhibited reduced macrophage and lymphocyte infiltration, along with significantly decreased expression of pro-inflammatory cytokines such as interferon-γ, MCP-1, interleukin-23, and TNF-α, indicating DDR1's crucial role in macrophage recruitment and infiltration.[88] Furthermore, the absence of DDR1 impaired the migratory capacity of macrophages in response to MCP-1, potentially affecting the regulation of renal inflammatory responses. Although the specific impact of DDR1 on macrophage M1/M2 polarization states remains unclear, inhibiting DDR1 expression through antisense oligonucleotides reduced inflammatory cell infiltration and pro-inflammatory cytokine expression, potentially involving macrophage regulatory mechanisms. Consistent with reduced inflammation, DDR1-deficient mice exhibited decreased Col3a1 and TGF-β mRNA expression, accompanied by reduced fibrous collagen accumulation.[123] During UUO-induced renal interstitial fibrosis, DDR2 expression was also significantly upregulated. Compared to WT mice, DDR2 KO mice exhibited less fibrosis.[124] Additionally, mice treated with the calcium channel blocker cilnidipine showed reduced renal interstitial fibrosis at 14 days post-surgery.[124] These results suggest that DDR2 may play a significant role in the development of renal interstitial fibrosis, and cilnidipine can improve renal interstitial fibrosis in mice by regulating DDR2 expression, providing a theoretical basis for its potential use as a therapeutic agent.[125]

In the nephrotoxic serum-induced glomerulonephritis model, DDR1 activation led to a significant increase in DDR1 mRNA expression in WT mice, accompanied by symptoms such as hypertension, weight gain (due to ascites), proteinuria, uremia, crescent formation within glomeruli, fibrinogen deposition, and tubular dilation.[112] In contrast, DDR1 KO mice showed significant improvements in these parameters, including increased survival rates, reduced macrophage infiltration, decreased mRNA expression of pro-inflammatory mediators, and reduced fibrous collagen deposition. Furthermore, prophylactic administration of antisense oligodeoxynucleotides targeting DDR1 (ODN AS) successfully reduced DDR1 expression and alleviated symptoms such as proteinuria, uremia, and weight gain, while preserving podocyte structure. In human glomerulonephritis, DDR1 expression was upregulated, particularly in injured

podocytes, bridging cells, and parietal epithelial cells forming cellular crescents. Using highly selective small molecule inhibitors in the nephrotoxic serum (NTS)-induced glomerulonephritis model, researchers found that pharmacological inhibition of DDR1 improved renal function and histological parameters.[112] Additionally, in the NEP25 mouse model, DDR1 inhibitors significantly reduced glomerular sclerosis and inflammation.[126] These results emphasize DDR1's important role in glomerulonephritis and support DDR1 inhibition as a potential therapeutic strategy.[125]

In studies of Alport syndrome, a genetic disorder of type IV collagen, the role of DDR1 was thoroughly investigated. By crossing Col4a3 KO mice with DDR1 KO mice, researchers found that double KO mice exhibited a slower progression of renal failure, a longer lifespan, and reduced proteinuria and uremia symptoms compared to mice with only Col4a3 KO.[64] Additionally, double KO mice showed decreased glomerular, periglomerular, and tubular interstitial fibrosis, accompanied by reduced protein expression of connective tissue growth factor and transforming growth factor β (TGF-β). At early disease stages, double KO mice had reduced T lymphocyte and macrophage infiltration, although this reduction did not persist over time. In the Alport syndrome mouse model, DDR1 activation was associated with increased collagen I (Col I) production, leading to podocyte lipotoxic injury. Experiments showed that DDR1 activation increased intracellular lipid droplet accumulation and free fatty acid (FFA) uptake in podocytes, with no significant change in cholesterol content.[64] Furthermore, the study found an interaction between DDR1 and CD36, and the drug ezetimibe was able to disrupt this interaction and reduce lipotoxicity, thereby protecting renal function in the Alport syndrome mouse model.[127] These results indicate that DDR1 deficiency significantly protects mice from renal injury caused by Alport syndrome, revealing DDR1's importance as a potential therapeutic target in slowing disease progression.[125]

However, studies in the autosomal dominant polycystic kidney disease (ADPKD) mouse model found that DDR1 expression was upregulated, but knocking out DDR1 through CRISPR/Cas9 gene editing technology did not observe slowed cyst growth or renal function protection, demonstrating that DDR1 does not play a role in the pathogenesis of polycystic kidney disease and is not a potential therapeutic target.[128]

In summary, these findings not only reveal the crucial role of DDR1 in macrophage behavior but also elucidate its potential impact in the development of renal diseases, providing a solid scientific basis for future therapeutic strategies targeting DDR1.

