

MCPIP1

Subjects: [Genetics & Heredity](#) | [Physiology](#)
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MCPIP1 (also known as regnase-1) is encoded by the ZC3H12A gene and is composed of 599 amino acids that encode a 66-kDa protein. MCPIP1 is a potent anti-inflammatory protein, and plays many roles within the regulation of the immune response.

MCPIP1

inflammation

immune response

chronic inflammation

interleukins

RNase

1. Introduction

MCPIP1 is a multifaceted anti-inflammatory protein that plays a critical downregulatory role in the immune inflammatory response through at least two independent mechanisms: destabilising the mRNA transcripts of many cytokines and inhibiting lipopolysaccharide (LPS)- and IL-1β-induced NF-κB signalling [\[1\]](#).

MCPIP1 possesses a well-documented ribonuclease ability, as demonstrated by its targeting of many cytokine mRNAs for direct degradation; specifically, previous studies have shown that MCPIP1 degrades IL-1β, IL-6, IL-8, IL-12p40, and IL-17 mRNA transcripts (Table 1) [\[2\]](#)[\[3\]](#)[\[4\]](#)[\[5\]](#)[\[6\]](#)[\[7\]](#)[\[8\]](#).

Table 1. mRNA of cytokines and chemokines degraded by MCPIP1 in various types of cells.

mRNA	Cells	References
IL12p40	Macrophages	[3]
IL6	Macrophages, cardiomyocytes	[3] [6]
IL1β	Macrophages	[2]
IL17RA, IL17RC	Lymphocytes, fibroblasts	[5]
IL8	Epithelial cells	[4]

IL2	T cells	[7]
Cxcl1, Cxcl2, Cxcl3	-	[8]

The regulation of mRNA transcripts is one of the primary mechanisms through which protein levels are controlled: these molecules can be protected or destroyed to alter the amount of protein being translated under specific circumstances.

Across all organisms, mRNA destabilisation and decay can be performed via a variety of pathways, such as the targeting of conserved AU-rich elements (AREs) and stem-loop structures (SLs) or nonsense-mediated decay (NMD), which prevents the translation of mRNAs. Mino and colleagues discovered that MCPIP1 degrades IL-6 mRNA via the SL structure in the 3'-UTR region, and IL-6 mRNA molecules lacking this sequence were not degraded [\[8\]](#). More recently, Wilamowski et al. observed that IL-6 is degraded by MCPIP1 in a progressive manner: after SL is cleaved, multiple shorter single-stranded RNA (ssRNA) molecules are generated, and these molecules are then further degraded by MCPIP1. Interestingly, these researchers also found that a 6-nt RNA molecule was bound but not degraded, possibly because it is too short to reach the catalytic site [\[9\]](#).

The critical RNase capability of MCPIP1 is due to its PIN domain (Figure 1) [\[9\]](#). PIN domains, which are a common motif found in both prokaryotic and eukaryotic nucleases, are primarily responsible for binding to and degrading RNA molecules and also play roles in the *bacterial* stress response and pathogenesis [\[10\]](#). The importance of the PIN domain was demonstrated by Matsushita and colleagues, who used site-directed mutagenesis to alter one amino acid (D141N) and found that this alteration completely abolished the RNase function [\[3\]](#).

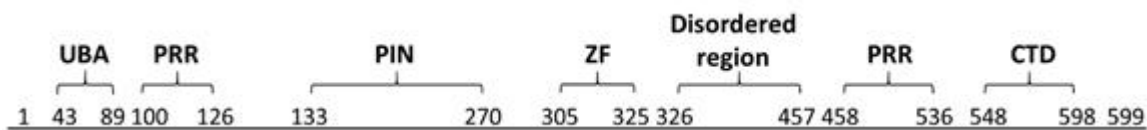


Figure 1. Domains of MCPIP1. Ubiquitin-associated domain (UBA) 43–89; proline-rich region (PRR) 100–126 and 458–536; PiIT N-terminus nuclease domain (PIN) 133–270; zinc-finger motif (ZF) 305–325; disordered region 326–457; and C-terminal conserved domain (CTD) 545–598. Based on Wilamowski et al., 2018 [\[9\]](#).

