Revealing the Roles of MOAP1 in Diseases: A Review

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Abstract: Modulator of apoptosis protein1 (MOAP1), also known as MAP1 and PNMA4, belongs to the PNMA gene family consisting of at least 15 genes located on different chromosomes. MOAP1 interacts with the BAX protein, one of the most important apoptosis regulators. Due to its critical role in a few of disease-associated pathways, MOAP1 is associated with many diseases such as cancers and neurological diseases. In this study, we introduced MOAP1 and its biological functions and reviewed the associations between MOAP1 and a few diseases including cancers, neurological diseases, and other diseases such as inflammation and heart diseases. We also explained possible biological mechanisms underlying the associations between MOAP1 and these diseases, and discussed a few future directions regarding MOAP1, especially its potential roles in neurodegenerative disorders. In summary, MOAP1 plays a critical role in the development and progression of cancers and neurological diseases by regulating a few genes related to cellular apoptosis such as BAX and RASSF1A and interacting with disease-associated miRNAs, including miR-25 and miR1228.

Keywords: MOAP1; cancer; neurodegenerative diseases; apoptosis; biomarker

1. Introduction

The modulator of apoptosis protein1 (MOAP1), also known as MAP1 and PNMA4, belongs to the PNMA gene family, which consists of at least 15 genes on different chromosomes [1]. Specifically, PNMA1 and PNMA4 are located in human chromosome 14; PNMA8A, PNMA8B, PNMA8C, and CCDC8 (a paralog of PNMA6F) are localized to chromosome 19; PNMA2 belongs to chromosome 8; and PNMA3, PNMA5, PNMA6A, PNMA6B, PNMA6E, PNMA6F, PNMA7A, and PNMA7B are located in X chromosome [1]. It is known that the PNMA family is highly expressed in the brain, testis, and heart with MOAP1, a resident protein in the mitochondria [1]. There are multiple acronyms existing for MOAP1 (e.g., MAP1, PNMA4, etc.), and we unified them to MOAP1 from now on to avoid any confusion.

Among the PNMA genes, MOAP1 is probably the most important because it not only plays a central role in mitochondria and death receptor-mediated apoptosis [2], but also is associated with many diseases like cancer [3]. The specific roles of MOAP1 in cellular apoptosis and various diseases are determined by its protein structure. Specifically, in the BH3L domain of MOAP1, a unique protein sequence or structure (UPD) between the NCD and CCD domains was identified. The protein sequence of MOAP1 also contains a domain rich in lysine and arginine residues, named KRs [1].

First identified by the yeast-two-hybridization assay, MOAP1 was a BAX-associated protein that binds to BAX only during apoptosis induction [2]. It plays a vital role in mitochondrial-dependent apoptosis by influencing and maintaining BAX activation. The down-regulation of MOAP1 leads to the instability and polymerization of BAX on the mitochondrial membrane so that cytochrome C is not released into the cytoplasm. The knockdown of this protein inhibited the apoptotic stimulation induced by TNFα and TRAIL. Therefore, abolishing this protein will cause cells to be insensitive to death signals mediated by the external and internal pathways of apoptosis [4].
In addition, the complement system is a tightly regulated network of proteins involved in defense against pathogens, inflammatory processes, and the coordination of innate and adaptive immune responses. Hertz et al. mentioned MOAP1 as a pattern-recognition molecule (PRM) related to inhibitors of the complement system's lectin pathway. The C4b binding protein (C4BP) regulates both classical and lectin pathways and MOAP1/C4BP chimeras have unique complement inhibition properties, providing a new therapeutic approach for upstream and central complement activation [4]. MOAP1 also plays a role in liver Fas signaling by promoting MITCH2-mediated tBid recruitment to mitochondria [5].

Besides BAX, MOAP1 also attenuates cell apoptosis by collaborating with other molecules. For example, it is known that RASSF1A and MOAP1 intimately interact to form the RASSF1A/MOAP1 molecular pathway in cancer. One potential function of this pathway is to link death receptors with BAX conformational change to promote tumor suppression [6]. MOAP1 also interacts with RASSF6 to attenuate RASSF6-induced cell apoptosis; however, the attenuation was not observed in a p53-negative background [7–9].

