



Midkine: A Cancer Biomarker Candidate and Innovative Therapeutic Approaches

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ABSTRACT

Midkine (MDK) is a protein that contributes to both physiological and pathological processes. Several studies provide insight into the different roles of MDK in development, tissue repair, neural plasticity, and health and disease processes. This research further examined how MDK contributed to conditions, including neurological diseases, inflammation, and ischaemia. Furthermore, MDK overexpression has been reported in many kinds of cancer and MDK is recognized as a malignancy marker. MDK stimulates pro-tumor activity by regulating a number of signaling pathways, which increase cancer cell proliferation, survival, metastasis, and treatment resistance. However, studies have shown that MDK also functions as a molecule that regulates drug resistance. Several cancer therapy techniques have been suggested to modify MDK function, including antibody-based therapies, oligonucleotides, oncolytic viruses, and small compounds. Further research and experimentation will be required to establish the therapeutic relevance and efficacy of these treatments. This review focuses on the role of MDK in cancer biology, as well as its multiple different roles in health and disease processes.

Keywords: Midkine; MDK; cancer; therapeutic target

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Key Points

- Midkine (MDK) is a protein that functions in both physiological and pathological processes.
- The role of MDK in physiological processes such as development, tissue repair and neuronal plasticity and its association with disorders such as neurodegenerative disease, inflammation and ischaemia have been investigated by many studies.
- MDK overexpression has been reported in many cancer types and identified as a biomarker in malignancy.
- MDK promotes proliferation, survival, metastasis and treatment resistance of cancer cells by activating pro-tumoral processes by activating many signalling pathways.
- MDK induces tumour formation through angiogenesis.
- Research suggests that MDK also functions as a molecule that regulates drug resistance.
- Many approaches to cancer therapy propose to target MDK.
- MDK and the proliferation of cancer cells have been suppressed by various approaches such as antibody-based therapies, oligonucleotides, oncolytic viruses and small molecules.
- However, further studies and experiments are required to determine the therapeutic relevance and efficacy of these therapies.
- This review focuses on the effects of MDK on cancer biology and its numerous roles in health and disease processes.

Introduction

Introduction to Midkine (MDK)

The Midkine (*MDK*) gene, which has a retinoic acid (RA) receptor in its promoter, is a heparin-binding growth factor or cytokine (1). MDK, a 13-kDa cysteine-rich protein, is activated by retinoic acid and generated in large quantities throughout development, especially in the nervous system (2, 3). It is generally overexpressed in adult tissues after injury, disease, and healing (2). *MDK* gene expression in

individuals who are healthy has been observed in a variety of organs, including the gastrointestinal system, kidney, spleen, lungs, and thyroid (4, 5). *MDK* expression in healthy tissues is usually low and many times lower than in malignant tissue (6-10). MDK promotes ligand-dependent receptor activation, leading to a biological response (11, 12). The *MDK* promoter region contains binding sites for Hypoxia-Inducible Factor 1-alpha (HIF-1 α), which, together with the retinoic acid receptor, has been associated with increased *MDK* expression in several cancers (13, 14). MDK was discovered in mouse embryonal

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cancer cells in 1988, and its molecular function is in embryonic development regulation (15, 16). MDK expression in mice increased only during the middle stages of gestation (days 8–11), after which it significantly decreased (15, 16). Only the kidneys in 15-day-old embryos showed significant MDK expression levels (15, 16). In one study, once RA was applied to cells in the early phases of embryonal cancer cell development, MDK mRNA levels increased (15, 16). The MDK family contains two members, MDK itself and pleiotropin (PTN) (16-18). These two proteins have similar receptors and physical attributes, including the ability to bind heparin (18). There are a number of evolutionarily conserved DNA sequences between MDK and PTN (17). Human MDK and PTN have been found to share around 50% sequence identity (17, 19). MDK and PTN have biological activity in processes such as fibrinolysis, anti-apoptosis, mitogenesis, and angiogenesis (18) (Figure 1). These activities suggest that growth factors play a role in cancer development (18). The increased expression of MDK and PTN in human carcinomas supports their function in cancer (18). MDK also plays a role in the pathogenesis of specific inflammatory diseases, including renal failure and vascular restenosis following angioplasty (18).