Within the PIN domain, four aspartate residues act in coordination with a single magnesium ion to assemble a catalytic cleft, which constitutes the active site of MCPIP1. This positively charged loop sequence might be responsible for binding to RNA by specifically attracting the negatively charged phosphate groups of oligonucleotide backbones [\[11\]](#).

The USP10-dependent deubiquitination of NEMO and TRAF6 proteins is another strategy through which MCPIP1 can regulate inflammation and the immune response [\[12\]](#). It results in the negative regulation of the transcription factors c-Jun N-terminal kinase (JNK) and NF-κB [\[13\]](#). JNK and NF-κB signalling mediate many cellular responses,

including infections, inflammation, and apoptosis, through the transcriptional activation of several cytokine genes (Figure 2) [14].

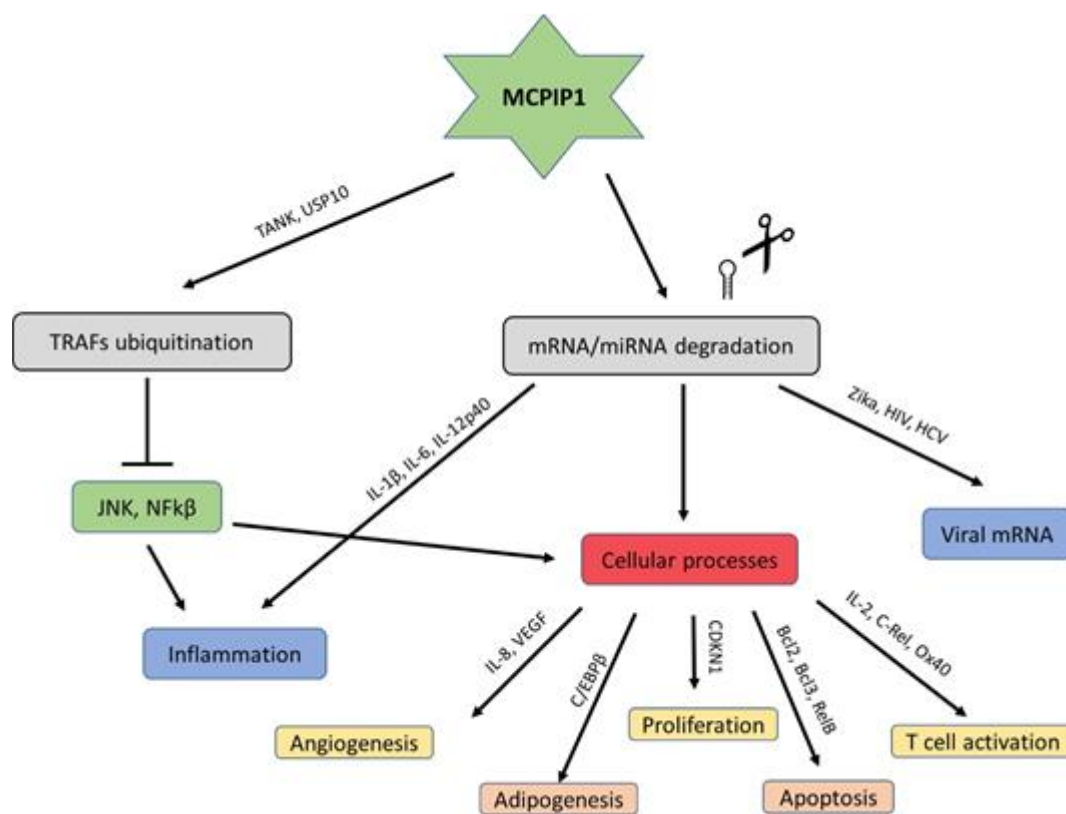


Figure 2. Schematic modes of action of MCPIP1.

MCPIP1 also possesses a CCCH zinc finger domain close to the C-terminal region of the PIN domain (Figure 2). Zinc finger domains are commonly regarded as DNA-binding, but CCCH-type zinc fingers, among others, are involved in binding to RNA molecules and regulating their metabolism [15]. CCCH zinc finger proteins are particularly associated with immune responses and play roles in antiviral innate immunity, the production of cytokines, immune cell activation, immune homeostasis, and the regulation of cell differentiation and cancer cell growth. For example, Roquin-1, another CCCH-type zinc finger protein, causes a lupus-like autoimmune disease in mice when mutated [16].

