Review

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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-1α), 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 α6β1 and α4β1 heterodimers (21). Syndecanes, glipican-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-1α 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-κB) binding site (30, 31). This leads to MDK overexpression under inflammatory conditions (31). In prostate cancer, tumor necrosis factor-α activates the NF-κB 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

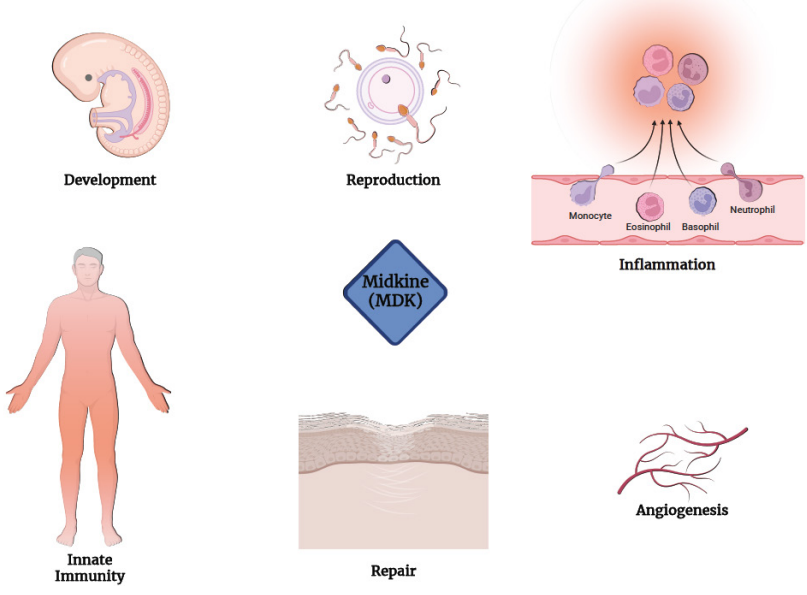

Figure 1. MDK plays a role in essential processes including as development, reproduction, repair, inflammation, innate immunity, and angiogenesis by activating various signaling pathways

*MDK: Midkine, *Created with Biorender.*

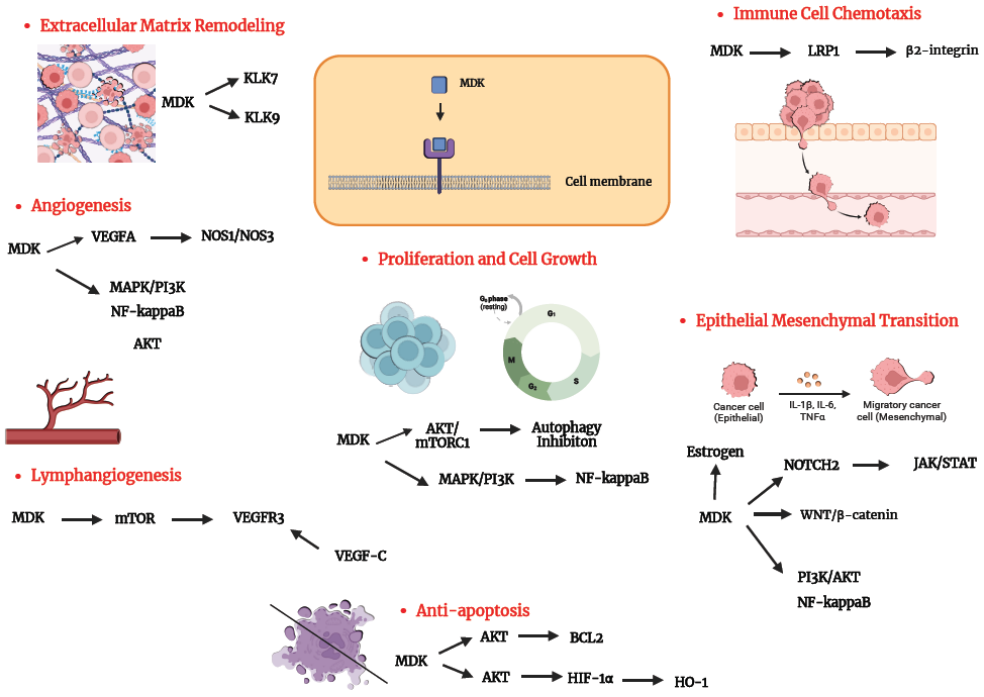

Figure 2. MDK is involved in cancer cell proliferation, survival, ECM remodeling anti-apoptosis, angiogenesis and EMT regulation through many different signalling pathways in tumor development

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

neutrophil adhesion during angiogenesis (39). This happens through increasing the affinity of β2-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-1α 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-kB/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, CAMKKβ, 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 AMPKα 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 AMPKα (112). Reducing or maintaining extracellular MDK expression caused enhanced AMPKα 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).

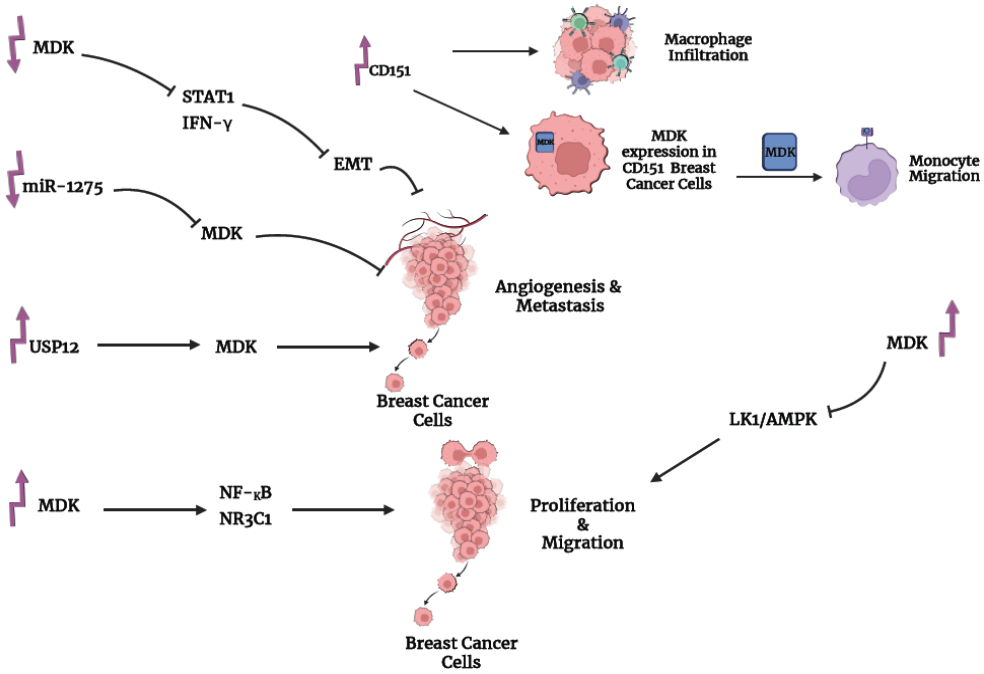

Figure 3. MDK modulates breast cancer through a variety of signaling mechanisms

*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 α6β1, and EV formation (Figure 3) (132).