Midkine-Associated Signaling Pathways

MDK receptors include integrins, neurogenic locus notch homolog protein 2 (Notch2), anaplastic lymphoma kinase, the low-density lipoprotein receptor gene (*LRP*), and receptor type tyrosine protein phosphatase zeta (*PTP-ζ*) (20-24). MDK-binding integrins form $\alpha6\beta1$ and $\alpha4\beta1$ heterodimers (21). Syndecanes, glypican-2, PG-M/versican, and neuroglycan C are a few such protein glycans that interact with MDK (6, 25-28). MDK consists of two domains and three antiparallel β -strands containing heparin-binding sites (3, 29, 30). This structure allows MDK to form molecular complexes with proteoglycans (3, 29, 30). MDK binding to sulfated glycosaminoglycans interacts with a large number of crucial receptors, initiating a variety of signaling pathways (3, 29, 30) (Figure 2). While MDK is involved in critical processes such as development, reproduction, repair, inflammation, innate immunity, blood pressure regulation, neurite outgrowth, and angiogenesis, it also plays an important role in cancer formation and

progression by stimulating cellular activity (1, 3, 25). MDK expression has been shown to be regulated by several kinds of transcription factors (30). The hormone estradiol (E2) has been shown to increase MDK mRNA levels in lung cancer cells (30). The *MDK* gene promoter region contains hypoxia response elements (14, 30). Under hypoxic conditions, HIF-1 α binds to the MDK promoter region, increasing expression (13, 14). This promotes the vascularization of pulmonary arteries, the development of vasculature, and cancer cell survival (14, 30). The promoter region of *MDK* has a functional nuclear factor kappa B (NF- κ B) binding site (30, 31). This leads to MDK overexpression under inflammatory conditions (31). In prostate cancer, tumor necrosis factor- α activates the NF- κ B pathway (Figure 2) (31). The SP1 specificity protein 1 (*SP1*) gene is essential for embryonic development and early postnatal life (32). *SP1* expression has been reported to be more significant in human glioma tissues than in normal tissue, and it interacts with MDK in tumor development and progression (30, 32). Thyroid transcription factor 1 (TTF-1) regulates lung parenchymal growth and gene expression (30, 33). TTF-1 binds to TTF regulatory elements located in the 5' region of the *MDK* promoter (33). TTF-null mice's lungs showed no expression of MDK (33). Various transcription factors may regulate MDK in various tissues (30). MDK could stimulate tumor development by activating TGF- β receptors, Janus kinase/signal transducers and activators of transcription (STAT), and STAT3 (34). Mitogen-activated protein kinase (MAPK) pathways promote epithelial mesenchymal transition (EMT), which regulates cancer development and metastasis (29, 35). MDK induces EMT by interacting with β -catenin through WNT signaling and the estrogen receptor (ER) (13). MDK interactions with the MAPK/phosphoinositide 3 kinase (PI3K)/AKT pathway induce proliferation and angiogenesis (35, 36) (Figure 2). Finally, MDK may inhibit Caspase-3, which decreases apoptosis (36).

Role of Midkine in Inflammation

MDK is a growth factors known to regulate inflammation since it is associated with antibacterial proteins that stimulate the innate immune system (37). MDK expression increases during inflammatory processes, which leads to increased angiogenesis (38). MDK promotes

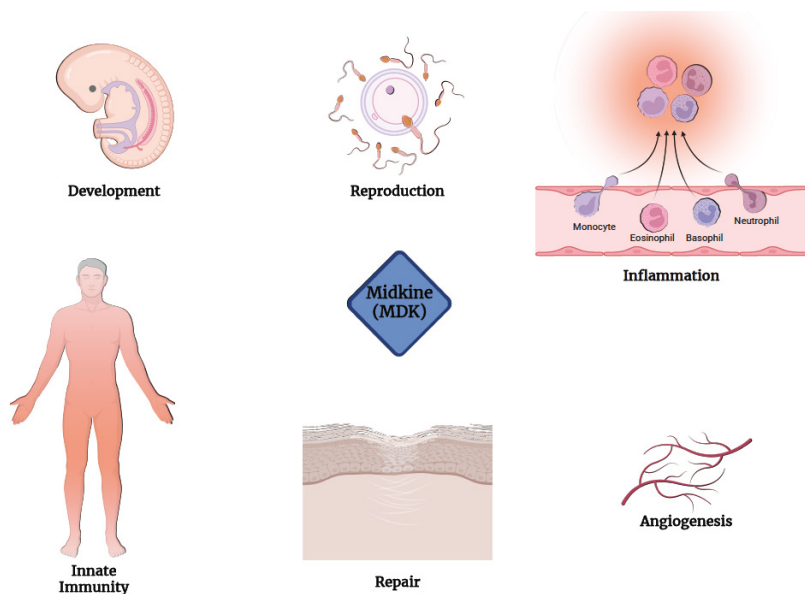


Figure 1. MDK plays a role in essential processes including as development, reproduction, repair, inflammation, innate immunity, and angiogenesis by activating various signaling pathways

