Monoamine oxidase A (MAO-A) is a flavoenzyme that catalyzes biogenic amines into the corresponding aldehydes by oxidative deamination. Although MAO-A is primarily associated with depression and antisocial behaviour, dysregulation of MAO-A has been associated with neurodegenerative diseases and cardiovascular disorders. Moreover, the contribution of MAO-A in the resolution of inflammation is well established. Recent reports reveal the unanticipated role of MAO-A in tumorigenesis. In this review we provide informations that MAO-A is involved in the progression and metastasis of many different cancer cells including prostate cancer, colorectal cancer, hepatocellular carcinoma and lung cancer. We further discuss the regulatory mechanisms that control tumorigenesis, progression and metastasis in these different type of cancer cells. Altogether these informations indicate that MAO-A can be a general therapeutic target in cancer treatment.

**Keywords:** EMT; Interleukin-13; Stat6, Proliferation; Invasion; Metastasis

To cite this article: Pritam Biswas, et al. Role of monoamine oxidase a (MAO-A) in cancer progression and metastasis. Can Cell Microenviron 2018; 5: e1623. doi: 10.14800/ccm.1623.

Copyright: © 2017 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

**Introduction**

Monoamine oxidase A (MAO-A) is a mitochondrial membrane-bound pro-oxidative enzyme which is widely present in all the mammalian cell types except erythrocytes [1]. In the presence of molecular oxygen, MAO-A, primarily catalyzes the oxidative deamination of biogenic and dietary amines like serotonin, dopamine, norepinephrine and tyramine and converting them into their corresponding aldehydes and reactive oxygen species (ROS) [2-5]. MAO-A has already been reported as a signature marker of alternatively activated monocytes/macrophages and has a major contribution in the resolution of inflammation [6].

Abnormalities of MAO-A levels and activity can lead to neuropsychiatric disorders as it plays a key role in the regulation of neurotransmitters. MAO-A hyperactivity has been shown to be associated with depression and previous reports implicate MAO-A inhibitors as effective therapeutics against clinical depression and anxiety [7, 8]. Involvement of MAO-A has also been shown in neurodegenerative diseases including Parkinson’s and Alzheimer's disease by inducing oxidative stress-mediated apoptosis [9, 10]. MAO-A deficiency and abnormal activity has been associated with impulsive aggressive behaviour [11], neuropsychiatric disorders [12], pancreatic beta cell function [13] and glucose metabolism [14]. MAO-A has also been reported as a vital regulator of
embryonic brain development [21]. In addition to neuroinflammatory syndromes, involvement of MAO-A has been established in the pathogenesis of many cardiovascular disorders including myocardial injury [15], heart failure [16], cardiac cell apoptosis [17] and vascular wall remodelling [18].

MAO-A-mediated production of ROS can lead to DNA damage and oxidative injury of cells and may cause tumor initiation and progression. This shows that MAO-A might have a significant role in cancer. Studies have demonstrated that MAO-A suppression can be linked to increased risk of cancer [19]. In contrast, it has been reported that tumors from patients with aggressive prostate cancer (PCa) showed increased expression of MAO-A [20]. MAO-A also suppresses hepatocellular carcinoma (HCC) metastasis by inhibiting the adrenergic system and its transactivation of EGFR signalling and increasing MAO-A expression or enzyme activity may be a new approach that can be used for HCC therapy [21].

It has been examined in prostate cancer cell line, that cytotoxic chemotherapy elevated the expression of MAO-A which in turn enhances cancer cell survival following docetaxel (chemotherapeutic drug) exposure [22]. MAO-A expression may be useful as a prognostic marker for cholangiocarcinoma progression and efforts to modulate MAO-A expression may prove useful in the treatment of cholangiocarcinoma [23]. Elevated expression of MAO-A in high-grade tumours of renal cell carcinoma specimens was confirmed by Hodorová I et al which further shows that MAO-A expression in high-grade tumours may have a direct role in maintaining a dedifferentiated phenotype and promoting aggressive behaviour [24]. Previous studies strongly support a role of MAO-A in inducing EMT in prostate cancer cells [20]. Inhibition of MAO-A in contrast, triggers a mesenchymal-to-epithelial transition in the MDA-MB-231 breast cancer cell line and lead to the conclusion that inhibition of MAO-A on breast cancer progression is dependent more on the cell's EMT status than on its ER status [25]. MAO-A is also reported as a novel decision-maker for activating autophagy and MAO-A inhibitors may be useful as a potential therapy for neuroendocrine tumors [26]. Considering the importance of MAO-A in cancer biology, this review is focused on the role of MAO-A in cancer progression and cancer metastasis.