NF-κB 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-κB 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-κB pathway, resulting in reduced NR3C1 expression (138). MDK promotes breast cancer cell proliferation and migration by upregulating NR3C1 expression and activating the NF-κB 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 inhibitör (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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References

1. Muramatsu T. Structure and function of midkine as the basis of its pharmacological effects. Br J Pharmacol 2014; 171: 814-826. (PMID: 23992440) [Crossref]
2. Winkler C, Yao S. The midkine family of growth factors: diverse roles in nervous system formation and maintenance. Br J Pharmacol 2014; 171: 905-912. (PMID: 24125182) [Crossref]
3. Christou C, Stylianou A, Gkretsi V. Midkine (MDK) in Hepatocellular Carcinoma: More than a Biomarker. Cells 2024; 13: 136. (PMID: 38247828) [Crossref]
4. Tsutsui J, Kadomatsu K, Matsubara S, Nakagawara A, Hamanoue M, Takao S, et al. A new family of heparin-binding growth/differentiation factors: increased midkine expression in Wilms' tumor and other human carcinomas. Cancer Res 1993; 53: 1281-1285. (PMID: 8383007) [Crossref]
5. Jones DR. Measuring midkine: the utility of midkine as a biomarker in cancer and other diseases. Br J Pharmacol 2014; 171: 2925-2939. (PMID: 24460734) [Crossref]
6. Ye C, Qi M, Fan QW, Ito K, Akiyama S, Kasai Y, et al. Expression of midkine in the early stage of carcinogenesis in human colorectal cancer. Br J Cancer 1999; 79: 179-184. (PMID: 10408712) [Crossref]
7. Moon HS, Park WI, Sung SH, Choi EA h, Chung HW, Woo BH. Immunohistochemical and quantitative competitive PCR analyses of midkine and pleiotrophin expression in cervical cancer. Gynecol Oncol 2003; 88: 289-297. (PMID: 12648577) [Crossref]
8. Huang Y, Cao G, Wang H, Wang Q, Hou Y. The expression and location of midkine in gastric carcinomas of Chinese patients. Cell Mol Immunol 2007; 4: 135-140. (PMID: 17484808) [Crossref]
9. Jia HL, Ye QH, Qin LX, Budhu A, Forgues M, Chen Y, et al. Gene Expression Profiling Reveals Potential Biomarkers of Human Hepatocellular Carcinoma. Clin Cancer Res 2007; 13: 1133-1139. (PMID: 17317821) [Crossref]
10. O'Brien T, Cranston D, Fuggle S, Bicknell R, Harris AL. The angiogenic factor midkine is expressed in bladder cancer, and overexpression correlates with a poor outcome in patients with invasive cancers. Cancer Res 1996; 56: 2515-2518. (PMID: 8653688) [Crossref]
11. Pedraza RC, Matsubara S, Muramatsu T. A Retinoic Acid-Responsive Element in Human Midkine Gene1. J Biochem 1995; 117: 845-849. (PMID: 7592548) [Crossref]
12. Kadomatsu K, Muramatsu T. Midkine and pleiotrophin in neural development and cancer. Cancer Lett 2004; 204: 127-143. (PMID: 15013213) [Crossref]
13. Filippou PS, Karagiannis GS, Constantinidou A. Midkine (MDK) growth factor: a key player in cancer progression and a promising therapeutic target. Oncogene 2020; 39: 2040-2054. (PMID: 31801970) [Crossref]
14. Reynolds PR, Mucenski ML, Le Cras TD, Nichols WC, Whitsett JA. Midkine Is Regulated by Hypoxia and Causes Pulmonary Vascular Remodeling. J Biol Chem 2004; 279: 37124-37132. (PMID: 15197188) [Crossref]
15. Kadomatsu K, Tomomura M, Muramatsu T. cDNA cloning and sequencing of a new gene intensely expressed in early differentiation stages of embryonal carcinoma cells and in mid-gestation period of mouse embryogenesis. Biochem Biophys Res Commun 1988; 151: 1312-1318. (PMID: 3355557) [Crossref]
16. Cai YQ, Lv Y, Mo ZC, Lei J, Zhu JL, Zhong QQ. Multiple pathophysiological roles of midkine in human disease. Cytokine 2020; 135: 155242. (PMID: 32799009) [Crossref]
17. Li YS, Milner PG, Chauhan AK, Watson MA, Hoffman RM, Kodner CM, et al. Cloning and expression of a developmentally regulated protein that induces mitogenic and neurite outgrowth activity. Science 1990; 250: 1690-1694. (PMID: 2270483) [Crossref]
18. Kadomatsu K. The midkine family in cancer, inflammation and neural development. Nagoya J Med Sci 2005; 67: 71-82. (PMID: 17375473) [Crossref]
19. Uehara K, Matsubara S, Kadomatsu K, Tsutsui J, Muramatsu T. Genomic structure of human midkine (MK), a retinoic acid-responsive growth/differentiation factor. J Biochem 1992; 111: 563-567. (PMID: 1639750) [Crossref]
20. Maeda N, Ichihara-Tanaka K, Kimura T, Kadomatsu K, Muramatsu T, Noda M. A Receptor-like Protein-tyrosine Phosphatase PTPζ/RPTPβ Binds a Heparin-binding Growth Factor Midkine. J Biol Chem 1999; 274: 12474-12479. (PMID: 10212223) [Crossref]
21. Neumaier EE, Rothhammer V, Linnerbauer M. The role of midkine in health and disease. Front Immunol 2023; 14: 1310094. (PMID: 38098484) [Crossref]
22. Huang Y, Hoque MO, Wu F, Trink B, Sidransky D, Ratovitski EA. Midkine induces epithelial-mesenchymal transition through Notch2/Jak2-Stat3 signaling in human keratinocytes. Cell Cycle 2008; 7: 1613-1622. (PMID: 18469519) [Crossref]
23. Stoica GE, Kuo A, Powers C, Bowden ET, Sale EB, Riegel AT, et al. Midkine Binds to Anaplastic Lymphoma Kinase (ALK) and Acts as a