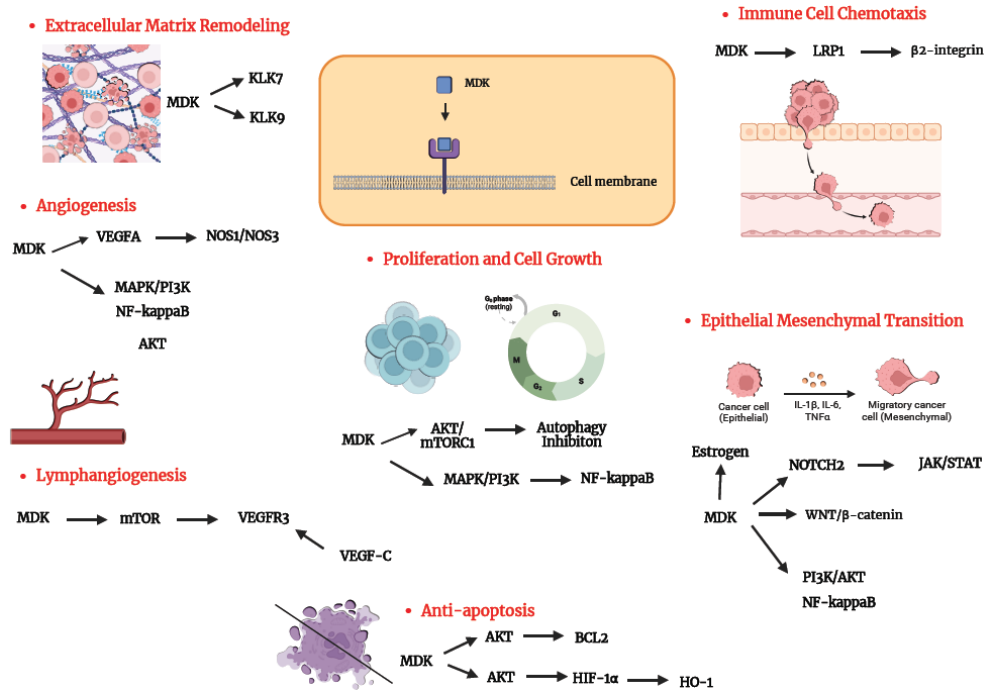


Figure 2. MDK is involved in cancer cell proliferation, survival, ECM remodeling anti-apoptosis, angiogenesis and EMT regulation through many different signalling pathways in tumor development

MDK: Midkine; EMT: Epithelial mesenchymal transition, *Created with Biorender.

neutrophil adhesion during angiogenesis (39). This happens through increasing the affinity of $\beta 2$ -integrins and suppressing LRP1 (13). It has been shown that in mice, the lack of MDK reduces neutrophil and macrophage numbers during the early stages of fracture healing (38, 40). Furthermore, the role of MDK in the inflammatory process has been attributed to its expression in endothelial cells under hypoxic conditions (14, 16). MDK is capable of maintaining tissue viability in adults after hypoxic stress (5, 25). MDK expression in tissues increases markedly following ischemia (41-45). In this case, increased MDK suppresses apoptosis and protects the tissue by decreasing cell death (5). Additionally, it promotes tissue repair through angiogenesis (46-48). Increased MDK during ischemia is characterized by an increase in blood MDK concentration (49). Serum MDK levels were shown to be significantly elevated in patients with heart failure than in the control group in studies on the treatment of the condition (49). MDK may induce neutrophil and macrophage migration to the injury site in renal ischemia-reperfusion damage, but it may decrease myocardial apoptosis in cardiac ischemia-reperfusion injury (21, 42, 50, 51). In endothelial cells, the PI3K/AKT and MAPK signaling pathways are critical for regulating vascular homeostasis and neovascularization (52, 53). AKT (protein kinase B) promotes the transcription of angiogenesis-related genes and refills tissue oxygen (54). Vascular endothelial growth factor alpha (VEGF-A) is a critical protein in the Chemokine (C-X-C motif) Ligand 1/Macrophage Inflammatory Protein 2-(CXCL1/MIP-2)-induced angiogenesis that interacts with VEGF receptor 2 (VEGFR2) (Figure 2) (16). Overexpression of MDK may affect the angiogenesis process by increasing VEGF-A levels and cellular release (Figure 2) (55, 56). These findings suggest that MDK plays an important role in angiogenesis and vascular homeostasis (16). A study suggested that MDK might be an effective therapeutic target for Th1 cell-induced autoimmune disorders such as experimental autoimmune encephalomyelitis (16). Moreover, it has been shown that

MDK may promote the survival of mature B lymphocytes through an autocrine pathway (Figure 2) (16). The data suggest that MDK has multiple functions and has significant effects on many different pathophysiological processes.

