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A Review Of Midkine As Biomarker Protein For Diagnostic Several Dieases

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ABSTRACT

Background: *This review deals with a collection of information about a protein marker that is very important and alternates presence in many cases of normal and pathological growth, as it can be observed in high concentrations in the stages of fetal development and can be expressed significantly in many cases and disorders and midkine is considered a diagnostic marker for them as in types of cancers. It has a protein structure of 121 amino acids and its expression is located on the eleventh chromosome and has several functions, especially its expression in nervous tissues during the mid-gestation.*

Conclusion: *Midkine plays an important role in the inflammatory process in terms of its importance in the infiltration of immune cells into the peripheral organs and targeting midkine may be a viable new therapeutic option for chronic infections, especially infections of the kidneys, joints, nervous system and colon.*

Keywords: Midkine, Neurogenesis, Therapeutic, Chronic Inflammation.

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INTRODUCTION

Midkine (MK) was initially recognized in embryonic cancer cells, and its levels were high during the early stages of differentiation (Purnak *et al*., 2020). In many disorders, it also has a pathogenic role (Y. Cai et al., 2020). MK is a soluble protein that is found in large amounts in a variety of disorders, including cancer, and might be used as a disease biomarker. MK has been found to be overexpressed in various cancers, mainly when tumors develop to more advanced stages (Filippou *et al*., 2020). Most of the circulating MK gene expression has been identified in a number of tissue locations in healthy persons; the kidneys appear to produce MK protein. MK is expressed in normal kidneys in distal and proximal tubular epithelial cells, as well as at a lesser quantity in endothelial cells (Gowhari Shabgah *et al*., 2021). MK is released by the cells that make it and enters the bloodstream. Because MK synthesis continues in healthy patients, there is a healthy amount of MK in the peripheral blood. It is critical to define healthy normal MK ranges as a first step in evaluating the efficacy of assessing MK as a disease biomarker (D. Zhang *et al*., 2017).

Structure of Midkine protein:

Human Midkine (MK) has a molecular mass of ~13-kDa; it consists of 121 amino acids and the position of the MK gene, which may be located on chromosome 11. MK is mostly made up of 2 domains, each of which contains three antiparallel B-sheets bound together by disulfide bridges. A flexible loop is also present in the domain closest to the C-terminus (C-domain) (Mashaly *et al*., 2018). The C-domain maintains certain MK functions and contains two sites of heparin-binding. Aside from the two domains, the MK molecule

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has short tails on both ends and a hinge linking the domains. The C-domain half of the C-domain molecules performs most of its biological functions(Fig1) (Zhang *et al*., 2021)