**MAO-A functions to induce epithelial to mesenchymal transition (EMT)**

As mentioned earlier, MAO-A-mediated generation of excessive intracellular level of hydrogen peroxide, a major ROS species can induce epithelial to mesenchymal transition (EMT) in cancer cells. Wu et al demonstrated that MAO-A-stimulated EMT can increase migration, invasion and metastatic potential of prostate cancer cells [20].

By overexpressing MAO-A in human prostate cancer cell lines their group showed that MAO-A induces EMT by activating VEGF-A and its co receptor neuropilin-1 which ultimately promoted AKT/FOXO1 signalling resulting in
enhanced expression of nuclear TWIST1\(^{[20]}\). As shown in Figure 1, in LNCaP cells, constitutively expressed MAO-A induces EMT by the generation of ROS which inhibits PHD activity and stabilizes HIF1\(\alpha\) activity. MAO-A further activates VEGF-A/NRP1 signalling and upregulates AKT/FOXO1 pathway to activate TWIST1 expression. Stimuli such as hypoxia can stimulate the ROS generation. Increased expression of MAO-A thus by promoting EMT and by elevating ROS production, enhances PCa tumorigenesis, progression and metastasis.

Recently it was reported that the Th2 cytokine IL-13 plays a crucial role in promoting EMT and enhancing aggressiveness (migration and invasion) in colorectal cancer (CRC) cells (HT29 and SW480 cells, as described in Figure 2) by triggering IL-13/IL-13R\(\alpha\)1/STAT6/STAT3 signalling pathway \(^{[27]}\). Contribution of Stat3/STAT6 signalling was also examined in mediating the EMT process in CRC \(^{[28]}\). As MAO-A is either constitutively expressed or induced by IL-13 in many CRC cells and as Stat6/STAT3 are important regulators of MAO-A \(^{[27, 28]}\), it is tempting to investigate whether MAO-A is involved in the EMT process of CRC progression. Our unpublished data in HCT116 cells (where high level of constitutively expressed MAO-A is present) show that MAO-A-mediated ROS generation is correlated with enhanced level of migration and invasion in HCT116 cells (as shown in Figure 2).

Recent findings from our group further suggest that IL-13/IL-13R\(\alpha\)1/STAT6 signalling pathway is involved in regulating the expression/activity of MAO-A in A549 lung epithelial carcinoma cells via a 15-LOX-dependent process involving PPAR\(\gamma\) (Figure 3) and that may be the cause of promoting EMT in this specific lung cancer cells (Unpublished observations by our group) after IL-13 stimulation which ultimately leads to enhanced migratory, invasive and metastatic potential (unpublished observations). Similar to HCT116 cells, the elevated level of MAO-A that is constitutively present in lung cancer cell H1299 can promote ROS generation and ultimately enhances H1299 cell migration and invasion (Figure 3).

On the other hand, inactivation of MAO-A by a selective inhibitor clorgyline (CLG) induces a mesenchymal to epithelial transition in MDA-MB-231 cells. CLG robustly induces epithelial protein marker E-cadherin in MDA-MB-231 cells via a non-canonical mechanism by interfering with the \(\beta\)-catenin/p-GSK3\(\beta\) complex as well as the E-cadherin/\(\beta\)-catenin complex \(^{[25]}\). Altogether these
results indicate that MAO-A is an important regulator of EMT.