Growth Factor for Different Cell Types. J Biol Chem 2002; 277: 35990-35998. (PMID: 12122009) [Crossref]

24. Muramatsu H, Zou K, Sakaguchi N, Ikematsu S, Sakuma S, Muramatsu T. LDL Receptor-Related Protein as a Component of the Midkine Receptor. Biochem Biophys Res Commun 2000; 270: 936-941. (PMID: 10772929) [Crossref]
25. Muramatsu T. Midkine: A Promising Molecule for Drug Development to Treat Diseases of the Central Nervous System. Curr Pharm Des 2011; 17: 410-423. (PMID: 21375488) [Crossref]
26. Kurosawa N, Chen GY, Kadomatsu K, Ikematsu S, Sakuma S, Muramatsu T. Glypican-2 binds to midkine: the role of glypican-2 in neuronal cell adhesion and neurite outgrowth. Glycoconj J 2001; 18: 499-507. (PMID: 12084985) [Crossref]
27. Zou K, Muramatsu H, Ikematsu S, Sakuma S, Salama RHM, Shinomura T, et al. A heparin-binding growth factor, midkine, binds to a chondroitin sulfate proteoglycan, PG-M/versican. Eur J Biochem 2000; 267: 4046-4053. (PMID: 10866805) [Crossref]
28. Ichihara-Tanaka K, Oohira A, Rumsby M, Muramatsu T. Neuroglycan C Is a Novel Midkine Receptor Involved in Process Elongation of Oligodendroglial Precursor-like Cells. J Biol Chem 2006; 281: 30857-30864. (PMID: 16901907) [Crossref]
29. Muramatsu T. Midkine, a heparin-binding cytokine with multiple roles in development, repair and diseases. Proc Jpn Acad Ser B 2010; 86: 410-425. (PMID: 20431264) [Crossref]
30. Saikia M, Cheung N, Singh AK, Kapoor V. Role of Midkine in Cancer Drug Resistance: Regulators of Its Expression and Its Molecular Targeting. Int J Mol Sci 2023; 24: 8739. (PMID: 37240085) [Crossref]
31. You Z, Dong Y, Kong X, Beckett LA, Gandour-Edwards R, Melamed J. Midkine is a NF-κB-inducible gene that supports prostate cancer cell survival. BMC Med Genomics 2008; 1: 6. (PMID: 18275606) [Crossref]
32. Safe S, Imanirad P, Sreevalsan S, Nair V, Jutooru I. Transcription factor Sp1, also known as specificity protein 1 as a therapeutic target. Expert Opin Ther Targets 2014; 18: 759-769. (PMID: 24793594) [Crossref]
33. Reynolds PR, Mucenski ML, Whitsett JA. Thyroid transcription factor (TTF) -1 regulates the expression of midkine (MK) during lung morphogenesis. Dev Dyn 2003; 227: 227-237. (PMID: 12761850) [Crossref]
34. Bie C, Chen Y, Tang H, Li Q, Zhong L, Peng X, et al. Insulin-Like Growth Factor 1 Receptor Drives Hepatocellular Carcinoma Growth and Invasion by Activating Stat3-Midkine-Stat3 Loop. Dig Dis Sci 2022; 67: 569-584. (PMID: 33559791) [Crossref]
35. Gowhari Shabgah A, Ezzatifar F, Aravindhan S, Olegovna Zekiy A, Ahmadi M, Gheibihayat SM, et al. Shedding more light on the role of Midkine in hepatocellular carcinoma: New perspectives on diagnosis and therapy. IUBMB Life 2021; 73: 659-669. (PMID: 33625758) [Crossref]
36. Sun B, Hu C, Yang Z, Zhang X, Zhao L, Xiong J, et al. Midkine promotes hepatocellular carcinoma metastasis by elevating anoikis resistance of circulating tumor cells. Oncotarget 2017; 8: 32523-32535. (PMID: 28430645) [Crossref]
37. Fernández-Calle R, Vicente-Rodríguez M, Gramage E, De La Torre-Ortiz C, Pérez-García C, Ramos MP, et al. Endogenous pleiotrophin and midkine regulate LPS-induced glial responses. Neurosci Lett 2018; 662: 213-218. (PMID: 29061398) [Crossref]
38. Weckbach LT, Muramatsu T, Walzog B. Midkine in Inflammation. Sci World J 2011; 11: 2491-2505. (PMID: 22235180) [Crossref]
39. Tazzyman S, Lewis CE, Murdoch C. Neutrophils: key mediators of tumour angiogenesis. Int J Exp Pathol 2009; 90: 222-231. (PMID: 19563607) [Crossref]