Moreover, MOAP1 is regulated by ubiquitin protein degradation [10]. Ubiquitin proteasome system is an indispensable process during the transformation from normal cells to cancer cells. There are a few studies showing that a new regulation factor, Trim39, can stabilize MOAP1 [11,12]. Moreover, UBR5 enhances MOAP1 ubiquitination. Matsuura et al. found that UBR5 ubiquitin ligase down-regulates MOAP1 in ovarian cancer, which contributes to its role in ovarian cancer resistance to cisplatin [13]. Since the in-vitro MOAP1 expression level is low in tumor cells, MOAP1 ubiquitin can be reduced by apoptosis stimulating processes [13].

Finally, there are a few studies suggesting a unique role of MOAP1 in promoting autophagy signal transduction. Autophagy goes through three different stages by phagocytic molecules and organelles, including initiation of recruitment, nucleation, and expansion of phagocytic membrane, followed by lysosomal degradation. P62 is an autophagy receptor. The BAX-binding protein MOAP1 regulates the p62-KEAP1-NRF2 signaling pathway by disrupting the p62 corpuscles. MOAP1 is recruited to p62 corpuscles by the induction of formation stimulated by cellular stress and reducing their levels independently of the autophagy pathway [14]. Interestingly, MOAP1 was found to be an LC3-binding protein, which plays a unique role in promoting autophagy by interacting with LC3 to promote efficient shutdown of autophagy during starvation [15].

In summary, MOAP1 can activate the apoptosis signaling pathway, promoting its role in many diseases, such as cancers and neurological diseases (Figure 1). For example, MOAP1 is involved in the progression, invasion, metastasis, and chemo-sensitization of various cancers, including lung cancer, colorectal cancer, and breast cancer [16–18]. In the nervous system, MOAP1 can induce neuronal loss, actuate cerebral infarction, depressive behavior, and stress response [19,20]. Finally, Fas, also known as Cd95 and APO1, is involved in diseases like atherosclerosis, heart disease, autoimmune disorders, liver disease, and myocardial infarction [21–25]. Since there is evidence that MOAP1 and Fas signaling are highly associated [5], MOAP1 may also play a role in these diseases. In the following, we will review the molecules mediating the association between MOAP1 and the diseases mentioned above and their acting mechanisms.
2. Roles of MOAP1 in Cancers

With the increasing of human lifespan, cancer has become one of the top three diseases threatening human lives [26]. The hallmarks of cancer, including evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potential, and sustained angiogenesis; the five processes are mutually interacted [27]. Previous studies have suggested that MOAP1 is highly associated with the apoptosis pathway [28], one of the most critical pathways and hallmarks in cancer. Thus, the roles of MOAP1 in various cancers and related biological mechanisms have been widely studied [16,29], among which lung cancer, colorectal cancer (CRC), and breast cancer are probably the most well studied.

2.1. MOAP1 in Lung Cancer

Lung cancer is the most prevalent cancer in China and the third most common cancer in the United States (https://www.cdc.gov/cancer/lung/ accessed on 9 December 2021), accounting for approximately 13% of new cancer incidences worldwide and causing 1.4 million deaths each year [30]. Lung cancer consists of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which can be further divided into squamous-cell carcinoma, adenocarcinoma, large-cell carcinoma, and so on.

The proteins in the BCL2 family can regulate the intrinsic apoptotic pathway [31]. BCL2 family proteins consist of pro-apoptotic proteins (like BAX, BAK, and BAD) and anti-apoptotic proteins (like BCL2, BCLW, and MCL1). Liu et al. observed abnormal expression of BCL2 protein in NSCLC and showed that BCL2 and MCL1 amplification is related to drug resistance [32]. Chan et al. found that MOAP1 can directly or indirectly interact with BCL2 family proteins, which promotes its role in lung cancer [15] (Figure 2). On the other way, the role of miRNAs in regulating the apoptosis pathway in lung cancer has been widely studied. For example, some miRNAs are critical in lung cancer treatment by targeting TP53-dependent cell apoptosis [33]. Previous studies also suggested that miRNAs regulating lung cancer cell apoptosis interact with many important cancer pathways, including PI3K/Akt, PTEN, GSK-3b, NF-kB, BCL2, BAX, P53, and mTOR [34]. However, the biological mechanisms underlying lung cancer-associated miRNAs are unknown. MOAP1 is one of the genes to mediate lung cancer-related miRNAs and lung cancer. That is, a few miRNAs can regulate MOAP1 and BAX, which may contribute to the apoptosis of lung cancer cells. For example, miR-25 is a critical biomarker for non-small-cell lung cancer. Wu et al. found that this miRNA down-regulates the expression of MOAP1, which promotes cell proliferation and inhibits caspase-dependent apoptosis in NSCLC.
cells (Figure 2). Thus, miR-25 antagomir can promote MOAP1 expression and thus inhibit lung cancer growth in a mouse xenograft model [16]. We refer to synthetic antagonists as silencing agents of miRNAs by the term antagomir.