Cancer

Increasing amounts of research evidence indicate that the expression of DDR1 (Discoidin Domain Receptor 1) is significantly upregulated in various cancers, including gastric cancer, breast cancer, ovarian cancer, and lung cancer.[129–131] This upregulated expression is closely related to tumor aggressiveness, metastatic ability, and modulation of the immune microenvironment.[93,132,133] DDR1 influences the immune characteristics of the tumor microenvironment by regulating the polarization state of tumor-associated macrophages (TAMs). Specifically, the DDR1 signaling pathway can promote the polarization of TAMs towards the M2 phenotype, which typically has immunosuppressive functions and can facilitate tumor growth and immune evasion.[72] Additionally, DDR1 indirectly regulates the composition and function of immune cells in the tumor microenvironment by influencing the DNA damage repair capacity of tumor cells. For instance, DDR1 deficiency may lead to increased expression of immune checkpoint proteins (such as PD-L1) on the surface of tumor cells, thereby inhibiting T-cell activity.[134] DDR1 also affects the infiltration and function of T-cells, dendritic cells, and natural killer cells by modulating the levels of cytokines and chemokines in the tumor microenvironment.[72] These interactions collectively shape the immunosuppressive or immunostimulatory state of the tumor microenvironment, exerting a significant impact on tumor progression and treatment response.

Digestive System Cancer

Gastric cancer is one of the common malignancies worldwide.[135] Currently, immune checkpoint inhibitors have become a first-line treatment for advanced gastric cancer. It is known that promoting intratumoral T-cell infiltration can significantly enhance the efficacy of PD-1 antibodies.[136,137] Sun et al demonstrated that the extracellular domain (ECD) of DDR1 is associated with tumor immune infiltration.[72] Wang et al showed that DDR1 expression is upregulated in gastric cancer and significantly correlated with poor prognosis.[138] Furthermore, studies have found that high DDR1

expression is significantly negatively correlated with the infiltration degree of various tumor-infiltrating immune cells (TIICs) in gastric adenocarcinoma, especially macrophages, $CD8^+$ T-cells, and dendritic cells. Macrophage infiltration is significantly associated with survival in gastric cancer patients. Interestingly, there is a significant correlation between DDR1 levels and T-cell exhaustion. Additionally, DDR1 is significantly negatively correlated with monocytes, tumor-associated macrophages (TAMs), and M2 macrophages, but not with M1 macrophages.[138] Therefore, DDR1 may be involved in regulating macrophage polarization and T-cell activation in gastric cancer, thereby affecting immune infiltration. Overall, DDR1 is associated with the invasion, metastasis, and immune infiltration of gastric cancer. Inhibiting DDR1 may potentially mitigate the aggressive and metastatic nature of advanced gastric cancer. The study found that DDR1 interacts with collagen I to activate the DDR1/PKCθ/SYK/NF-κB signaling pathway, inducing tumor-associated neutrophils (TANs) in pancreatic ductal adenocarcinoma (PDAC) to produce neutrophil extracellular traps (NETs), thereby promoting cancer cell invasion and metastasis.[139] The research indicates that DDR1 is a key driver in PDAC, promoting disease progression by modulating the tumor microenvironment, and its inhibition may be a potential strategy for treating PDAC. Additionally, it was discovered that the expression of DDR2 is significantly upregulated in colorectal cancer (CRC) tissues and is associated with poor patient prognosis. DDR2 promotes the invasive and metastatic capacity of CRC cells by activating the AKT/GSK-3β/Slug signaling pathway, inducing epithelial-mesenchymal transition (EMT).[140] Therefore, DDR2 may serve as an effective therapeutic target for local advanced and metastatic CRC.