MCPIP1 appears to undergo homooligomerisation during interaction with RNA substrates (Figure 3). Size-exclusion chromatography revealed that a dimeric form of MCPIP1 appears to be the most common under native conditions, although tetrameric and monomeric fractions might also be present [9]. This homooligomerisation occurs through the proline-rich C-terminal domain [17]. Mutations that prevent oligomerisation also abolish RNase activity, which indicates that oligomerisation is crucial for MCPIP1 enzyme function [18]. Other RNases and RNase domains also function in an oligomerised state; for example, RNase A oligomerises via a proline-dependent arm exchange mechanism [19].

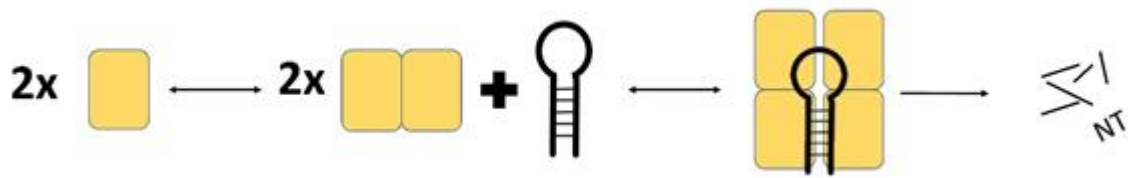


Figure 3. Schematic presentation of the ternary complex model of MCPIP1. Based on the size exclusion chromatography results Wilamowski et al. proposed a sequential binding model: oligo + MCPIP1_{dimer} + MCPIP1_{dimer} \rightleftharpoons oligo-MCPIP1_{dimer} + MCPIP1_{dimer} \rightleftharpoons oligo-MCPIP1_{tetramer} (MCPIP1 marked as a yellow box). MCPIP1 degrades RNA molecules as a tetramer [9].

The C-terminal region appears to be crucial for another function of MCPIP1: MCPIP1 plays a broad role in suppressing microRNA (miRNA) activity and biogenesis [17]. miRNAs are small non-coding RNA molecules that perform RNA silencing and post-transcriptional regulation of gene expression. MCPIP1 RNase blocks Dicer processing and prevents pre-miRNAs from developing into mature miRNAs. MCPIP1 might recognize and degrade pre-miRNAs in a similar way to mRNAs by targeting terminal loop structures and cleaving RNA with the PIN domain [17]. Both human and viral pre-miRNAs are cleaved by MCPIP1. However, some viral miRNAs might be able to resist this effect and repress MCPIP1 expression, as evidenced by Happel and colleagues, who studied the relationship between MCPIP1 and miRNAs in Kaposi's sarcoma-associated herpesvirus (KSHV) [20].

2. Broad Roles of MCPIP1 in the Immune System

The crucial role that MCPIP1 plays in the regulation of inflammation can be clearly demonstrated by knockout mice. *ZC3H12A*^{-/-} mice exhibit a severely altered phenotype characterized by drastic immune system dysregulation: these mice suffer growth retardation and spontaneous death usually within 12 weeks [3]. In these mice, immune cells are overactivated and hyperinvading, resulting in splenomegaly, lymphadenopathy, anaemia, and hyperimmunoglobulinemia. These deviations from normal physiology do not appear until after birth; newborn *ZC3H12A*^{-/-} mice do not exhibit many obvious differences from their wild-type littermates. After approximately 3 weeks, however, the spleen sizes are notably larger, and leukocyte infiltration into the interstitial spaces of the lungs can be observed. In addition, proinflammatory cytokines, such as IL-6 and IL-1 β , exhibit markedly higher expression in MCPIP1-deficient mice.

Interestingly, treatment with antibiotics improves the lifespan and ameliorates hyperinflammatory syndrome in knockout mice [21]. This finding might be explained by host-microbiota interactions: it has been hypothesized that commensal microbiota in mucosal surfaces and the digestive system can elicit TLR signalling and thereby contribute to the development of some autoimmune diseases such as IBD [22]. Therefore, this finding might indicate another function of MCPIP1 within the immune system: attenuation of baseline TLR signalling by resident microorganisms.