Anti-Bacterial and Anti-Apoptotic Properties of Midkine

A recent study showed that MDK has significant anti-fungal and anti-bacterial effects (1, 16, 57-59). MDK contains a heparin-binding motif (Cardin-Weintraub Motif), which is a common feature of antibacterial proteins, and MDK has been proposed to have antibacterial activity by disrupting the bacterial plasma membrane, in addition to antibacterial properties, especially against gram-positive organisms (16, 57, 58). The anti-apoptotic activity of MDK has been associated with a number of pathological events, including cancer, neurogenesis, and tissue repair (16). MDK functions as an anti-apoptotic growth factor, which allows cancer cells to proliferate more efficiently (60, 61). For example, in developed G401 cells (derived from a rhabdoid tumor of the kidney), MDK has been shown to prevent apoptosis by increasing B-cell leukemia/lymphoma 2 (Bcl-2) protein expression (61). MDK is also known to suppress Caspase-3 activation through extracellular signal-regulated kinase (ERK) activation, which avoids neuronal death (62). In contrast, MDK has been shown to protect against cardiac ischemia-reperfusion (I/R) damage by increasing Bcl-2 and ERK levels, which inhibit cardiomyocyte apoptosis (42). MDK has been reported to decrease myocyte cell death by activating the PI3K/AKT signaling pathway (Figure 2) (63). MDK and Bcl-2 collaborate to suppress apoptosis, and Bcl-2 and ERK play critical roles in MDK's anti-apoptotic activity (16).

Midkine in Oxidative Stress and Cholesterol

Reactive oxygen species may cause oxidative stress due to an imbalance of pro- and anti-oxidants (64). One study found that following 5/6

nephrectomy, MDK expression increased in tubular epithelial cells and infiltrating macrophages in the kidneys of MDK+/+ mice (65). In addition, oxidative stress increased MDK expression in capillaries, lung endothelium, and alveolar-capillary endothelial cells (65). Furthermore, it was demonstrated that MDK expression increased when angiotensin I (Ang I) was converted to Ang II by angiotensin-converting enzyme (65).

MDK is expressed at extremely low levels in healthy arteries and veins (66). However, a recent study suggests an association between high blood MDK levels and serum total and low-density lipoprotein cholesterol levels (67). In apolipoprotein E (*ApoE*)-/- mice, MDK treatment has been shown to improve atherosclerotic plaque development (68). These findings suggest that MDK may have a role in the development of atherosclerosis (16, 68).

CNS and Midkine

The role of MDK in the central nervous system (CNS) has been studied extensively during development and in conditions such as traumatic brain injury (TBI) (21). MDK is expressed in the CNS during development and until mid-pregnancy, after which its mRNA levels decrease (29, 69). In mice, oligodendrocyte precursor cells express MDK before fetal astrocytes, neurons, and newly formed oligodendrocytes develop (69). In humans, fetal astrocytes are the main source of MDK in the CNS (69).

MDK is expressed early in cerebral infarction as well as in additional clinical conditions (43). MDK has been shown to function as a repairing neurotrophic factor in these situations, and its presence is recognized in damaged nerve regions (43). HIF-1 α transcriptionally regulates MDK, a repair mechanism in hypoxia-induced diseases (21). Animal studies suggest that MDK mRNA and protein levels increase after short-term forebrain damage, but MDK expression increases in areas of traumatic spinal cord injury (44, 70). These findings indicate that MDK plays an important role in tissue repair in conditions such as brain damage and traumatic spinal cord injuries (70).

Secondary damage in TBI is caused by primary tissue damage, leading to disruption of the blood-brain barrier, immune cell infiltration into the brain, and neuroinflammation (71). *In vivo* studies suggested that a decrease in MDK has no effect on astrogliosis after TBI (72). Astrogliosis occurs when astrocytes respond to CNS injury by changing their transcriptional expression (73). Microglia respond to CNS injury in a similar fashion (74). However, it has been suggested that MDK may contribute to that injury in TBI by allowing immune cells to pass through the CNS (75).

Circulating MDK levels have also been shown to be significantly higher in patients with Alzheimer disease than in healthy individuals (5). This shows that MDK might be utilized as a marker in neurological disorders like Alzheimer's disease. MDK's representation in the CNS may be characterized as having a complicated process that MDK functions significantly throughout developmental stages but also in pathological situations such as TBI (21). Targeting MDK might be an effective approach for treating CNS-associated neoplastic conditions such as glioblastomas (21). These findings suggest that serum MDK levels might be used to diagnose and monitor a wide range of diseases. However, further research is required to support these findings (5).