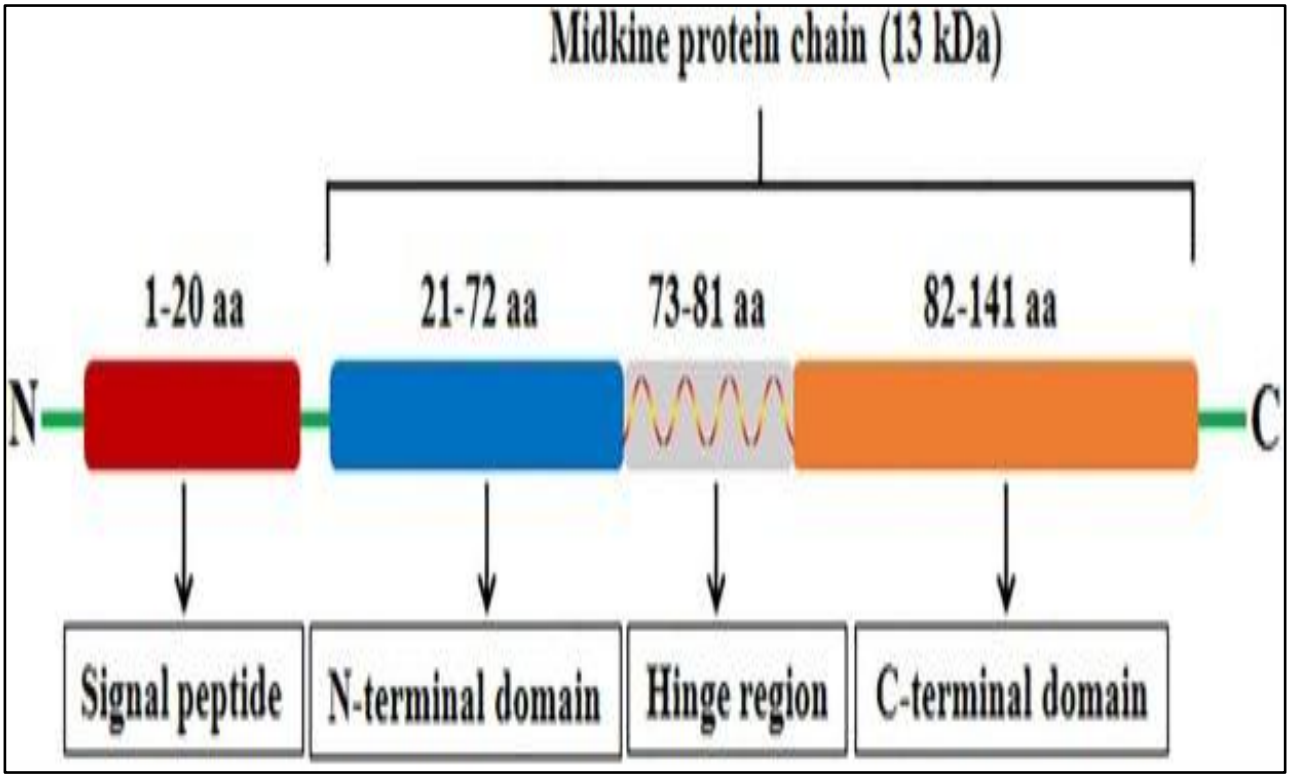

Figure (1): Structure of human midkine protein (Zhang *et al*., 2021).

Midkine protein Function:

Midkine (MK) is a versatile molecule that functions throughout fetal development and in the pathophysiology of inflammatory and malignant disorders (Muramatsu, 2014). MK has significant biological involvement in three areas: inflammation, cancer, and the neurological system (Karadeniz *et al*., 2020).

Neurogenesis

Midkine (MK) expression is high in neural tissues during mid-gestation when neurons emerge. MK is located in the neural anlagen and is highly expressed in the spinal cord and brain. MK expressed in the neural plate is necessary for the early phases of cell speciation at the neural plate boundary and is required for the development of sensory neurons and neural crest cells, according to knockdown and overexpression experiments (Vieceli & Bronner, 2018). Extended structures called radial glial processes are formed from neural stem cells that allow neurons to move outside along them. MK is highly expressed in these processes. MK promotes brain precursor cell survival and development. Furthermore, the MK is involved in the development of synapses. MK levels have been shown to be high in cases of nerve tissue and brain damage, leading to the assumption that MK helps to treat these ailments (Ross-Munro *et al*., 2020). The appearance of the buildup of MK in plaques and neurofibrillary tangles are two histological markers of Alzheimer's disease (AD).

Although the exact pathogenic process is unknown, the accumulation of Ab peptide is assumed to be the primary cause of memory loss and neuronal death in AD *(*Muralidar *et al*., 2020). MK had previously been discovered in human AD patients' senile plaques in the brain. MK binds to Ab and stops it from causing neurotoxicity.

Alzheimer's patients who previously had MK deficiency showed significantly increased Ab plaque accumulation, and the presence of MK was found to slow the onset of AD (Zou et al., 2020).

Cancer:

MK is strongly linked to a bad outcome in human carcinomas. In adulthood, MK protein expression is observed at a deficient level in the kidney (Komata *et al*., 2021). Multiple cancer forms, including thyroid papillary carcinomas, Wilms' tumors, glioblastoma, neuroblastoma, stomach, esophagus, lung, breast, bladder, ovary, liver, colorectal, and prostate cancers, have been discovered to have high MK expression. MK levels in the blood are typically less than 0.5-0.6 ng/ml in healthy people, whereas patients with certain cancers have substantially greater amounts (Chang *et al*., 2020).

1- Colorectal Carcinomas: MK expression may be detected in both adenocarcinomas and adenomas during precancerous stages. Generally, MK expression rises with the progression of the tumor stage. In many malignancies, MK serum concentrations are a potential tumor marker (Kemper *et al*., 2020).

2- Neuroblastoma: is an expected solid tumorous growth in children that arise from neural crest cells. MK levels in the blood were found to be considerably higher in neuroblastoma patients (Ji *et al*., 2020).

3- Cancer of the pancreas: is one of the worst forms of human cancer, having a fast progression rate. Patients with pancreatic cancer had much more significant MK in their blood than healthy persons, indicating that MK might be utilized as a diagnostic marker for this disease (Rawnaq *et al*., 2014).

4- Lung Cancer: The most common kind of cancer that results in death is lung cancer, which is prevalent all over the globe. This disease identification at an early stage may provide patients with other therapeutic alternatives and an increased possibility of survival. MK is a biomarker that can be used to diagnose lung cancer in its early stages in people at risk. It has been shown that an increased risk of cancer is related to MK overexpression (Xia *et al*., 2016).

5- Bladder cancer (BCa): is the most prevalent cancer in men worldwide, as well as the frequent malignancy of the urinary system among old pepole. MK levels are elevated, suggesting that MK may be a viable biomarker for identifying BCa-prone persons (Vu Van *et al*., 2016).

6- Hepatocellular Carcinoma (HCC): is a prevalent kind of first-stage liver cancer that is also one of the most aggressive malignancies globally. It has been determined that early detection is the single most significant aspect for HCC patients to have a chance at survivability throughout the long term. It has become clear that developing new biomarkers that are both specific and sensitive is vital. Serum MK protein concentration in HCC patients revealed elevated MK expression (Osman *et al*., 2018).