Breast Cancer

In breast cancer, upregulated DDR1 expression is associated with tumor aggressiveness and poor prognosis.[141] Studies have shown that higher DDR1 protein expression is related to breast cancer, promoting proliferation by inhibiting antitumor immunity.[73] In the triple-negative breast cancer subtype (TNBC, or basal breast cancer), dysregulation of DDR1 and DDR2 is associated with increased aggressiveness and poor prognosis.[142] In TNBC, collagen IV activates DDR1, inducing increased expression of the cell surface CD9 and secretion of metalloproteinases MMP-2 and MMP-9, thereby facilitating migration through the extracellular matrix.[143,144] Similarly, in TNBC, co-expression of DDR1 and protein phosphatase 1 regulatory subunit 1B (PPP1R1B, also known as DARPP-32) inhibits tumor cell migration.[145] Inhibiting DDR1 expression can significantly enhance the chemosensitivity of breast cancer cells to genotoxic treatments.[146] Interestingly, DDR1 signaling has also been shown to enhance the chemoresistance of breast cancer cells through NFκB-mediated cyclooxygenase-2 (COX-2) expression, and downregulation of DDR1 significantly enhances drug sensitivity.[147] In studies correlating DDR1 with clinical breast cancer parameters, DDR1 protein expression was not significantly correlated with disease-free survival (DFS) or overall survival (OS).[148] However, in postmenopausal breast cancer patients, a specific DDR1 kinase domain mutation, R776W, is closely associated with poor prognosis.[149] The H-Ras pathway can induce mesenchymal-like phenotypic changes in breast epithelial cells, and H-Ras inhibits DDR1 expression through ZEB1 (a transcriptional repressor of DDR1). This H-Ras/ZEB1/DDR1 network interaction promotes tumor progression.[150] In breast cancer, DDR1 may affect the tumor immune microenvironment and progression by regulating the polarization state of macrophages.

Ovarian Cancer

Ovarian cancer is a highly aggressive gynecological tumor, and the role of DDR1 in its development is increasingly being recognized. Studies have shown that DDR1 protein expression is higher in serous ovarian cancer compared to normal ovarian epithelial tissue, and DDR1 is mainly expressed in epithelial ovarian cancer (EOC) cells.[151] In EOC, the protein expression of DDR1, Claudin-3 (CLDN3), and epithelial cell adhesion molecule (Ep-CAM) is significantly upregulated, indicating that this upregulation is an early driving event in EOC.[152] Additionally, studies have shown that DDR1 overexpression is closely related to patient disease-free survival (DFS), with significantly higher DDR1 protein expression observed in high-grade and advanced tumors.[129] In ovarian cancer tissues, DDR1 expression is negatively correlated with the expression of miR-199a-3p, which inhibits DDR1 overexpression and significantly reduces the migration, invasiveness, and tumorigenic ability of ovarian cancer cells.[153] In ovarian cancer, DDR1 may promote immune evasion and progression of tumors by promoting the polarization of tumor-associated macrophages (TAMs)

towards the M2 phenotype. Furthermore, TAMs are known to be recruited from circulating monocytes by various chemokines, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and monocyte chemoattractant protein-1 (MCP-1) (CCL2).[154] Targeting NF-κB is an attractive target in cancer cells, but in the tumor microenvironment of ovarian cancer, inhibiting NF-κB may unexpectedly promote the recruitment of tumor-associated macrophages (TAMs) and the formation of an immunosuppressive microenvironment, leading to poor treatment outcomes.[155] For effective treatment of ovarian cancer, it is necessary to more precisely target NF-κB in tumor cells rather than the entire tumor microenvironment to avoid activating compensatory mechanisms of stem cells, thereby increasing the number of TAMs.[154] In metabolic dysfunction-associated fatty liver disease (MAFLD), GATA3 inhibits the expression of PPARγ1 by binding to GATA binding protein 2 (GATA2) on the PPARγ1 promoter, leading to the activation of NF-κBp65 and Kupffer cells with an M1 phenotype, contributing to the development of MAFLD.[156]