Midkine as a Marker with Multiple Effects in Cancer

MDK overexpression has been reported in at least 20 distinct malignancies (5). Overexpression of MDK protein within tumors is a common feature of malignancy. MDK activates pro-tumoral activities in numerous cancer types via several signaling pathways (4, 12). MDK levels are frequently much greater in cancer patients than in healthy persons, and MDK expression has been shown to rise in direct proportion to the severity of illness (13, 53, 76-78). When tumors are surgically excised, circulating MDK levels often fall before increasing again when the cancer recurs (13). As a result, circulating MDK levels may act as a diagnostic, prognostic, or therapeutic marker for cancer (5).

MDK promotes cancer through a variety of processes (1). These mechanisms include cancer cell proliferation, survival, anti-apoptosis, angiogenesis, and EMT regulation (1, 79). MDK initiatives are simplified by specific receptor binding, which activates well-known downstream signaling pathways associated with tumor development and metastasis, including MAPK, PI3K/AKT, and ERK1/2 (Figure 2) (1, 79).

MDK's efficiency in promoting tumor development derives from its ability to trigger tumor angiogenesis (76). MDK is an effective pro-angiogenic factor (80, 81). Multiple studies have shown that MDK promotes angiogenesis, which enhances tumor development (13). In cancer cell culture studies with MDK overexpression, *in vitro* proliferation of endothelial cells increased, which led to angiogenesis (13, 80). The enhanced tumor development following subcutaneous MDK injection into nude mice has been attributed to increased microvessel density (76). This shows that endothelial cells are proliferating in the tumor (76). Furthermore, significant MDK expression has been found in tumor endothelial cells in human neural tumor tissues (82). A previous study focused on the interaction between the Notch2 receptor and MDK in pancreatic ductal adenocarcinoma (PDAC) cells (83). Soluble MDK has been demonstrated to stimulate Notch2 and its downstream targets, HES-1 and NF- κ B/RelA (83). This suggests that MDK may regulate both phases of carcinogenesis (18).

MDK promotes tumor development partially by improving the probability of metastasis formation (84). MDK has been predicted to mediate metastasis through mitogenic, pro-inflammatory, and angiogenic activities (84-86). MDK interacts with TGF- β pathway proteins, which are necessary for EMT (Figure 2) (87-89). Furthermore, MDK regulates cell survival and proliferation through activating the PI3K and ERK signaling pathways (60, 90). MDK's interaction with the WNT/ β -Catenin pathway is a key regulatory mechanism in glioma growth (91). MDK expression is increased in glioma cells (13). The *MDK* proximal promoter has a T-cell factor/lymphoid enhancer factor (TCF/LEF) family binding site that interacts with β -Catenin (91).

MDK may promote metastasis through proteolytic enzyme networks (92, 93). Expanded human kallikrein (KLKs) play an important role in these networks (94). KLKs may stimulate cancer development through extracellular hydrolysis (95). MDK has been recognized as an important protein, especially for KLK7 and KLK9 (Figure 2) (95, 96). This suggests a potential role for the KLK7/9-MDK axis in cancer development and metastasis (95, 96). MDK promotes metastatic development in melanoma through the mammalian target

of rapamycin (mTOR)/VEGFR3 signaling pathway (97). MDK regulates the mTOR signaling pathway by interacting with heparan sulfate and lymphatic endothelial cells (97). These signals promote lymphangiogenesis and metastasis in the lymph nodes and lungs (97). Silencing MDK reduces lymphangiogenesis and metastasis (97). These data suggest that MDK regulates the mTOR signaling pathway in melanoma metastasis (13). In an *in vitro* study to determine the effects of MDK concentration on drug cytotoxicity, MDK's effect on cells in the tumor microenvironment was studied in an ovarian cancer cell line (98, 99). MDK has been shown to stimulate the AKT signaling pathway in ovarian cancer cells, reducing the cytotoxic effect of cisplatin, whereas inhibiting MDK increased cisplatin cytotoxicity (98). Another study examining the role of MDK in the interaction between stromal cells and tumor cells showed that cancer-associated fibroblasts (CAFs) contribute to increased MDK levels in tumors and that CAF-derived MDK may promote cisplatin resistance (100).