**Figure 2.** MOAP1 acts as a modulator on cancer-associated miRNAs and cancers.

### 2.2. MOAP1 in Colorectal Cancer

Colorectal cancer (CRC), also known as bowel cancer, is among the top three most common cancers in the world. This cancer is caused by uncontrolled cell growth in the colon or rectum; the tumors in the two body parts are genetically the same and thus are called uniformly as colorectal cancer (https://www.nature.com/subjects/colorectal-cancer accessed on 9 December 2021). One major issue in CRC and probably all cancers is recurrence and metastasis, which eventually leads to the death of most cancer patients. That is, the cancer cell re-grows in the same location after surgical resection or move to another body location through blood flow and proliferation [35].

In recent years, much effort has been placed on revealing the biological mechanisms behind the progression, recurrence, and metastasis of CRC. Among many pathways related to CRC, p53-dependent apoptosis is probably the most studied. BAX and BCL2 are two important regulators of p53-dependent apoptosis and thus are critical in many processes of CRC. For example, Katkoori et al. suggested that the expression level of BAX in a CRC patient can be used to predict his/her prognosis [36]. Low BAX expression was considered a negative prognostic factor for CRC patients with liver metastasis in an early study [37]. The BAX/BCL2 ratio was also considered one of the prognostic markers for tumor location in CRC [38]. Besides the prognostic value, BAX and BCL2 are also important for CRC at molecular levels. Pryczynicz et al. found that BAX protein could reduce CRC invasion [38]. Jansson and Sun found that the expression of BAX was significantly higher in metastatic CRC than in primary CRC [39]. In addition, BAX is also involved in other inhibition mechanisms associated with CRC, such as the PGC1α pro-apoptotic effect [40], regulating autophagy-related genes [41], and mediating CRC with microsatellite instability [42]. Similarly, BCL2 is a suppressor of p53-dependent apoptosis in CRC [43] and is found to regulate the invasion and metastasis of CRC cells [44].

It is known that BAX could be regulated by MOAP1 in CRC [3,6], which promotes the roles of MOAP1 in various processes of CRC (Figure 2). Specifically, the function of BAX and MOAP1 might be regulated by a few miRNAs. For instance, miR-92a-3p and miR-572 are two known colorectal cancer-associated miRNAs. High miR-92a-3p expression contributes to chemotherapy resistance and metastasis of CRC [17]. A recent study suggested that these functions of miR-92a-3p were achieved by inhibiting FBXW7 and MOAP1 directly to activate the Wnt/β-catenin pathway and inhibit cell apoptosis, respectively [17] (Figure 2). In addition, the up-regulation of miR-572 can inhibit MOAP1 expression, which promotes
the migration, invasion, and growth of CRC cells [29] (Figure 2). As a result, miR-572 antagonir might be a potential therapeutic means for treating colorectal cancer.

2.3. MOAP1 in Breast Cancer

Breast cancer is the second most common woman cancer in the United States (https://www.cdc.gov/cancer/breast/statistics/ accessed on 9 December 2021). There are five main molecular subtypes of breast cancer: Luminal A, Luminal B, Triple-negative/basal-like, HER2-enriched, and Normal-like. HER2 is probably the most important gene for breast cancer, with HER2-positive and HER2-negative patients accounting for about 25–30% and 70–75% of all breast cancer incidences, respectively [45–47]. Even after trastuzumab adjuvant treatment, a large portion of breast cancer develops recurrence and metastasis, especially for the HER2-positive subtype.