40. Haffner-Luntzer M, Heilmann A, Rapp AE, Beie S, Schinke T, Amling M, et al. Midkine-Deficiency Delays Chondrogenesis during the Early Phase of Fracture Healing in Mice. Awad HA, editor. PLoS One 2014; 9: e116282. (PMID: 25551381) [Crossref]
41. Horiba M, Kadomatsu K, Nakamura E, Muramatsu H, Ikematsu S, Sakuma S, et al. Neointima formation in a restenosis model is suppressed in midkine-deficient mice. J Clin Invest 2000; 105: 489-495. (PMID: 10683378) [Crossref]
42. Horiba M, Kadomatsu K, Yasui K, Lee JK, Takenaka H, Sumida A, et al. Midkine Plays a Protective Role Against Cardiac Ischemia/Reperfusion Injury Through a Reduction of Apoptotic Reaction. Circulation 2006; 14: 1713-1720. (PMID: 17015789) [Crossref]
43. Yoshida Y, Goto M, Tsutsui J ichiro, Ozawa M, Sato E, Osame M, et al. Midkine is present in the early stage of cerebral infarct. Brain Res Dev Brain Res 1995; 85: 25-30. (PMID: 7781164) [Crossref]
44. Mochizuki R, Takeda A, Sato N, Kimpara T, Onodera H, Itoyama Y, et al. Induction of Midkine Expression in Reactive Astrocytes Following Rat Transient Forebrain Ischemia. Exp Neurol 1998; 149: 73-78. (PMID: 9454616) [Crossref]
45. Sato W, Kadomatsu K, Yuzawa Y, Muramatsu H, Hotta N, Matsuo S, et al. Midkine Is Involved in Neutrophil Infiltration into the Tubulointerstitium in Ischemic Renal Injury. J Immunol 2001; 167: 3463-3469. (PMID: 11544339) [Crossref]
46. Weckbach LT, Groesser L, Borgolte J, Pagel JI, Pogoda F, Schymeinsky J, et al. Midkine acts as proangiogenic cytokine in hypoxia-induced angiogenesis. Am J Physiol Heart Circ Physiol 2012; 303: H429-H438. (PMID: 22707563) [Crossref]
47. Fukui S, Kitagawa-Sakakida S, Kawamata S, Matsumiya G, Kawaguchi N, Matsuura N, et al. Therapeutic Effect of Midkine on Cardiac Remodeling in Infarcted Rat Hearts. Ann Thorac Surg 2008; 85: 562-570. (PMID: 18222265) [Crossref]
48. Takenaka H, Horiba M, Ishiguro H, Sumida A, Hojo M, Usui A, et al. Midkine prevents ventricular remodeling and improves long-term survival after myocardial infarction. Am J Physiol-Heart Circ Physiol 2009; 296: H462-469. (PMID: 19060126) [Crossref]
49. Kitahara T, Shishido T, Suzuki S, Katoh S, Sasaki T, Ishino M, et al. Serum Midkine as a Predictor of Cardiac Events in Patients With Chronic Heart Failure. J Card Fail 2010; 16: 308-133. (PMID: 20350697) [Crossref]
50. Li X, Ma N, Xu J, Zhang Y, Yang P, Su X, et al. Targeting Ferroptosis: Pathological Mechanism and Treatment of Ischemia-Reperfusion Injury. Jiang DS, editor. Oxid Med Cell Longev 2021; 2021: 1587922. (PMID: 34745412) [Crossref]
51. Sato W, Sato Y. Midkine in nephrogenesis, hypertension and kidney diseases. Br J Pharmacol 2014; 171: 879-887. (PMID: 24106831) [Crossref]
52. Shiojima I, Walsh K. Role of Akt signaling in vascular homeostasis and angiogenesis. Circ Res 2002; 90: 1243-1250. (PMID: 12089061) [Crossref]
53. Qi M, Ikematsu S, Maeda N, Ichihara-Tanaka K, Sakuma S, Noda M, et al. Haptotactic Migration Induced by Midkine. J Biol Chem 2001; 276: 15868-15875. (PMID: 11340082) [Crossref]
54. Sluimer JC, Daemen MJ. Novel concepts in atherogenesis: angiogenesis and hypoxia in atherosclerosis. J Pathol 2009; 218: 7-29. (PMID: 19309025) [Crossref]
55. Scapini P, Morini M, Tecchio C, Minghelli S, Di Carlo E, Tanghetti E, et al. CXCL1/Macrophage Inflammatory Protein-2-Induced Angiogenesis In Vivo Is Mediated by Neutrophil-Derived Vascular Endothelial Growth Factor-A. J Immunol 2004; 172: 5034-5040. (PMID: 15067085) [Crossref]
56. Zhao SL, Zhang YJ, Li MH, Zhang XL, Chen SL. Mesenchymal stem cells with overexpression of midkine enhance cell survival and attenuate