MDK and Breast Cancer

Breast cancer is the world's most prevalent malignant tumor (101). Metastases in distant locations are the leading cause of mortality in breast cancer patients (102, 103). In a study comparing gene expression levels in breast cancer, it was found that *MDK* gene expression increased in tumor tissues (104). Some research has focused on the function of MDK in breast cancer. Plasma MDK levels were measured in 111 patients with primary invasive breast cancer and 25 patients with distant metastatic breast cancer (105). The results demonstrated that plasma MDK levels were markedly elevated in breast cancer patients compared to healthy controls (105). Although the mechanism is uncertain, plasma MDK levels in primary invasive carcinoma are significantly associated with the menopausal state. MDK is a substantially more effective biomarker for breast cancer than CA15-3, CEA, and NCCST-439, especially for individuals with initial invasive cancer (105). Furthermore, the MDK combination diagnoses breast cancer at significantly higher rates than the combination of two conventional tumor markers (CA15-3/CEA, CA15-3/NCCST-439, or

CEA/NCCST-439) (105). As a result, MDK may be as effective, if not more so, than conventional markers in diagnosing breast cancer (105). The upstream kinases LKB1, CAMKK β , and TAK1 phosphorylate adenosine monophosphate protein kinase (AMPK) at the Thr172 site (106). Among these kinases, the serine/threonine kinase, LKB1, regulates the conventional AMPK activation pathway, which has been clarified in cancer cells (107). It is well-established that LKB1 forms a heterotrimer with the pseudokinase STRAD and the scaffolding protein MO25 prior to self-phosphorylating at a number of amino acids to activate its own kinase activity (108). A recent study found that altering the LKB1-STRAD-MO25 complex reduced AMPK α Thr172 phosphorylation levels and AMPK activity (109-111). In another study, intracellular MDK suppressed AMPK activation by interacting with LKB1 and STRAD to depolymerise the LKB1-STRAD-MO25 complex, decreasing LKB1 activity and phosphorylation of AMPK α (112). Reducing or maintaining extracellular MDK expression caused enhanced AMPK α phosphorylation (108). Furthermore, MDK has been shown to increase cancer cell proliferation by inhibiting the LKB1-AMPK pathway, which proved to be negatively associated with LKB1/AMPK signaling pathway activity (Figure 3) (108). The treatment of locally advanced breast cancer is a combination of neoadjuvant chemotherapy (NCT), surgery, and adjuvant systemic and local treatments (113, 114). NCT increases the probability of breast-conserving surgery by minimizing the breast lesion, monitoring drug resistance, and determining prognosis and micrometastases (115). However, more than 80% of patients who get NCT do not respond effectively, causing risks that the treatment might delay surgery and drug resistance (116). As a result, early diagnosis of treatment response and resistance to chemotherapy may enhance the efficacy of NCT (117). In one study it was demonstrated that liquid biopsies, which are less invasive and less costly, were preferred, and that high levels of miR-1275 in plasma increased in response to NCT. However, reduced miR-1275 levels regulated chemoresistance in cancer stem cells by inhibiting the MDK/AKT pathway (Figure 3) (117).