The role of BAX apoptosis signaling in breast cancer has been widely studied. BAX and BCL2 are known prognostic biomarkers for breast cancer. BCL2, also known as BCL2 Apoptosis Regulator and B-cell lymphoma-2, is a gene capable of suppressing apoptosis. Specifically, the integral outer mitochondrial membrane protein encoded by BCL2 can block the apoptotic death of many cells like lymphocytes, making it a prognostic biomarker for cancers. Sjostrom et al. identified the predictive value of BAX and BCL2 in chemotherapy responses in advanced breast cancer [48]. Azimian et al. found that the ratio between the expressions of BAX and BCL2 (BAX/BCL2) could be used to predict the effect of breast cancer radiotherapy in an individual patient [49]. In addition, Binder et al. found that the differential BAX/BCL2 expression pattern is important for cancer cell proliferation and thus is a predictive marker for cancer malignant progression [50]. Linjawi et al. identified that BCL2 expression is significantly correlated with hormonal receptors in breast cancer patients. Sehrawat suggested that BAX activation can mediate the selective death of human breast cancer cells and might provide some direction for breast cancer treatment. Finally, a recent study suggested that the tricistronic expression of MOAP1, BAX, and RASSF1A enhances chemo-sensitization in breast cancer cell lines [51].

As a result, MOAP1, its upstream genes, and miRNAs play critical roles in the progression, invasion, and migration of breast cancer. For example, miR-1228 is a miRNA responsible for breast cancer invasion and migration. Lin et al. found that miR-1228 could be attenuated by increasing the expression of MOAP1 (Figure 2), suggesting the potential of MOAP1 in breast cancer studies and therapies.

Together, the downregulation of MOAP1 could reduce the effect of BAX, which may suppress p53-dependent cancer cell apoptosis. This process places an important role in bridging various cancers and their associated miRNAs. Overexpression of these miRNAs usually inhibits the expression of MOAP1, thus promoting cancer cell proliferation, migration, and invasion.

2.4. MOAP1 in Cancer Drug Resistance and Chemo-Sensitization

MOAP1 was involved in cancer drug resistance and chemo-sensitization (Figure 3). For example, Matsuura et al. found that UBR5 down-regulates proapoptotic MOAP1 in ovarian cancer, which results in cisplatin resistance [13] (Figure 3). In cancer cells, tricistronic expression of MOAP1, BAX, and RASSF1A (MBR) expression will induce cell death and thus increase chemo-sensitization. Recently, Lee et al. found that this process requires the involvement of the BH3L domain of MOAP1 [51]. As a member of the PNMA family, MOAP1 also interacts with other members in this family to promote chemo-sensitization. In MCF-7 cells, overexpression of MOAP1 and PNMA1 will promote chemo-sensitization; however, the chemo-sensitization will be greatly inhibited when co-expressing with PNMA2, indicating that PNMA2 might be an antagonist of MOAP1 and PNMA1 induced chemo-sensitization [52]. In addition, the co-expression of PNMA5 and MOAP1 greatly enhances the chemo-sensitivity of MCF-7 cells to Etoposide treatment [52].
Figure 3. MOAP1 interacts with other genes to perform cancer-related functions and the literature supporting the interactions and functions.

3. Roles of MOAP1 in Neurological Diseases

Previous studies suggested that PNMA2, PNMA3, and MOAP1 mRNAs are abundantly expressed in mouse brains. In the neocortex, PNMA2, PNMA3, and MOAP1 mRNAs are expressed throughout all layers, although the expression levels of the genes differ slightly among the layers [19]. It is known that neurological diseases, especially neuron-degenerative diseases such as Alzheimer’s disease and Parkinson’s disease, are highly associated with mitochondrial-dependent neuron cell apoptosis [53,54]. In addition, MOAP1 is abundantly expressed in other brain tissues [20,55]. MOAP1 is speculated to be associated with neurological diseases, and there are a few studies in this area.