cardiac dysfunction in a rat model of myocardial infarction. Stem Cell Res Ther 2014; 5: 37. (PMID: 24635859) [Crossref]

57. Andersson E, Rydengård V, Sonesson A, Mörgelin M, Björck L, Schmidtchen A. Antimicrobial activities of heparin-binding peptides. Eur J Biochem 2004; 271: 1219-1226. (PMID: 15009200) [Crossref]
58. Svensson SL, Pasupuleti M, Walse B, Malmsten M, Mörgelin M, Sjögren C, et al. Midkine and Pleiotrophin Have Bactericidal Properties: preserved antibacterial activity in a family of heparin-binding growth factors during evolution. J Biol Chem 2010; 285: 16105-16115. (PMID: 20308059) [Crossref]
59. Englund C, Birve A, Falileeva L, Grabbe C, Palmer RH. Miple1 and miple2 encode a family of MK/PTN homologues in Drosophila melanogaster. Dev Genes Evol 2006; 216: 10-18. (PMID: 16220264) [Crossref]
60. Ohuchida T, Okamoto K, Akahane K, Higure A, Todoroki H, Abe Y, et al. Midkine protects hepatocellular carcinoma cells against TRAIL-mediated apoptosis through down-regulation of caspase-3 activity. Cancer 2004; 100: 2430-2436. (PMID: 15160348) [Crossref]
61. Qi M, Ikematsu S, Icbihara-Tanaka K, Sakuma S, Muramatsu T, Kadomatsu K. Midkine Rescues Wilms, Tumor Cells from Cisplatin-Induced Apoptosis: Regulation of Bcl-2 Expression by Midkine. J Biochem 2000; 127: 269-277. (PMID: 10731694) [Crossref]
62. Owada K, Sanjo N, Kobayashi T, Mizusawa H, Muramatsu H, Muramatsu T, et al. Midkine inhibits caspase-dependent apoptosis via the activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase in cultured neurons. J Neurochem 1999; 73: 2084-2092. (PMID: 10537068) [Crossref]
63. Harada M, Hojo M, Kamiya K, Kadomatsu K, Murohara T, Kodama I, et al. Exogenous midkine administration prevents cardiac remodeling in pacing-induced congestive heart failure of rabbits. Heart Vessels 2016; 31: 96-104. (PMID: 25155308) [Crossref]
64. Touyz RM. Reactive oxygen species in vascular biology: role in arterial hypertension. Expert Rev Cardiovasc Ther 2003; 1: 91-106. (PMID: 15030300) [Crossref]
65. Hobo A, Yuzawa Y, Kosugi T, Kato N, Asai N, Sato W, et al. The growth factor midkine regulates the renin-angiotensin system in mice. J Clin Invest 2009; 119: 1616-1625. (PMID: 19451697) [Crossref]
66. Ito F. Polyphenols can Potentially Prevent Atherosclerosis and Cardiovascular Disease by Modulating Macrophage Cholesterol Metabolism. Curr Mol Pharmacol 2020; 14: 175-190. (PMID: 32196455) [Crossref]
67. Guzel S, S Cinemre F, Guzel E, Kucukyalcin V, Kiziler A, Cavusoglu C, et al. Midkine levels and its relationship with atherosclerotic risk factors in essential hypertensive patients. Niger J Clin Pract 2018; 21: 894-900. (PMID: 29984722) [Crossref]
68. Takemoto Y, Horiba M, Harada M, Sakamoto K, Takeshita K, Murohara T, et al. Midkine Promotes Atherosclerotic Plaque Formation Through Its Pro-Inflammatory, Angiogenic and Anti-Apoptotic Functions in Apolipoprotein E-Knockout Mice. Circ J 2018; 82: 19-27. (PMID: 28781288) [Crossref]
69. Ross-Munro E, Kwa F, Kreiner J, Khore M, Miller SL, Tolcos M, et al. Midkine: The Who, What, Where, and When of a Promising Neurotrophic Therapy for Perinatal Brain Injury. Front Neurol 2020; 11: 568814. (PMID: 33193008) [Crossref]
70. Sakakima H, Yoshida Y, Muramatsu T, Yone K, Goto M, Ijiri K, et al. Traumatic Injury-Induced Midkine Expression in the Adult Rat Spinal Cord during the Early Stage. J Neurotrauma 2004; 21: 471-477. (PMID: 15115596) [Crossref]
71. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth 2007; 99: 4-9. (PMID: 17573392) [Crossref]
72. Takada S, Sakakima H, Matsuyama T, Otsuka S, Nakanishi K, Norimatsu K, et al. Disruption of Midkine gene reduces traumatic brain injury through the modulation of neuroinflammation. J Neuroinflammation 2020; 17: 40. (PMID: 31996236) [Crossref]
73. Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG, et al. Genomic Analysis of Reactive Astrogliosis. J Neurosci 2012; 32: 6391-6410. (PMID: 22553043) [Crossref]
74. Streit WJ, Walter SA, Pennell NA. Reactive microgliosis. Prog Neurobiol 1999; 57: 563-581. (PMID: 10221782) [Crossref]
75. Shlosberg D, Benifla M, Kaufer D, Friedman A. Blood–brain barrier breakdown as a therapeutic target in traumatic brain injury. Nat Rev Neurol 2010; 6: 393-403. (PMID: 20551947) [Crossref]
76. Choudhuri R, Zhang HT, Donnini S, Ziche M, Bicknell R. An angiogenic role for the neurokines midkine and pleiotrophin in tumorigenesis. Cancer Res 1997; 57: 1814-1819. (PMID: 9135027) [Crossref]
77. Muramatsu H, Shirahama H, Yonezawa S, Maruta H, Muramatsu T. Midkine, A Retinoic Acid-Inducible Growth/Differentiation Factor: Immunochemical Evidence for the Function and Distribution. Dev Biol 1993; 159: 392-402. (PMID: 8405666) [Crossref]
78. Owada K, Sanjyo N, Kobayashi T, Kamata T, Mizusawa H, Muramatsu H, et al. Midkine inhibits apoptosis via extracellular signal regulated kinase (ERK) activation in PC12 cells. J Med Dent Sci 1999; 46: 45-51. (PMID: 12160213) [Crossref]
79. Kadomatsu K, Kishida S, Tsubota S. The heparin-binding growth factor midkine: the biological activities and candidate receptors. J Biochem 2013; 153: 511-521. (PMID: 23625998) [Crossref]
80. Muramaki M, Miyake H, Hara I, Kamidono S. Introduction of midkine gene into human bladder cancer cells enhances their malignant phenotype but increases their sensitivity to antiangiogenic therapy. Clin Cancer Res Off J Am Assoc Cancer Res 2003; 9: 5152-5160. (PMID: 14613994) [Crossref]
81. Gustavsson H, Jennbacken K, Welén K, Damber J. Altered expression of genes regulating angiogenesis in experimental androgen-independent prostate cancer. Prostate 2008; 68: 161-170. (PMID: 18076023) [Crossref]
82. Mashour GA, Ratner N, Khan GA, Wang HL, Martuza RL, Kurtz A. The angiogenic factor midkine is aberrantly expressed in NF1-deficient Schwann cells and is a mitogen for neurofibroma-derived cells. Oncogene 2001; 20: 97-105. (PMID: 11244508) [Crossref]
83. Güngör C, Zander H, Effenberger KE, Vashist YK, Kalinina T, Izbicki JR, et al. Notch Signaling Activated by Replication Stress–Induced Expression of Midkine Drives Epithelial–Mesenchymal Transition and Chemoresistance in Pancreatic Cancer. Cancer Res 2011; 71: 5009-5019. (PMID: 21632553) [Crossref]
84. Jono H, Ando Y. Midkine: A Novel Prognostic Biomarker for Cancer. Cancers (Basel) 2010; 2: 624-641. (PMID: 24281085) [Crossref]
85. Kishida S, Kadomatsu K. Involvement of midkine in neuroblastoma tumourigenesis. Br J Pharmacol 2014; 171: 896-904. (PMID: 24116381) [Crossref]
86. Muramatsu T, Kadomatsu K. Midkine: an emerging target of drug development for treatment of multiple diseases. Br J Pharmacol 2014; 171: 811-813. (PMID: 24460672) [Crossref]
87. Papageorgis P. TGFβ Signaling in Tumor Initiation, Epithelial-to-Mesenchymal Transition, and Metastasis. J Oncol 2015; 2015: 587193. (PMID: 25883652) [Crossref]
88. Grupp K, Melling N, Bogoevska V, Reeh M, Uzunoglu FG, El Gammal AT, et al. Expression of ICAM-1, E-cadherin, periostin and midkine in metastases of pancreatic ductal adenocarcinomas. Exp Mol Pathol 2018; 104: 109-113. (PMID: 29355490) [Crossref]
89. Katsuno Y, Lamouille S, Derynck R. TGF-β signaling and epithelial–mesenchymal transition in cancer progression. Curr Opin Oncol 2013; 25: 76-84. (PMID: 23197193) [Crossref]
90. Sandra F, Harada H, Nakamura N, Ohishi M. Midkine induced growth of ameloblastoma through MAPK and Akt pathways. Oral Oncol 2004; 40: 274-280. (PMID: 14747058) [Crossref]

