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# Gene Section
Review

# MIF (macrophage migration inhibitory factor (glycosylation-inhibiting factor))

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## Identity

**Other names:** GIF, GLIF, MMIF

**HGNC (Hugo):** MIF

**Location:** 22q11.23

## DNA/RNA

### Description

0,84 kb; mRNA: 561 bp; 3 Exons.

### Transcription

The promoter region contains no TATA box.

### Pseudogene

There are no MIF pseudogenes in the human genome. In contrast 5 pseudogenes have been described in the murine genome.

## Protein

### Description

MIF is comprised of 115 amino acids with a molecular weight of 12,5 kDa (Weiser et al., 1989). In addition, research on the secondary structure revealed the existence of two antiparallel alpha-helices and six beta-pleated sheets with a high degree of similarity to MHC molecules (Suzuki et al., 1996). MIF acts as a pro-inflammatory protein, exists as a homo-trimer and displays enzymatic action (Rosengren et al., 1996).

### Expression

Widely.

### Localisation

Intracellular, cytoplasm, cytosolic, near the plasma membrane, perinuclear.

### Function

MIF monomers are able to align in order to form a homotrimeric molecule that is homologous to the enzyme D-Dopachrome-tautomerase (Sun et al., 1996). From this structural analysis, some researches suggested that MIF may also display enzymatic activity (Rosengren et al., 1996). To date, the physiological importance of this enzymatic activity has not yet been revealed. Interestingly, using ISO-1, a known inhibitor of the enzyme D-Dopachrome-tautomerase led to reduced activity of MIF (Lubetsky et al., 2002). Therefore, it was hypothesized that this enzymatic activity may be related to its proper functioning. The protein MIF is involved in inducing angiogenesis, promoting cell cycle progression, inhibiting apoptosis and inhibiting lysing of tumor cells by NK cells (Takahashi et al., 1998; Shimizu et al., 1999; Mitchell and Bucala, 2000; Morrison et al., 2001; Fingerle-Rowson et al., 2003). Recently, the CD74 molecule has been suggested to act as a potential receptor for MIF (Leng et al., 2003).

### Homology

MIF shows homology to the enzyme D-Dopachrome tautomerase.

## Mutations

**Note**

Not known.

# Implicated in

## Colon cancer

**Disease**

MIF is upregulated in tumors as well as precancerous lesions (Wilson et al., 2005). They examined patients suffering from adenomas. In addition, an animal model of adenomatous polyposis coli was used. In both settings, the authors describe an increase in MIF mRNA levels in the diseases group when this was compared to healthy controls. Interestingly, in a mouse model of intestinal tumorigenesis, MIF deletion leads to a significant decrease in tumor size. In addition, reduced angiogenesis was taking place. The involvement of MIF in angiogenesis was also shown by Ogawa et al., using a mouse model of colon cancer (Ogawa et al., 2000). The application of MIF antibodies leads to suppression of angiogenesis in this disease model. Further work by Sun et al. demonstrated an involvement of MIF in tumor cell migration (Sun et al., 2005). They used siRNA technique and were able to show inhibition of cell migration after addition of siRNA directed against MIF. In an animal model, they injected colon cancer cells into mice portal vein after pretreatment with siRNA. The number of liver metastases was significantly reduced in the pretreated model. In summary, there is sufficient evidence to assume a role of MIF in both angiogenesis and tumor cell migration in colon cancer (Bach et al., 2009).

**Prognosis**

MIF expression is correlated with outcome (Legendre et al., 2003). Legendre et al. (2003) examined MIF distribution in 99 specimens of colorectal cancer. Primarily, they applied immunohistochemistry. They describe that the expression of MIF (and also galectin-3) were increased in tumor tissue compared to normal tissue. For MIF, they could provide evidence that in Dukes C or D tumors with high concentration of MIF, this was associated with significantly better prognosis than in tumors with low MIF concentrations. They suggest that MIF could be used to identify patients at risk needing more aggressive treatment strategies.

## Melanoma

**Disease**

MIF inhibits lysis of melanoma cells by NK cells (Repp et al., 2000). This was shown by Apte et al., who demonstrated that NK cells are prevented from cell lysis of melanoma cells (Apte et al., 1998). This underlines the influence of MIF on the immune system. In addition, it enhances tumor cell proliferation.