3.1. MOAP1 and Cerebral Ischemia

Stroke remains one of the top diseases for human disability and death worldwide. This is largely due to the narrow time window for recognition and the administration of outcome-modifying treatment [56]. Acute stroke can result in permanent damage to the human brain and even cognitive death, making it critical to unveil the mechanism behind its formation and treatments.

A few early studies suggested that upregulation of BAX proteins in neuronal cells is a risk factor for cerebral ischemia [57,58]. BAX ablation might be a feasible direction to control cerebral ischemia [59], which makes MOAP1 critical in cerebral ischemia since it can regulate BAX and BCL2 in neurons. Studies have shown that the MOAP1–/– primary cortical neurons and MOAP1+/+ primary neurons are resistant against oxygen and glucose deprivation (OGD) treatment; MOAP1–/– primary cortical neurons are stronger. In the mouse transient middle cerebral artery occlusion (tMCAO) model, cerebral ischemia causes the MOAP1/BAX association, activating the MOAP1-dependent apoptosis cascade. In the study, the authors found that 24 h after tMCAO, MOAP1–/– mice showed less neuron loss and smaller infarct volume than MOAP1+/+ mice. Similarly, MOAP1–/– mice also have better integrity in neurological functions, which was proved in their rotarod test [20]. Together, these studies suggested that MOAP1 plays an important role in regulating apoptosis in cerebral ischemic injury.

3.2. MOAP1 and Depression

Stress response is closely related to one of the most important mental diseases, namely depression. Depression, also called major depressive disorder, is a serious mental illness that negatively affects people’s the feelings and actions.

Depression and BAX apoptosis signaling are highly correlated. For example, the signal cascade composed of BAD, BAX, and Caspase 3 is sufficient for synaptic depression [60].
In addition, the upregulation of BAX and downregulation of BCL2 were observed in the olfactory bulb of a rat depression model [61]. Due to its regulatory role in BAX apoptosis, MOAP1 plays an important role in regulating stress response by the Dorsal raphe nucleus (DRN). Forced swimming test is one of the famous techniques in wet lab to develop depression model in mice [62]. Compared with age-matched wild-type mice, young MOAP1−/− mice in the forced swimming test showed depressive behavior with increased stationary time, which was eliminated by acute fluoxetine treatment. In young wild-type (WT) control mice, repeated forced swimming stress resulted in upregulation of tryptophan hydroxylase 2 (TPH2) and down-regulation of brain-derived neurotrophic factor (BDNF) in the dorsal renal nucleus (DRN). In contrast, TPH2 was not upregulated in aging WT mice. Interestingly, this stress response was not present in both young and old MOAP1−/− mice [55].

3.3. MOAP1 and Parkinson’s Disease

Parkinson’s disease (PD) becomes the second most common neurodegenerative disease in the world after Alzheimer’s disease, affecting nearly five million people worldwide, and this number is expected to double by 2030 [63]. In Parkinson’s disease, the main pathological features are connected with progressive neurodegeneration of dopaminergic neurons and typical motor characteristics in the substantia nigra striatum (SNC), which locates in the dense region of the black substantia [64]. It results from genetic, environmental, and aging factors and currently has no good treatment. Apoptosis and autophagy play a vital function in the pathogenesis of PD. Therefore, adjusting their balance is a potential therapeutic strategy [63]. Previous studies have suggested that the BCL2 protein family is a therapeutic biomarker in Parkinson’s disease [53,65–67]. Specifically, proteins in the BCL2 family, such as BAX, can mediate the apoptosis of dopaminergic neurons in the Parkinson’s disease. For example, Vila et al. found that the ablation of BAX protein can prevent neurodegeneration in Parkinson’s disease [68]. By targeting BAX, some miRNAs like MicroRNA-216a also inhibit neuronal cell apoptosis in Parkinson’s disease [69]. Thus, proteins in the BCL2 family might be a promising target in treating Parkinson’s disease.