91. Tang SL, Gao YL, Chen XB. Wnt/β-catenin up-regulates Midkine expression in glioma cells. Int J Clin Exp Med 2015; 8: 12644-12649. (PMID: 26550177) [Crossref]
92. Yu Y, Prassas I, Dimitromanolakis A, Diamandis EP. Novel Biological Substrates of Human Kallikrein 7 Identified through Degradomics. J Biol Chem 2015; 290: 17762-17775. (PMID: 26032414) [Crossref]
93. Filippou PS, Farkona S, Brinc D, Yu Y, Prassas I, Diamandis EP. Biochemical and functional characterization of the human tissue kallikrein 9. Biochem J 2017; 474: 2417-2433. (PMID: 28559305) [Crossref]
94. Filippou PS, Karagiannis GS, Musrap N, Diamandis EP. Kallikrein-related peptidases (KLKs) and the hallmarks of cancer. Crit Rev Clin Lab Sci 2016; 53: 277-291. (PMID: 26886390) [Crossref]
95. Haddada M, Draoui H, Deschamps L, Walker F, Delaunay T, Brattsand M, et al. Kallikrein-related peptidase 7 overexpression in melanoma cells modulates cell adhesion leading to a malignant phenotype. Biol Chem 2018; 399: 1099-1105. (PMID: 29498930) [Crossref]
96. Geng X, Liu Y, Diersch S, Kotzsch M, Grill S, Weichert W, et al. Clinical relevance of kallikrein-related peptidase 9, 10, 11, and 15 mRNA expression in advanced high-grade serous ovarian cancer. Ulrich H, editor. PLoS One 2017; 12: e0186847. (PMID: 29095848) [Crossref]
97. Olmeda D, Cerezo-Wallis D, Riveiro-Falkenbach E, Pennacchi PC, Contreras-Alcalde M, Ibarz N, et al. Whole-body imaging of lymphovascular niches identifies pre-metastatic roles of midkine. Nature 2017; 546: 676-680. (PMID: 28658220) [Crossref]
98. Rebbaa A, Chou PM, Mirkin BL. Factors secreted by human neuroblastoma mediated doxorubicin resistance by activating STAT3 and inhibiting apoptosis. Mol Med 2001; 7: 393-400. (PMID: 11474132) [Crossref]
99. Wu X, Zhi X, Ji M, Wang Q, Li Y, Xie J, et al. Midkine as a potential diagnostic marker in epithelial ovarian cancer for cisplatin/paclitaxel combination clinical therapy. Am J Cancer Res 2015; 5: 629-638. (PMID: 25973302) [Crossref]
100. Zhang D, Ding L, Li Y, Ren J, Shi G, Wang Y, et al. Midkine derived from cancer-associated fibroblasts promotes cisplatin-resistance via up-regulation of the expression of lncRNA ANRIL in tumour cells. Sci Rep 2017; 7: 16231. (PMID: 29176691) [Crossref]
101. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424. Erratum in: CA Cancer J Clin 2020; 70: 313. (PMID: 30207593) [Crossref]
102. Weigelt B, Peterse JL, van't Veer LJ. Breast cancer metastasis: markers and models. Nat Rev Cancer 2005; 5: 591-602. (PMID: 16056258) [Crossref]
103. Sheng B, Wei Z, Wu X, Li Y, Liu Z. USP12 promotes breast cancer angiogenesis by maintaining midkine stability. Cell Death Dis 2021; 12: 1074. (PMID: 34759262) [Crossref]
104. Tian Z, Tang J, Liao X, Yang Q, Wu Y, Wu G. An immune-related prognostic signature for predicting breast cancer recurrence. Cancer Med 2020; 9: 7672-7685. (PMID: 32841536) [Crossref]
105. Ibusuki M, Fujimori H, Yamamoto Y, Ota K, Ueda M, Shinriki S, et al. Midkine in plasma as a novel breast cancer marker. Cancer Sci 2009; 100: 1735-1739. (PMID: 19538527) [Crossref]
106. Goodman M, Liu Z, Zhu P, Li J. AMPK Activators as a Drug for Diabetes, Cancer and Cardiovascular Disease. Pharm Regul Aff 2014; 3: 118. (PMID: 27478687) [Crossref]
107. Woods A, Johnstone SR, Dickerson K, Leiper FC, Fryer LGD, Neumann D, et al. LKB1 is the upstream kinase in the AMP-activated protein kinase cascade. Curr Biol 2003; 13: 2004-2008. (PMID: 14614828) [Crossref]
108. Xia T, Chen D, Liu X, Qi H, Wang W, Chen H, et al. Midkine noncanonically suppresses AMPK activation through disrupting the LKB1-STRAD-Mo25 complex. Cell Death Dis 2022; 13: 414. (PMID: 35487917) [Crossref]
109. Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Mäkelä TP, et al. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol 2003; 2: 28. (PMID: 14511394) [Crossref]
110. Zeqiraj E, Filippi BM, Deak M, Alessi DR, van Aalten DMF. Structure of the LKB1-STRAD-MO25 complex reveals an allosteric mechanism of kinase activation. Science 2009; 326: 1707-1711. (PMID: 19892943) [Crossref]
111. Zeqiraj E, Filippi BM, Goldie S, Navratilova I, Boudeau J, Deak M, et al. ATP and MO25α Regulate the Conformational State of the STRADα Pseudokinase and Activation of the LKB1 Tumour Suppressor. PLoS Biol 2009; 7: e1000126. (PMID: 19513107) [Crossref]
112. Lin R, Elf S, Shan C, Kang HB, Ji Q, Zhou L, et al. 6-Phosphogluconate dehydrogenase links oxidative PPP, lipogenesis and tumour growth by inhibiting LKB1-AMPK signalling. Nat Cell Biol 2015; 17: 1484-1496. (PMID: 26479318) [Crossref]
113. Singletary SE, McNeese MD, Hortobagyi GN. Feasibility of breast-conservation surgery after induction chemotherapy for locally advanced breast carcinoma. Cancer 1992; 69: 2849-2852. (PMID: 1571916) [Crossref]
114. Tryfonidis K, Senkus E, Cardoso MJ, Cardoso F. Management of locally advanced breast cancer-perspectives and future directions. Nat Rev Clin Oncol 2015; 12: 147-162. Erratum in: Nat Rev Clin Oncol 2015; 12: 312. (PMID: 25668732) [Crossref]
115. Heil J, Kuerer HM, Pfob A, Rauch G, Sinn HP, Golatta M, et al. Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: current evidence and future challenges. Ann Oncol 2020; 31: 61-71. (PMID: 31912797) [Crossref]
116. Debled M, Mauriac L. Neoadjuvant chemotherapy: are we barking up the right tree? Ann Oncol 2010; 21: 675-679. (PMID: 20338876) [Crossref]
117. Han X, Li M, Xu J, Fu J, Wang X, Wang J, et al. miR-1275 targets MDK/AKT signaling to inhibit breast cancer chemoresistance by lessening the properties of cancer stem cells. Int J Biol Sci 2023; 19: 89-103. (PMID: 36594100) [Crossref]
118. Parker BS, Rautela J, Hertzog PJ. Antitumour actions of interferons: implications for cancer therapy. Nat Rev Cancer 2016; 16: 131-144. (PMID: 26911188) [Crossref]
119. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol 2005; 5: 375-386. (PMID: 15864272) [Crossref]
120. Du W, Frankel TL, Green M, Zou W. IFNγ signaling integrity in colorectal cancer immunity and immunotherapy. Cell Mol Immunol 2022; 19: 23-32. (PMID: 34385592) [Crossref]
121. Singh S, Kumar S, Srivastava RK, Nandi A, Thacker G, Murali H, et al. Loss of ELF5-FBXW7 stabilizes IFNGR1 to promote the growth and metastasis of triple-negative breast cancer through interferon-γ signalling. Nat Cell Biol 2020; 22: 591-602. Erratum in: Nat Cell Biol 2021; 23: 1048. (PMID: 32284542) [Crossref]
122. Zheng L, Liu Q, Li R, Chen S, Tan J, Li L, et al. Targeting MDK Abrogates IFN-γ-Elicited Metastasis inCancers of Various Origins. Front Oncol 2022; 12: 885656. (PMID: 35747815) [Crossref]
123. Chow KT, Gale M Jr. SnapShot: Interferon Signaling. Cell 2015; 163: 1808-1808.e1. (PMID: 26687364) [Crossref]
124. Hao H, Maeda Y, Fukazawa T, Yamatsuji T, Takaoka M, Bao XH, et al. Inhibition of the growth factor MDK/midkine by a novel small molecule compound to treat non-small cell lung cancer. PLoS One 2013; 8: e71093. (PMID: 23976985) [Crossref]
125. Mevissen TET, Komander D. Mechanisms of Deubiquitinase Specificity and Regulation. Annu Rev Biochem 2017; 86: 159-192. (PMID: 28498721) [Crossref]