7- Brain Tumors: Gliomas are the most frequent primary malignant brain tumor, and they are exceedingly deadly. Glioma patients with high levels of MK overexpression have a reduced chance of surviving. Prognostic and diagnostic indicators for glioma patients may be improved if MK overexpression is detected earlier in the disease (Cheng *et al*., 2014).

8- Esophageal Cancer: Overexpression of MK has been discovered in various human esophageal malignant cancers. MK expression has been linked to a lack of tumor cell differentiation. The size of the tumor was linked to high MK levels in the blood (S. Li et al., 2018).

9- Breast Cancer: is a genetically complicated and widely spread disease. New prognostic biomarkers are still urgently needed today MK levels in breast cancer patients' tissue, and plasma were discovered to be excessively high as compared to healthy people. The therapeutic relevance of MK in the plasma of breast cancer patients has to be investigated further (Hadida *et al*., 2019).

10- Ovarian Cancer: is the most frequent kind of gynecological cancer in women worldwide. The development of more reliable and early detection diagnostics for ovarian cancer is unquestionably the most critical step in lowering death rates. MK proteins have been shown to be useful as plasma biomarkers for ovarian cancer in a previous investigation (Wu *et al*., 2015).

Inflammation:

Midkine is also critical for immune cell infiltration into peripheral organs; in MK-deficient, the number of neutrophils and macrophages invading the kidney is much

lower. Thus, due to MK's function in inflammation, chemokines and leukocytes are produced, and the influx into the body; targeting MK might be a viable new therapy option for chronic inflammation, such as autoimmune disorders (Tsai *et al*., 2020). Diabetes-related nephropathy, multiple sclerosis, rheumatoid arthritis, and vascular restenosis have all been linked to MK (Weckbach *et al*., 2018).

1- **Kidney**:

During inflammation, MK is critical. Within the adult organism, MK is found to be expressed continuously in the epithelial cells of the renal tubules, and increased MK expression has been associated with a variety of pathological kidney diseases, including diabetic nephropathy. Healthy patients had much less MK expression in their glomeruli interstitium and tubules than those with diabetic kidney disease, which is connected to inflammation of the tubulointerstitial tissue (Y. Cai *et al*., 2020).

This indicates that MK might exacerbate the inflammatory response in diabetic nephropathy. In the absence of MK, however, decreased renal injury was linked to a decrease in inflammatory cell infiltration into the renal tissue. By inducing chemokine expression in the kidney. There is a possibility that MK may contribute to the mobilization of leukocytes (Y. Cai *et al*., 2020). Thus, MK-induced chemotaxis may explain the main reason for decreased mobilization and stimulation of inflammatory cells in inflamed kidneys when MK is absent(Wang *et al*., 2020).

Chemokine stimulation might not be the only way leukocytes recruit to the kidney, MK may worsen many renal diseases by increasing leukocyte recruitment (Campbell *et al*., 2021). Immune cell infiltration and smooth muscle cell migration produce Neointima development(Said *et al*., 2022). MK is involved in diabetic nephropathy, and the data show that MK speeds up the intracellular signaling network triggered by hyperglycemia in diabetic nephropathy and is involved in tubulointerstitial inflammation(Metwalley *et al*., 2021)

2- Joints:

Rheumatoid arthritis (RA) is a chronic disorder that causes deterioration and deformation of the joints, and it has a clinical and epidemiological impact. RA affects between 0.5%-1% of people globally, and it was found that women are more affected by this disease than males(Guo *et al*., 2018).. MK levels are found to be elevated in synovial fluid and serum by 90% in RA patients (Shindo *et al*., 2017).

3- Central Nervous System:

Multiple sclerosis (MS) cases are often examined using the MK marker. To be more precise, MS should be highlighted because it is a disease known to devastate the central nervous system (Lassmann, 2018). MS is an autoimmune disorder in which activated T cells and demyelinating antibodies promote the demyelination of CNS axons. Furthermore, clinical symptoms and their severity, such as limb weakness in MS, have been linked with elevated levels of MK in the spinal cord (Zhang *et al*., 2015). Histological investigation of the spinal cord indicated reduced inflammatory cell infiltration in MK-deficient patients. At the same time, MK treatment reversed this effect, indicating a positive association between clinical findings and histological analyses (Yamauchi., 2016).

4- Colon:

In Europe, around 1.4 million persons were diagnosed with inflammatory bowel disease (IBD) in early adulthood or late adolescence, with two primary kinds, ulcerative colitis (UC) and Crohn's disease (CD) (Tontini, 2015). Inflammation occurs in the digestive system and is a hallmark of both disorders due to an immune response.

MK serum levels correlated positively with Crohn's Disease Activity Index (CDAI), which comprises medical history, vital indicators, and clinical results. As a result, MK has been identified as a sensitive biomarker with diagnostic value; MK was discovered to be expressed in the distal colon of mice, especially in the submucosal layers and fibroblasts of the mucosal.

CONCLUSION

Midkine plays an important role in the inflammatory process in terms of its importance in the infiltration of immune cells into the peripheral organs and targeting midkine may be a viable new therapeutic option for chronic infections, especially infections of the kidneys, joints, nervous system and colon.

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