The role of MCPIP1 as a broad negative regulator of inflammation is also evidenced by the stimuli that can induce its expression. *ZC3H12A* expression is induced by a number of proinflammatory factors, although the strongest

inducers might depend on the cell type. For example, in human hepatoma HepG2 cells, IL-1 β is an effective stimulant, whereas in promonocytic U937 cells, TNF is the strongest inducer of MCPIP1 [2]. The expression of the *ZC3H12A* gene is also rapidly induced by many factors that are present during infectious attack by pathogens. MCPIP1 expression is increased during viral, bacterial, and fungal infections [23]. LPS, the main outer membrane component of gram-negative bacteria, and the mycobacterium tuberculosis 38-kDa antigen both trigger TLR signalling and subsequently increase MCPIP1 expression [24][25].

However, MCPIP1 appears to exert an overall relaxing effect on immune cell activation. Conditional T-cell MCPIP1-knockout mice exhibit greatly increased rates of T-cell activation, which leads to the conclusion that MCPIP1 plays a role in suppressing the activation of immune cells. MCPIP1 degrades the mRNAs of the genes c-Rel, Ox40, and IL-2, which are responsible for the activation of T cells [26]. MCPIP1 works cooperatively with Roquin to suppress the differentiation of proinflammatory T helper 17 (Th17) cells [27]. Moreover, MCPIP1 negatively regulates group 2 innate lymphoid cells (ILC2s) functions, which are a critical innate source of type 2 cytokines in allergic inflammation. Matsushita et al. discovered that I κ B kinase (IKK) complex-mediated MCPIP1 degradation is essential for IL-33- and IL-25-induced ILC2 activation [28].

Despite this effect of limiting immune cell activation, MCPIP1 might play a role in defending the host from foreign nucleic acids such as viruses. Qian and colleagues demonstrated that MCPIP1 can distinguish between mRNAs from exogenously transfected plasmids and those from the host genome and selectively degrade foreign transcripts. Additionally, these researchers showed that the induction of MCPIP1 can restrict Zika virus infection and thereby significantly decrease the viral RNA levels [29][30][31][32]. MCPIP1 also potently inhibits other viral infections, including HIV-1 and Hepatitis C Virus (HCV) infection [21][23].

2.1. MCPIP1 Regulation

The undisputed main role of MCPIP1 is to suppress the inflammatory immune response, which is crucial for preventing a state of chronic inflammation. However, the strong activation of MCPIP1 during pathogen infection would create a favourable environment for the pathogen to invade and replicate. Therefore, pathways need to be in place for the regulation of MCPIP1 and prevent its interference in the immune system's fight against pathogens. Uehata and colleagues discovered that T-cell receptor activation triggers MCPIP1 degradation by the protease Malt1 [26]. Similarly, the IKK complex ubiquitinates and degrades MCPIP1 after stimulation via TLRs or IL-1 β [33].

Another mode of MCPIP1 regulation is the self-degradation of its own transcript [3]. This behaviour establishes a feedback loop to ensure that the immune response is never significantly handicapped by high levels of MCPIP1 expression. Similar to the mechanism through which MCPIP1 degrades many mRNA transcripts, it is thought that this self-regulatory activity is also stimulated by the targeted nucleolytic cleavage of the stem-loop structure contained within the 3'-UTR of MCPIP1 mRNA; luciferase assays with truncated 3'-UTR sequences provide evidence to support this finding [33]. However, another study found that MCPIP1 mRNA without this 3'-UTR sequence is also degraded by MCPIP1 protein [30]. Clearly, further studies are needed to precisely identify the mechanism through which this feedback loop is established.

2.2. Roles of MCPIP1 in the Regulation of Cellular and Bodily Processes

MCPIP1 does not exclusively play important roles in immune function. This factor is expressed in many different cell types and tissues throughout the body. Moreover, MCPIP1 is most highly expressed in leukocytes but is also present in the heart, placenta, spleen, liver, kidney, and lung [3]. This RNase is also involved in many different processes and has subsequently been implicated in many diseases. Many of these involvements are caused indirectly by molecules that regulate or are regulated by MCPIP1. For example, MCP-1, IL-1 β , IL-6, and TNF α are involved in different diseases, including rheumatoid arthritis [34], scleroderma [35], COPD [36], diabetes [37], obesity [38], and cancer [39], among many others.