126. Reyes-Turcu FE, Ventii KH, Wilkinson KD. Regulation and Cellular Roles of Ubiquitin-Specific Deubiquitinating Enzymes. Annu Rev Biochem 2009; 78: 363-397. (PMID: 19489724) [Crossref]

127. Hou K, Zhu Z, Wang Y, Zhang C, Yu S, Zhu Q, et al. Overexpression and Biological Function of Ubiquitin-Specific Protease 42 in Gastric Cancer. PLoS One 2016; 11: e0152997. (PMID: 27030989) [Crossref]

128. Wu Y, Wang Y, Lin Y, Liu Y, Wang Y, Jia J, et al. Dub3 inhibition suppresses breast cancer invasion and metastasis by promoting Snail1 degradation. Nat Commun 2017; 8: 14228. (PMID: 28198361) [Crossref]

129. Song IK, Kim HJ, Magesh V, Lee KJ. Ubiquitin C-terminal hydrolase-L1 plays a key role in angiogenesis by regulating hydrogen peroxide generated by NADPH oxidase 4. Biochem Biophys Res Commun 2018; 495: 1567-1572. (PMID: 29128359) [Crossref]

130. Lim R, Sugino T, Nolte H, Andrade J, Zimmermann B, Shi C, et al. Deubiquitinase USP10 regulates Notch signaling in the endothelium. Science 2019; 364: 188-193. (PMID: 30975888) [Crossref]

131. Vishnoi M, Boral D, Liu H, Sprouse ML, Yin W, Goswami-Sewell D, et al. Targeting USP7 Identifies a Metastasis-Competent State within Bone Marrow–Resident Melanoma CTCs. Cancer Res 2018; 78: 5349-5362. (PMID: 30026332) [Crossref]

132. Hayward S, Gachehiladze M, Badr N, Andrijes R, Molostvov G, Paniushkina L, et al. The CD151-midkine pathway regulates the immune microenvironment in inflammatory breast cancer. J Pathol 2020; 251: 63-73. (PMID: 32129471) [Crossref]

133. Gharesouran J, Taheri M, Sayad A, Ghafouri-Fard S, Mazdeh M, Omrani MD. The Growth Arrest-Specific Transcript 5 (GAS5) and Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1): Novel Markers Involved in Multiple Sclerosis. Int J Mol Cell Med 2018; 7: 102-110. (PMID: 30276165) [Crossref]

134. Han Z, Zhang C, Wang Q, Li L, Wang M, Li X, et al. MicroRNA-19b Downregulates NR3C1 and Enhances Oxaliplatin Chemoresistance in Colon Cancer via the PI3K/AKT/mTOR Pathway. Clin Med Insights Oncol 2021; 15: 11795549211012666. (PMID: 34017210) [Crossref]

135. Lovšin N, Marc J. Glucocorticoid Receptor Regulates TNFSF11 Transcription by Binding to Glucocorticoid Responsive Element in TNFSF11 Proximal Promoter Region. Int J Mol Sci 2021; 22: 1054. (PMID: 33494362) [Crossref]

136. Chen Z, Lan X, Wu D, Sunkel B, Ye Z, Huang J, et al. Ligand-dependent genomic function of glucocorticoid receptor in triple-negative breast cancer. Nat Commun 2015; 6: 8323. (PMID: 26374485) [Crossref]

137. Pan D, Kocherginsky M, Conzen SD. Activation of the Glucocorticoid Receptor Is Associated with Poor Prognosis in Estrogen Receptor-Negative Breast Cancer. Cancer Res 2011; 71: 6360-6370. (PMID: 21868756) [Crossref]

138. Zhang L, Song L, Xu Y, Xu Y, Zheng M, Zhang P, et al. Midkine promotes breast cancer cell proliferation and migration by upregulating NR3C1 expression and activating the NF-κB pathway. Mol Biol Rep 2022; 49: 2953-2961. (PMID: 35028860) [Crossref]