**Prognosis**

To date, there is no clear association between MIF concentration and prognosis in melanoma cells.

## Prostate cancer

**Disease**

MIF was shown to be abundant in prostate cancer (Meyer-Siegler et al., 1998). In addition, MIF was shown to influence cell viability and invasiveness. Specifically in prostate cancer, androgen independent cancer cells relied on MIF activated pathways in order to grow and for their invasiveness. Androgen dependent tumor cells did not require these signal transduction pathways. Meyer-Siegler et al. were able to show that CD74, a potential MIF surface receptor, was abundant in androgen-independent tumor cells (Meyer-Siegler et al., 2006). Receptor blockage as well as strategies to reduce MIF resulted in decreased cell proliferation, MIF secretion and invasion of tumor cells.

**Prognosis**

MIF expression clearly correlates with disease progression (Meyer-Siegler et al., 2002). In androgen independent prostate cancer, cells require MIF activated signal transduction pathways for invasion and growth, in contrast to androgen dependent tumor cells. In a study by Meyer-Siegler, serum MIF concentration was measured in dependence of Gleason score in patients with prostate cancer (Meyer-Siegler et al., 2002). They were able to show that increased MIF concentration is positively associated with a Gleason Score greater than 5. In addition, even in patients with normal prostate-specific antigen, MIF concentration was increased. From their data, they conclude that MIF may be a suitable biomarker for prostate cancer.

## Lung adenocarcinoma

**Note**

Treatment with siRNA leads to a significant reduction in cell invasiveness and cell migration (Rendon et al., 2007), paralled by a reduction of a Rho GTPase. MIF overexpression led to adverse effects.

**Prognosis**

Kamimura and colleagues analysed the role of MIF with respect to prognosis in lung cancer (Kamimura et al., 2000). They used immunofluorescence staining in primary lung tissue that had been obtained surgically. They were able to demonstrate a diffuse staining pattern within the cytoplasm. Furthermore, sometimes, a nuclear staining was also observed. Interestingly, the authors were able to demonstrate a correlation between a lack of nuclear staining and a poorer prognosis.
From this observation, they concluded that MIF might play different roles with respect to subcellular localization. It needs to be mentioned however, that only thirty-eight cases were reviewed.

## Glioblastoma

**Note**

MIF is involved in angiogenesis and cell cycle regulation. It was demonstrated that MIF expression is induced following hypoxia and hypoglycemia (Bacher

et al., 2003), which are both considered activators of angiogenesis. Using immunofluorescence techniques, MIF could be demonstrated around necrotic tissue and in blood vessels surrounding tumor cells. Therefore it was concluded that neovascularization is enhanced by MIF. In line with this observation is the work published by Munaut et al. (2002). They demonstrated that there is a correlation between MIF expression and the expression of vascular endothelial growth factor (VEGF). They analysed primary glioblastoma tissue using RT-PCR and immmunohistochemistry and they were able to show a strong correlation between MIF expression and VEGF mRNA concentration. >From these data, it was suggested that there may be a common triggering factor. Inactivation of p53 may be of central importance, as it is a common event in glioblastoma progression (Bach et al., 2009). In addition, p53 inactivation is also involved in increased VEGF expression (Kieser et al., 1994). Since the angiogenic potential of a tumor is vital for formation of metastases, it may be a potential target for antitumor therapy.

### *Hepatocellular carcinoma*

**Note**

MIF expression and increased angiogenesis were also demonstrated in hepatocellular carcinoma following hypoxia (Hira et al., 2005).

**Prognosis**

MIF overexpression correlates with negative prognosis (Hira et al., 2005). 56 samples of hepatocellular carcinoma were analysed using Western blot and correlated these values with clinical parameters. In addition, they used immunohistochemistry. They showed that MIF expression was correlated with high alpha fetoprotein level and the recurrence of hepatic tumor. In addition, tumor free survival was reduced when MIF expression was increased. In addition, increased mRNA concentrations can be seen (Ren et al., 2003).

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