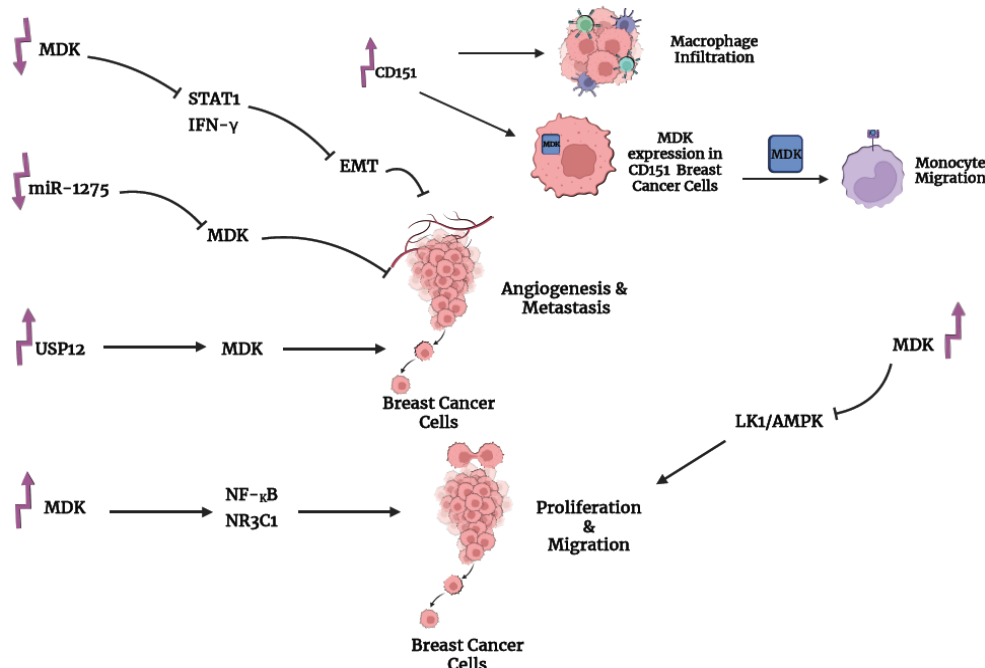


Figure 3. MDK modulates breast cancer through a variety of signaling mechanisms

MDK: Midkine, *Created with Biorender.

Interferons (IFNs) are a type of cytokine with antiviral, antiproliferative, and immunomodulatory properties (118). These cytokines play crucial roles in immune surveillance against cancer cells (119). IFN- γ increases anti-tumor immunity by directly targeting cancer cells (118, 120). Although IFN- γ has anti-tumor capabilities, it has been linked to an increased risk of metastasis in triple-negative breast cancer (TNBC) (121). A study showed that increasing IFN- γ levels increased MDK levels in TNBC cells (122). IFN- γ stimulates STAT1, promoting downstream signaling (123). The study demonstrated that reducing STAT1 decreased IFN- γ -induced MDK activation across all cancer cell lines. The use of midkine inhibitor (iMDK) (124), a small molecule for therapeutic use, reduced MDK levels and IFN- γ -induced EMT activation in cells (Figure 3) (122). Inhibiting MDK can inhibit IFN- γ -induced cancer migration and metastases (122).

Deubiquitination, mediated by multiple deubiquitinases (DUBs), regulates substrate protein levels by cleaving ubiquitin chains and is involved in many kinds of physiological processes (125, 126). DUBs have been found to play an important role in extracellular matrix degradation (127), epithelial-mesenchymal transition (128), angiogenesis (129, 130), and circulating tumor cell behavior (131). However, the role and mechanisms of DUBs in breast cancer metastasis are not established (103). In contrast, the ubiquitin regulator, ubiquitin specific protease 12 (USP12) is a member of the USP family that dehydrogenates and has been related to breast cancer (103). One study demonstrated that USP12 induced angiogenesis and metastasis by dehydrogenating and stabilizing the MDK protein (Figure 3) (103).

The immunological microenvironment in inflammatory breast cancer (IBC) is still undetermined, although one study demonstrated an interaction between the expression of the tetraspanin protein, CD151, and increased macrophage accumulation in malignant regions (132). It was established that higher CD151 expression and the amount of macrophages inhabiting the tumor were associated with a better response to chemotherapy in patients (132). IBC cells attract monocytes by many pathways, including CD151, MDK, integrin $\alpha 6 \beta 1$, and EV formation (Figure 3) (132).

NF- κ B regulates several genes to enhance tumor cell proliferation, angiogenesis, differentiation, and metastasis across various cancer types (133). NR3C1, a member of the nuclear hormone receptor superfamily, encodes the glucocorticoid receptor (133). After binding to glucocorticoids, NR3C1 transfers from the cytoplasm to the nucleus and function as a transcription factor (134). In human cell lines, NR3C1/GR binds to the proximal RANKL promoter region, promoting RANKL transcription (135). High NR3C1/GR expression increased breast cancer growth and has a poor prognosis in TNBC and ER(-) subtypes (136, 137). A study showed NF- κ B to be a crucial regulator, positively correlated with NR3C1 (138). Silencing MDK has been shown to inhibit breast cancer cell growth and migration (138). Transduction silencing of MDK inhibits the NF- κ B pathway, resulting in reduced NR3C1 expression (138). MDK promotes breast cancer cell proliferation and migration by upregulating NR3C1 expression and activating the NF- κ B pathway (Figure 3) (138).

Midkine Targeting

According to studies, MDK is a key regulator of drug resistance (15, 30). Previous studies have demonstrated that MDK protects cancer cells against cannabinoid and doxorubicin treatments and MDK expression was shown to increase the effects of chemotherapeutic drugs on lymphoblastic leukemia cells (139-142). In addition, drug-

resistant gastric cancer cells were shown to express more MDK than drug-sensitive cells (143). Another study reported that decreased MDK expression enhances cisplatin resistance in oral squamous and renal carcinomas (144, 145). These findings show that MDK may produce either a drug-resistant or drug-sensitive cancer cell phenotype in different conditions (13).