Lung Cancer

Research on DDR1 in lung cancer has gradually deepened, revealing its multiple roles in tumorigenesis and development. Firstly, DDR1 expression levels are typically high in non-small cell lung cancer (NSCLC), and its overexpression is closely related to tumor aggressiveness, metastatic capacity, and poor prognosis.[157] DDR1 promotes the proliferation and survival of lung cancer cells by activating downstream signaling pathways such as PI3K/AKT and RAS/RAF/MAPK, while enhancing cell migration and invasion.[158] Additionally, DDR1 is involved in the regulation of the tumor microenvironment, promoting the activation of cancer-associated fibroblasts (CAFs). CAFs further promote the growth and metastasis of tumor cells by secreting various cytokines and growth factors. Macrophages are important immune cells in the tumor microenvironment, and DDR1 can influence their polarization state. Studies have shown that DDR1 interacts with specific receptors on the surface of macrophages, inducing their polarization towards the M2 phenotype, ie, tumor-associated macrophages (TAMs).[72] M2 macrophages have the ability to promote tumor growth and inhibit antitumor immune responses, secreting various immunosuppressive factors such as IL-10 and TGF-β, providing an immune-evasive microenvironment for tumor cells.[159] This process further exacerbates the progression of lung cancer. The study found that the expression of DDR1b and DDR2 significantly accelerates tumor growth in the presence of collagen I, but not in the absence of DDR induction. Additionally, the expression of DDR1b can significantly reduce the lung colonization ability of HT1080 cells, while DDR2 does not have this inhibitory effect.[160] These findings reveal the divergent roles of DDRs in tumor growth and metastasis and highlight the critical role of collagen in supporting tumor growth.

Despite the evidence provided by the aforementioned studies on the role of DDR1 in different types of cancer, these studies still have some limitations. Firstly, most studies rely on retrospective analyses and in vitro experiments, lacking validation from prospective clinical trials and in vivo models. Secondly, the specific mechanisms of DDR1 in the tumor microenvironment have not been fully elucidated, requiring more research to explore the detailed molecular mechanisms of its interaction with tumor cells and immune cells. Furthermore, the role of DDR1 may be heterogeneous across different cancer types, necessitating in-depth studies specific to each cancer type. Finally, the complex interaction between DDR1 expression and the tumor immune microenvironment has not been fully understood, limiting our comprehensive understanding of DDR1's role in tumor immune evasion.

Given the pivotal role of DDR1 in various cancers, therapeutic strategies targeting DDR1 exhibit immense potential. Small-molecule inhibitors and antibodies against DDR1 are under development and have demonstrated therapeutic efficacy in several cancer models. These therapeutic strategies may exert their effects by inhibiting tumor cell proliferation, invasion, and metastasis, as well as modulating immune responses within the tumor microenvironment. However, the clinical application of DDR1-targeted therapeutic strategies still faces challenges, including issues related to drug specificity, side effects, and drug resistance. Future research is required to further optimize these therapeutic strategies and validate their safety and efficacy in clinical trials. Additionally, there is a need to explore combination therapeutic strategies targeting DDR1 along with other therapeutic targets to enhance treatment efficacy and reduce the occurrence of drug resistance.

DDR2 is Involved in the Regulation of Disease (Figure 3)

The role of DDR2 in various diseases has gradually garnered attention, exhibiting complex functionalities in macrophages, osteoclasts, breast cancer cells, and hepatic stellate cells (HSCs), among others. Studies have reported that DDR2 transgenic mice exhibit a significant decrease in body weight.[161] Conditional knockout mice with adipocyte-specific DDR2 deletion display a leaner phenotype when challenged with a high-fat diet (HFD).[162] Conversely, mice with conditional knockout of DDR2 in macrophages exhibit obesity, accompanied by more severe inflammatory responses and metabolic disturbances,[90] suggesting that DDR2 may play a role in inhibiting inflammation and regulating metabolism by promoting the polarization of macrophages towards an anti-inflammatory M2 phenotype. However, DDR2-deficient macrophages are more sensitive to the M1 phenotype in rheumatoid arthritis and desensitized to M2 inducers, indicating that the effects of DDR2 on macrophage polarization differ under different disease states. The specific regulatory mechanisms and roles of DDR2 in disease progression require further investigation. Additionally, studies have found that mice with DDR2 deficiency in bone marrow cells (cKO) exhibit more severe bone destruction and loss in collagen-induced arthritis (CAIA).[90] The number and activity of osteoclasts are significantly increased in cKO mice. Depletion of DDR2 in osteoclast precursor macrophages stimulates osteoclast formation.[163] Furthermore, inflammatory M1 macrophages release pro-inflammatory cytokines that stimulate osteoclasts, leading to their further activation.[164] DDR2 inhibits osteoclastogenesis.