A growing body of evidence shows that MCPIP1 regulates the differentiation and proliferation of many different cell types, and this effect might be related to the MCPIP1-induced increase in reactive oxygen species (ROS), which leads to endoplasmic reticulum stress. For example, Wang and colleagues demonstrated that the forced expression of MCPIP1 induces monocytes into osteoclast precursors and that this effect is accompanied by increased ROS production via the MCPIP1-mediated upregulation of p47PHOX [40]. Similarly, the blockage of MCPIP1 translation with small interfering RNA (siRNA) can result in less ROS production after cholesterol treatment and thereby lower DNA damage [41]. In contrast, MCPIP1 overexpression suppresses the formation of stress granules (SGs) when cells are exposed to arsenite-induced oxidative stress [42]. Although whether MCPIP1 increases or decreases cellular stress levels is currently unclear, the links to cell differentiation are abundant: neural progenitor differentiation to glial cells [43], angiogenic tube formation [44], and adipogenesis induction in 3T3-L1 preadipocytes [45] are all processes regulated by MCPIP1.

2.3. Adipogenesis

In fact, adipogenesis is one of the most well-studied aspects of the non-immune functions of MCPIP1 (Figure 4). Adipogenesis is regulated by a set of transcription factors, including CCAAT/enhancer-binding protein (C/EBP) β , C/EBP δ , C/EBP α and peroxisome proliferator-activated receptor γ (PPAR γ) [46]. Although Younce et al. (2009) observed increased adipogenesis after MCPIP1 overexpression [45], later studies observed an opposite effect of MCPIP1 on adipogenesis. In 2014, Lipert and colleagues demonstrated that MCPIP1 impairs adipogenesis: the overexpression of MCPIP1 decreases the C/EBP β and PPAR γ mRNA levels, whereas the silencing of MCPIP1 increases the expression of these mRNAs [47]. Later studies showed that the MCPIP1 level is decreased in the adipose tissue of obese subjects and that MCPIP1 downregulates genes encoding proteins involved in carbohydrate and lipid metabolism while upregulating genes involved in cellular assembly and movement [48].

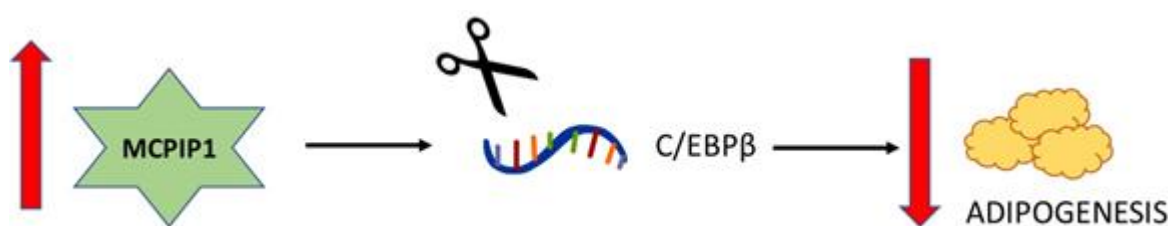


Figure 4. Schematic relationship between the level of MCPIP1 and adipogenesis. A. The overexpression of MCPIP1 decreases the C/EBP β mRNA level and impairs adipogenesis.

2.4. Angiogenesis

MCPIP1 has also been linked to angiogenesis. Prior to the discovery of MCPIP1, its inducer MCP-1 was associated with angiogenesis: the direct application of MCP-1 to culture media of human aortic endothelial cells (HAECs) results in upregulated expression of hypoxia-inducible factor 1 α (HIF-1 α) and vascular endothelial growth factor-A165 (VEGF-A165) [49]. Later studies have shown that these proangiogenic effects are instead most likely caused by MCPIP1 rather than MCP-1. The siRNA silencing of MCPIP1 prevents the occurrence of any angiogenic response; the pro-angiogenic cadherin genes *Cdh12* and *Cdh19* are upregulated by MCPIP1 [44]. The angiogenic capacity of MCPIP1, along with its ability to enhance the cardiac differentiation of mesenchymal stem cells (MSCs), might make MCPIP1 a therapeutic target in the myocardial repair and regeneration of ischaemic tissues [50]. However, more recent studies performed using the clear cell renal cell carcinoma (ccRCC) cell line Caki-1 (metastatic) showed the anti-angiogenic effect of MCPIP1. Caki-1 cells overexpressing MCPIP1 exhibited decreased levels of HIFs, glucose transporter 1 (GLUT1), VEGFA, and IL-6 [51].

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