139. Xu YY, Mao XY, Song YX, Zhao F, Wang ZN, Zhang WX, et al. Midkine confers Adriamycin resistance in human gastric cancer cells. Tumour Biol 2012; 33: 1543-1548. (PMID: 22576950) [Crossref]

140. Lorente M, Torres S, Salazar M, Carracedo A, Hernández-Tiedra S, Rodríguez-Fornés F, et al. Stimulation of the midkine/ALK axis renders glioma cells resistant to cannabinoid antitumoral action. Cell Death Differ 2011; 18: 959-973. (PMID: 21233844) [Crossref]

141. Chu F, Naiditch JA, Clark S, Qiu YY, Zheng X, Lautz TB, et al. Midkine Mediates Intercellular Crosstalk between Drug-Resistant and Drug-Sensitive Neuroblastoma Cells In Vitro and In Vivo. ISRN Oncol 2013; 2013: 518637. (PMID: 24083030) [Crossref]

142. Hu R, Yan Y, Li Q, Lin Y, Jin W, Li H, et al. Increased drug efflux along with midkine gene high expression in childhood B-lineage acute lymphoblastic leukemia cells. Int J Hematol 2010; 92: 105-110. (PMID: 20544404) [Crossref]

143. Kang HC, Kim IJ, Park JH, Shin Y, Ku JL, Jung MS, et al. Identification of Genes with Differential Expression in Acquired Drug-Resistant Gastric Cancer Cells Using High-Density Oligonucleotide Microarrays. Clin Cancer Res 2004; 10: 272-284. (PMID: 14734480) [Crossref]

144. Kawai H, Sato W, Yuzawa Y, Kosugi T, Matsuo S, Takei Y, et al. Lack of the Growth Factor Midkine Enhances Survival against Cisplatin-Induced Renal Damage. Am J Pathol 2004; 165: 1603-1612. (PMID: 15509530) [Crossref]

145. Ota T, Jono H, Ota K, Shinriki S, Ueda M, Sueyoshi T, et al. Downregulation of midkine induces cisplatin resistance in human oral squamous cell carcinoma. Oncol Rep 2012; 27: 1674-1680. (PMID: 22344722) [Crossref]

146. Takei Y, Kadomatsu K, Matsuo S, Itoh H, Nakazawa K, Kubota S, et al. Antisense oligodeoxynucleotide targeted to Midkine, a heparin-binding growth factor, suppresses tumorigenicity of mouse rectal carcinoma cells. Cancer Res 2001; 61: 8486-8491. (PMID: 11731432) [Crossref]

147. Dai LC, Wang X, Yao X, Lu YL, Ping JL, He JF. Enhanced therapeutic effects of combined chemotherapeutic drugs and midkine antisense oligonucleotides for hepatocellular carcinoma. World J Gastroenterol 2007; 13: 1989-1994. (PMID: 17461503) [Crossref]

148. Inoh K, Muramatsu H, Torii S, Ikematsu S, Oda M, Kumai H, et al. Doxorubicin-Conjugated Anti-Midkine Monoclonal Antibody as a Potential Anti-Tumor Drug. Jpn J Clin Oncol 2006; 36: 207-211. (PMID: 16611663) [Crossref]

149. Zhao S, Zhao G, Xie H, Huang Y, Hou Y. A conjugate of an anti-midkine single-chain variable fragment to doxorubicin inhibits tumor growth. Braz J Med Biol Res 2012; 45: 230-237. (PMID: 22267001) [Crossref]

150. Maehara H, Kaname T, Yanagi K, Hanzawa H, Owan I, Kinjou T, et al. Midkine as a novel target for antibody therapy in osteosarcoma. Biochem Biophys Res Commun 2007; 358: 757-762. (PMID: 17506984) [Crossref]

151. Toyoda E, Doi R, Kami K, Mori T, Ito D, Koizumi M, et al. Midkine promoter-based conditionally replicative adenovirus therapy for midkine-expressing human pancreatic cancer. J Exp Clin Cancer Res 2008; 27: 30. (PMID: 18717994) [Crossref]

152. Rawnaq T, Dietrich L, Wolters-Eisfeld G, Uzunoglu FG, Vashist YK, Bachmann K, et al. The Multifunctional Growth Factor Midkine Promotes Proliferation and Migration in Pancreatic Cancer. Mol Cancer Res 2014; 12: 670-680. (PMID: 24567526) [Crossref]

153. Tian W, Shen J, Chen W. Suppression of midkine gene promotes the antitumoral effect of cisplatin on human gastric cancer cell line AGS in vitro and in vivo via the modulation of Notch signaling pathway. Oncol Rep 2017; 38: 745-754. (PMID: 28656262) [Crossref]

154. Sajid MI, Moazzam M, Kato S, Yeseom Cho K, Tiwari RK. Overcoming Barriers for siRNA Therapeutics: From Bench to Bedside. Pharmaceuticals (Basel) 2020; 13: 294. (PMID: 33036435) [Crossref]

155. Karadeniz Z, Aynacıoğlu AŞ, Bilir A, Tuna MY. Inhibition of midkine by metformin can contribute to its anticancer effects in malignancies: A proposal mechanism of action of metformin in context of endometrial cancer prevention and therapy. Med Hypotheses 2020; 134: 109420. (PMID: 31634770) [Crossref]

156. Ueno M, Kariya R, Gunya S, Cheevapruk K, Okada S. Midkine inhibitor (iMDK) induces apoptosis of primary effusion lymphoma via G2/M cell cycle arrest. Leuk Res 2022; 116: 106826. (PMID: 35316715) [Crossref]

157. Masui M, Okui T, Shimo T, Takabatake K, Fukazawa T, Matsumoto K, et al. Novel Midkine Inhibitor iMDK Inhibits Tumor Growth and Angiogenesis in Oral Squamous Cell Carcinoma. Anticancer Res 2016; 36: 2775-2781. (PMID: 27272788) [Crossref]

158. Wang J, Takeuchi H, Sonobe Y, Jin S, Mizuno T, Miyakawa S, et al. Inhibition of midkine alleviates experimental autoimmune encephalomyelitis through the expansion of regulatory T cell population. Proc Natl Acad Sci U S A 2008; 105: 3915-3920. (PMID: 18319343) [Crossref]