Breast cancer (BC) is the most common malignancy in women.[165,166] Recent studies have revealed the role of DDR2 in BC progression, particularly its ability to stimulate collagen-dependent protease secretion by tumor cells in post-partum-related cancers, activating their migration and invasion potential, and triggering metastasis.[167–170] Toy et al

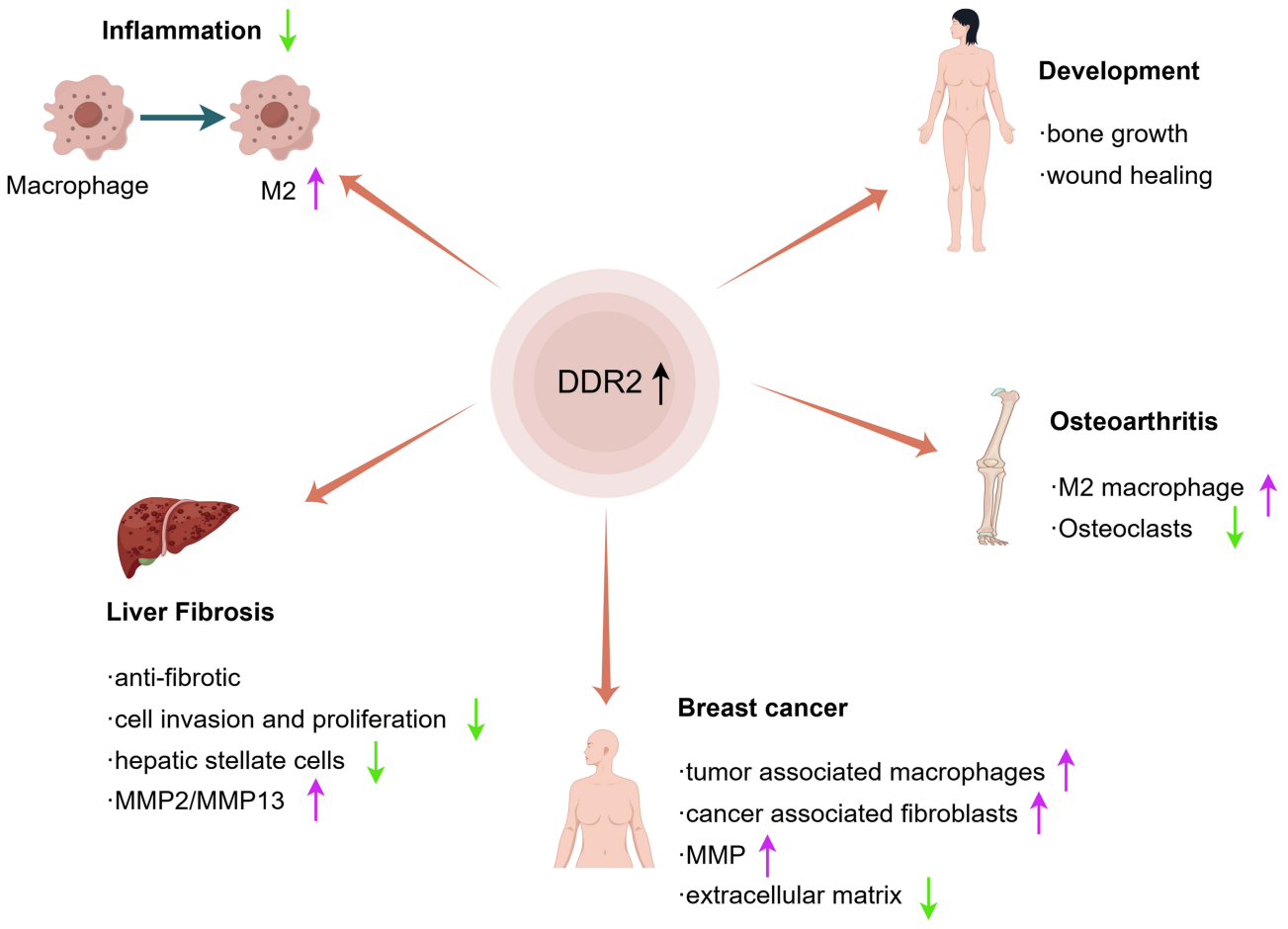

Figure 3 DDR2 expression and/or activation play a role in physiological (eg developmental) and pathological (eg inflammation, fibrosis, cancer) conditions by controlling key cellular processes, including macrophage recruitment, protease production, cell proliferation and matrix production.
Abbreviations: DDR2, discoidin domain receptor 2; MMP, matrix metalloproteinase.