It is well known that MOAP1 directly binds to BAX, which suggests that MOAP1 may play a role in Parkinson’s disease. Capurro et al. used external laser capture micro-anatomical data to verify the differentially expressed genes identified by PSEA (population-specific expression analysis) in the dense part of substantia nigra neurons. In this study, the expression of the MOAP1 gene was found to be reduced in cortical neurons of Parkinson’s disease (PD) [70]. In Table 1, we summarized the genes involved in the connection between MOAP1 and neuron-related traits and diseases. Besides BAX, MOAP1 also interacts with other molecules like PNMA2. For example, in immunoprecipitation studies, PNMA2 was closely related to PNMA1 and MOAP1 and functionally antagonized the pro-apoptotic of MOAP1 and PNMA1 [71].

| Gene Symbol | Neuron-Related Traits or Diseases | Function |
|-------------|----------------------------------|----------|
| PNMA2       | Abundant in brain                | Antagonize the signal transduction of apoptotic cells both MOAP1 and PNMA1 [71] |
| PNMA3       | Abundant in brain                | Gene Ontology (GO) annotations related to this gene include nucleic acid binding [https://www.genecards.org/ accessed on 9 December 2021] |
| BAX         | Ischemic injury                  | Binding with a novel BAX-related protein (MOAP1) mediates apoptosis [2] |
| TPH2        | Depression                       | Catalytic biosynthesis of serotonin [72] |
| BDNF        | Depression                       | Bind with its homologous receptor promotes neuronal survival in the adult brain [https://www.genecards.org accessed on 9 December 2021] |

Table 1. The molecules involved in the action of MOAP1 in neuron-related traits or diseases and their functions.
Besides cancers and neuronal diseases, MOAP1 was also related to a few other diseases. For example, MOAP1 was targeted by miR-25 to block the apoptosis of vascular smooth muscle cells, which plays a critical role in inflammation and heart disease [21]. MOAP1 is also commonly identified differential genes of coronary artery disease, ischemic cardiomyopathy, and myocardial infarction [73,74]. In addition, it is known that Fas, also known as Cd95 and Apo1, is implicated in a few diseases like liver diseases, autoimmune disorders, and fulminant hepatitis [22–25]. Tan et al. found that MOAP1 is involved in the Fas signaling for apoptosis in the liver [5] and thus is associated with liver diseases. In summary, MOAP1 might be implicated in many diseases and its acting mechanisms are yet to be discovered.

4. Conclusions and Future Perspectives on MOAP1

In this study, we reviewed the roles and mechanisms of MOAP1 in a few biological processes including cell apoptosis, innate and adaptive immunity, ubiquitin protein degradation, and autophagy. We also reviewed the molecules mediating the association between MOAP1 and a few diseases like cancers and neurological diseases.

As an important gene in the PNMA gene family, MOAP1 can bind with the BAX protein to activate mitochondria and death receptor-mediated cell apoptosis, which will inhibit the progression and metastasis of a few cancers like lung cancer, breast cancer, and colorectal cancer and may mediate neurological diseases. In addition, a few miRNAs can directly interact with MOAP1 in a few cancers. For example, miR-25 can directly inhibit MOAP1 in lung cancer; miR-92a-3p and miR-572 can inhibit MOAP1 in colorectal cancer, and miR-1228 can inhibit MOAP1 in breast cancer. These may explain the functions of these miRNAs in cancer etiology. Moreover, MOAP1 also interacts with other genes to perform specific functions. For example, MOAP1 and RASSF1A collaborate to form the RASSF1A/MOAP1 pathway, which is important for cell apoptosis and chemosensitivity. MOAP1 also interacts with RASSF6 and MBR to promote cell apoptosis and is co-expressed with PNMA5 and PNMA1 to enhance chemosensitivity.

Interestingly, the role of MOAP1 in cancers is relatively well studied in the literature; however, its roles in other diseases are yet to be revealed. Other diseases driven by mitochondrial-dependent apoptosis might also have a close relationship with MOAP1 and need to be further studied. Moreover, it is worthy of mentioning that there are many other biomarkers associated with MOAP1, such as long non-coding RNA (IncRNA), DNA methylation, and histone modification, regulating the expression of a gene. For example, the regulating roles of IncRNA in cancer have been widely studied recently [75], and a few IncRNAs such as SNHG1 also play important roles in neuronal cells [76,77]. The co-expression between IncRNA SNHG5 and MOAP1 in thyroid cancer has been reported; however, the underlying mechanism is unclear [78]. In the future, studies on the relationship between MOAP1 and other regulation molecules should be explored.

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