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Review

# Midkine proteins in cardio-vascular disease. Where do we come from and where are we heading to?

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ABSTRACT

Midkine is a recently identified new growth factor/cytokine with pleiotropic functions in the human organism. First discovered in the late eighties, midkines have now become the subject of numerous studies in cardiovascular, neurologic, renal diseases and also various types of cancers.

We summarize here the most important functions of midkine in cardiovascular diseases, emphasizing its role in inflammation and its antiapoptotic and proangiogenetic effects. Midkine has multiple roles in the organism, with the specific feature of being either beneficial or harmful depending on which tissue it acts on. Even though midkine has been shown to have cardiac protective effects against acute ischemia/reperfusion injury and to inhibit cardiac remodeling, it also promotes intimal hyperplasia and vascular stenosis. As such, different therapeutic strategies are currently being evaluated, consisting of administering either midkine proteins or midkine inhibitors depending on the desired outcome. More data is gathering to suggest that these novel therapies could become an adjunctive to standard cardiovascular therapy. Nonetheless, much is still to be learned about midkine. The encouraging results up till now require further studying in order to fully understand the complete profile of its mechanism of action and the clinical safety and efficacy of novel therapeutic opportunities offered by midkine molecular targeting.



**Contents**



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## 1. The rise of the midkine – discovery, structure and function

Midkine (MK) is a new growth factor/cytokine with pleiotropic roles in the human organism (Muramatsu, 2010). MK proteins were discovered in the late 80s when Kadomatsu et al. (1988) published a paper describing these novel molecules for the first time. MK was discovered as a product of a gene up-regulated in the early stages of retinoic acid-induced differentiation of embryonic carcinoma cells. Because the ribonucleic acid (RNA) was originally detected only in midgestation mouse embryos and in the kidney of adults, MK was initially called "midgestation embryo and kidney (MK) gene", only to receive its current name at a later time (Jono and Ando, 2010).

Midkine is a 13-kDa heparin-binding growth factor, now part of a small protein family made of two heparin-binding growth associated molecules, the other member being pleiotrophin (PTN) (Kadomatsu et al., 2013). MK has a 50% structural sequence identity with PTN, both of them having two structural domains (N- and C- domain) (Kadomatsu et al., 1988; Kaname et al., 1993; Muramatsu, 1993). Each of these domains are assembled out of three antiparallel β-strands held together by 2 disulfide bridges in the C-domain and 3 disulfide bridges in the N-domain, as shown by NMR (nuclear magnetic resonance). A hinge region connects the N-domain to the C-domain. The C-domain is responsible for most of the biological activities. It has a more complex structure, with a long flexible hairpin loop at the center, where one heparin binding site is located, the other one being formed by basic residues on the β-sheet of the same domain (Iwasaki et al., 1997). In turn, it was suggested that the N-domain functions mainly as a stabilizing domain against proteolytic degradation of the C-domain (Matsuda et al., 1996). PTN shares many MK receptors and shows similar biological activities, such as promoting the growth, survival, and migration of various cells, involvement in neurogenesis and epithelial mesenchymal interactions during organogenesis. Plasma levels of both MK and PTN increase during ischemic injury and tumorigenesis. However, in general, MK is expressed more intensely and in a wider range of carcinomas than PTN (Kadomatsu and Muramatsu, 2004).

The MK is coded by the human MK gene, located on chromosome 11 at p11.2 (Kaname et al., 1996). The MK gene has four coding exons, and, due to the different splicing and site of transcription initiation, there are 7 isoforms of MK mRNA. A truncated form of MK derived from mRNA lacking the second coding exon was found and thought to possibly have diagnostic value as it appears to be tumor-specific (Takada et al., 2005).

In recent years, a large body of evidence has accumulated to sustain a wide range of functions for MK in the human organism (see Fig. 1), starting from cell proliferation, differentiation, survival and migration, and moving on to a variety of biological processes, including neuronal development, angiogenesis, oncogenesis and inflammation (Garver et al., 1993, 1994; Horiba et al., 2006).

### 1.1. Midkine physiology

MK is involved in growth, development and repair. Therefore, the highest expression can be found during embryogenesis, especially in the mid-gestation period (Kadomatsu et al., 1990). Limited data suggests midkine levels suffer no age-related changes. In adults, significant MK expression is observed only in restricted sites such as the kidney, gut, epidermis, bronchial epithelium, lymphocytes, and macrophages. MK expression in other sites can be induced after any type of injury including cancer (Muramatsu, 2014). Table 1 summarizes the physiological and pathological conditions in which MK expression is enhanced as well as their subsequent tissue-specific effect.

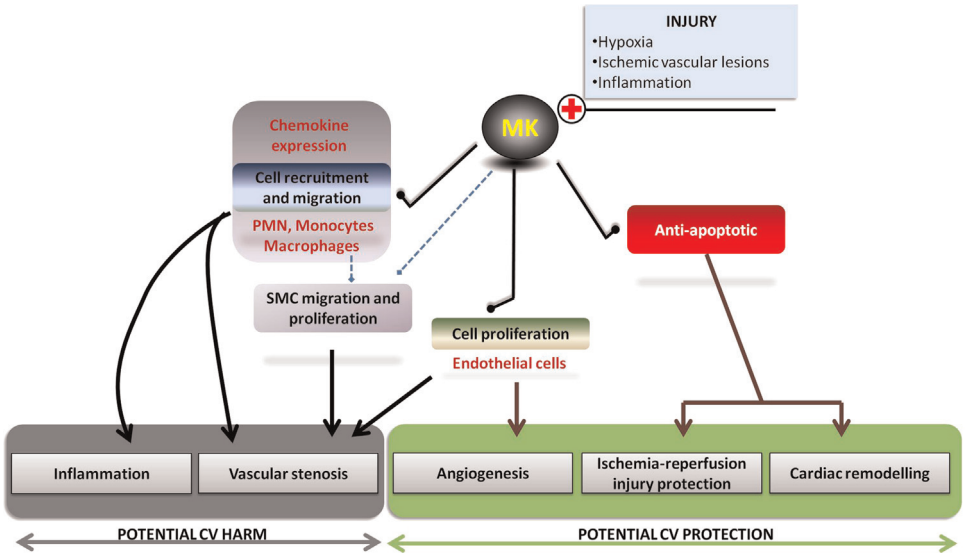


**Fig. 1.** Midkine mechanism of action: Midkine (MK) expression is increased by several types of tissue injuries such as hypoxia, ischemia and inflammation. MK has a wide range of actions including cell recruitement and migration, chemokine expression, induction of SMC (smooth muscle cell) migration and proliferation as well as endothelial cell proliferation and anti-apoptotic effects. MK expression can result in both beneficial and harmful cardiovascular (CV) effects. Through its anti-apoptotic effects, MK offers protection against acute cardiac injury such as ischemia-reperfusion injury and inhibits negative cardiac remodeling. Moreover, while inducing endothelial cell proliferation MK promotes angiogenesis which further inhibits cardiac remodeling. On the other hand, MK promotes inflammatory processes through cell recruitment and migration as well as chemokine expression and, along with SMC proliferation, plays a significant role in vascular stenosis.