MDK has been shown to be effective as a cancer biomarker at multiple stages, such as early disease identification, treatment response monitoring, and recurrence follow-up (5). Researchers are investigating ways to target MDK for cancer treatment since it plays a crucial role in tumor growth (30). An MDK antisense oligodeoxynucleotide was given to naked mice expressing rectal cancer cells, and tumor growth was significantly inhibited (146). Antisense oligonucleotides that target MDK effectively suppressed hepatocellular carcinoma (HCC) and increased its chemosensitivity to adriamycin (147).

Antibody-based therapeutics have been designed to target MDK (30). Monoclonal antibodies (mAbs) with high specificity for cell surface antigens are effective against cytotoxic pharmaceuticals (30). For example, anti-MDK mAbs combined with doxorubicin have been demonstrated to inhibit HCC proliferation (148). MDK-specific doxorubicin-conjugated single-chain variable fragments (scFv) showed similar characteristics (149). Another study showed that effective anti-MDK antibodies suppressed the growth of osteosarcoma cells (150).

In vitro viral therapy in pancreatic cancer cell lines is a different approach for treating peripheral tumors that express MDK (151). In this process, an oncolytic virus (adenovirus) containing part of the MDK promoter may eliminate tumor cells, and the process is carried out through tumor-selective replication (151). In contrast, siRNA or shRNA down-regulation of MDK has been shown to significantly inhibit PDAC growth (152). Another study found that knocking down MDK through siRNA increased cisplatin's anti-tumor activity in human gastric cancer cells (153). However, negatively charged siRNAs have limited pass-through into cells since they are not membrane-permeable and are swiftly eliminated by the kidneys due to their small size (154). They are also vulnerable to enzymatic degradation by serum endonucleases and RNAases, which may have a negative effect on their systemic distribution (154).

Metformin is utilized to treat Type II diabetes and is now being investigated as a potential anticancer drug since it affects MDK activity (30, 155). Metformin has been reported to beneficially interfere with the several MDK pathways that trigger cancer growth and its associated side effects (155). As a result, metformin may be effective as an MDK inhibitor (155). iMDK may decrease MDK expression while reducing cell growth and proliferation, possibly through blocking the PI3K signaling pathway (124). iMDK treatment of primary effusion lymphoma (PEL) cells led to cell cycle arrest in the G2/M phase in addition to a decrease in p-Cyclin-dependent kinase 1 levels (156). This might stimulate caspases, triggering PEL cell apoptosis (156). In studies of oral squamous cell carcinoma, iMDK treatment reduced CD31 expression, cell proliferation, and inhibited VEGF-induced angiogenesis (157).

Besides pharmaceuticals targeting MDK, there are many approaches for increasing MDK expression levels (21). It has been shown that cytotoxic T-cells with enhanced MDK expression may lyse tumor cells, suggesting that MDK may have potential for cancer vaccine development (13, 21). Another study used MDK RNA aptamers to activate T regulatory cells, showing that autoimmune diseases may be

prevented (158). These findings suggest that MDK-targeted treatments may be effective in inhibiting cancer formation and reducing drug resistance (30).

Discussion and Conclusion

This review discusses the effects of the MDK in cancer biology, as well as additional functions for MDK in health and disease processes. The crucial role of MDK in physiological processes, such as development, tissue repair, and neuronal plasticity, as well as its association with diseases such as neurodegenerative disorders, inflammation, and ischemia, are explained in detail. MDK's neuroprotective effects, impact on tissue regeneration, and potential effects to regulate inflammatory processes contribute to its biological importance. In this regard, a better understanding of MDK's cellular and molecular functions might lead to the development of innovative approaches for managing and treating a number of medical conditions. As a result, it is important to do more studies on MDK's role in diseases and health issues.

However, MDK's effects on cancer cell proliferation, survival, metastasis, and drug resistance have been studied. Various techniques and therapeutic approaches involving the use of MDK as a target for cancer therapy are also discussed. The approaches described include antibody-based therapy, small chemical inhibitors such as iMDK, siRNA, and RNA Aptamers. The published evidence concerning MDK's effects on cancer cell characteristics and its potential effects on cancer therapy shows that MDK plays an important biological role and that targeting it in cancer therapy has significant potential. A comprehensive understanding of the contribution of MDK to cancer biology could help in the development of innovative cancer therapies, as well as more effective cancer-fighting approaches. However, further study is required to identify these innovative approaches to cancer treatment and controlling the disease.

Authorship Contributions

Concept: A.B.; Data Collection or Processing: B.Y., A.B.; Analysis or Interpretation: A.B.; Literature Search: B.Y., K.K.; Writing: B.Y., K.K., A.B.

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