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described a significant correlation between high DDR2 protein levels and poor prognosis in patients with triple-negative BC.[142] DDR2 is also involved in processes within the tumor microenvironment (TME), contributing to disease progression. In this regard, Corsa et al proposed that DDR2 expressed by BC cells determines the activation of cancer-associated fibroblasts (CAFs) to enhance tumor invasion and metastasis.[171] Similarly, tumor DDR2 regulates collagen signaling in CAFs during BC progression.[172] Romayor et al suggested that DDR2 overexpression is associated with higher infiltration of CAFs and tumor-associated macrophages (TAMs) in breast tumor tissue.[173] Regarding the latter, TAMs are highly relevant stromal populations in extracellular matrix (ECM) remodeling and carcinogenesis, as they secrete various cytokines and chemokines, creating a favorable microenvironment for tumor growth and promoting cancer cell proliferation, migration, and chemotherapy resistance[174] DDR2 is associated with the secretion of metalloproteinases (MMPs) by tumor cells,[175] leading to ECM degradation and promoting stromal cell infiltration, as well as cancer cell migration and invasion.[176] Therefore, the regulation of MMP production by BC cells through DDR2 can promote the recruitment of CAFs and TAMs. Taken together, these results suggest that DDR2 may play a crucial role in the regulation of the TME and may represent a potential target for anti-tumor therapy in early and metastatic BC. However, there are still many knowledge gaps regarding the specific mechanisms of DDR2 in different stages of BC, its interactions with other signaling pathways, and its potential and challenges as a therapeutic target, which require in-depth exploration.

Hepatic fibrosis is a complex inflammatory and fibrotic process caused by chronic liver injury and is a result of HSC activation.[177,178] In acute liver injury, HSCs interact with fibrous collagen through DDR2, leading to exacerbated fibrosis.[179] In contrast to the changes observed in acute injury, after long-term administration of CCl4, DDR2-/- livers exhibit increased collagen deposition, gelatinolytic activity, and HSC density, resulting in enhanced liver fibrosis.[180] Macrophages maintain the inflammatory phase by releasing a large amount of pro-inflammatory cytokines, including TNF-α, IL-6, and activate HSCs.[181] Although liver macrophages do not express DDR2, the changes in the liver microenvironment resulting from chronic DDR2 signaling in activated HSCs affect the profibrotic activity of macrophages. For example, HSCs express DDR2-dependent cytokines, MCP-1, and osteopontin, regulating macrophage recruitment and the release of MMPs[182] and TGF-β[183] by macrophages. In the absence of DDR2 in HSCs, the enhancement of fibrosis after chronic liver injury is due to the disruption of the balance between activation factors secreted by activated macrophages and HSCs, thereby enhancing the recruitment of activated HSCs to fibrotic scars and the secretion of macrophage anti-migration factors by activated HSCs recruited to scars.[180] In summary, these findings indicate that DDR2 generally coordinates gene programs and paracrine interactions between HSCs and macrophages, jointly mitigating chronic liver fibrosis.

In conclusion, the mechanisms of DDR2 in various diseases are complex and diverse, with differing functions in different cell types and disease stages. Future research should focus on in-depth analysis of the specific mechanisms of DDR2 in various diseases, revealing its interactions with other signaling pathways, and assessing its potential and challenges as a therapeutic target. This will provide new ideas and strategies for the treatment of related diseases and fill the current knowledge gaps in understanding the role of DDR2 in disease.

Conclusion

This article focuses on the relationship between discoidin domain receptors (DDRs) and macrophages. DDRs are expressed in macrophages and involved in regulating macrophage adhesion, migration, as well as the secretion of cytokines and chemokines. Studies have revealed that p38 mitogen-activated protein kinase (p38MAPK) plays a pivotal role in the secretory processes of macrophages, and interventions targeting p38MAPK exert significant effects on the interaction between DDRs and macrophages. Despite numerous studies reporting on the relationship between DDRs and macrophages, the regulatory role of DDRs in macrophages during disease progression remains incompletely elucidated, necessitating further research to delve deeper into the associated mechanisms. DDRs facilitate the onset and progression of various diseases by modulating macrophages. Therefore, specific inhibition of DDRs holds promise for providing novel strategies in inflammation control, as well as the prevention of fibrosis and cancer. Currently, DDRs have emerged as important potential molecules for exploring targeted therapies for immune-related diseases. With the deepening of research, novel drugs developed targeting DDRs are poised to demonstrate immense value and broad application prospects in disease treatment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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