MAO-A promotes aggressiveness of cancer cells

Increased expression of MAO-A is associated with high grade aggressive prostate cancer [29, 30]. The ability of MAO-A to induce EMT in prostate cancer cells results in increased migratory, proliferative, invasive and metastatic potential through an elevation of ROS [20]. MAO-A-produced ROS modulates HIF1α (a master regulator of hypoxia) activity by suppressing PHD (oxygen dependent prolyl hydroxylases) activity. It was further verified that MAO-A enzymatic activity rather than the protein expression is responsible for enhanced level of migration, invasion and proliferation of prostate cancer cells by the induction of EMT (as shown in Figure 1) which increases the MAO-A-mediated ROS generation, an important mediator of MAO-A function in prostate cancer cells [20]. Recent evidence further suggests that MAO-A expression in high-grade advanced PCA (VCaP cells) may have a direct role in maintaining a dedifferentiated phenotype and promoting aggressive behaviour [31]. Based on the findings in normal cells, it is also hypothesized that elevated expression of MAO-A in high-grade renal carcinoma cells contributes to its poorly differentiated phenotype [24]. These results thus suggest that MAO-A expression in high-grade tumours may play a key role in maintaining a dedifferentiated phenotype and promoting aggressive behaviour [24]. Our group also investigated the contribution of MAO-A in enhancing the aggressiveness of different type of cancer cells. We observed that in H1299 lung cancer cells and in HCT116 colorectal cancer cells MAO-A is constitutively expressed and is responsible for promoting migration and invasion of these cancer cells (unpublished observations by our group as shown in Figures 2 and 3). On the other hand, MAO-A expression/activity is induced by IL-13 in A549 lung epithelial carcinoma cells and expression/activity of this induced MAO-A mediates ROS generation which is believed to have significant role on A549 cell migration, invasion and proliferation (Unpublished data by our group, Figure 3), which are all associated with the aggressiveness of this particular cancer cell. We are currently exploring the mechanistic details of this process in different type of cancer cells where constitutive as well as inducible expression/activity of MAO-A is observed.
MAO-A in promoting cancer metastasis

Several studies on prostate cancer (PCa) suggest that MAO-A upregulation in PCa cells is positively correlated with the PCa progression \[30, 32\]. MAO-A-dependent generation of ROS is associated with the activation and stabilization of the transcription factor HIF1α which further elevates the level of ROS and ultimately drives PCa progression and metastasis. It is also established that MAO-A-dependent HIF1α/VEGF-A/FOXO1/TWIST1 signalling pathway is activated in high Gleason grade prostate cancer specimens and knockdown of MAO-A (by shMAO-A) shows reduced level of prostate tumor growth and metastasis in xenograft mouse models \[20\]. Moreover, higher MAO-A expression is also associated with poor clinical outcomes in prostate cancer patients \[20\]. MAO-A has also been reported as an important mediator of PCa bone and visceral metastases by stimulating IL-6 release from osteoblasts resulting the activation of the paracrine Shh-IL6-RANKL signalling \[33\]. Our group found that MAO-A is either constitutively present in lung cancer cells like in H1299 cells (not induced by IL-13 incubation) and promoting migration and invasion of these cells (unpublished observations by our group) or it is induced by IL-13 in A549 lung carcinoma cells which causes increased migration and invasion (data not shown) and thereby enhances the metastatic potential of this lung cancer cells. But these results definitely need to be verified in in vivo models to conclusively comment on the role of MAO-A in lung cancer progression and metastasis. In contrast, suppression of MAO-A is observed in cholangiocarcinoma by the coordinated control of promoter hypermethylation and IL-6 signalling, and the reduced level of MAO-A expression enhances cancer invasiveness \[23\]. These studies thus suggest that regulation and function of MAO-A vary in different cancer types. MAO-A expression is silenced in Hepatocellular Carcinoma (HCC) by epigenetic methylation and histone acetylation and further identified MAO-A as a negative regulator of HCC malignancy \[21\]. To investigate the underlying mechanism of MAO-A-dependent HCC invasion and metastasis, comprehensive level of studies were performed and the results indicate that MAO-A reduces HCC cell invasion and metastasis by inhibiting both NE/E-dependent canonical adrenergic signalling and ADR-mediated transactivation of EGFR signalling \[21\]. These results thus indicate MAO-A as a key player in the adrenergic system in the control of invasion and metastasis during human HCC \[21\]. Altogether, these data propose that MAO-A is an important mediator of cancer metastasis.

MAO-A is a potential therapeutic target in different type of cancer

Earlier it is shown that MAO-A expression is required for prostate tumor growth \[20\]. Knock-down of MAO-A gene expression by a highly specific shRNA provided evidence that MAO-A is essential for the growth of prostate tumor xenografts by regulating EMT, hypoxia and ROS generation. Further studies suggest that shRNA-mediated knockdown of MAO-A significantly abrogates prostate cancer metastasis implicating MAO-A as a key determinant of prostate cancer growth and metastasis \[20\]. MAO-A specific small molecule inhibitor Clorgyline also affected the enzymatic activity of MAO-A in prostate cancer xenograft mouse model \[20\]. It has been further demonstrated that Clorgyline treated LNCaP cells showed reduced level of cell proliferation, migration, invasion and ROS generation \[20\]. Prostate cancer metastasis to bone and visceral organs was also effectively reduced by the potent irreversible MAO-A inhibitor Clorgyline which disrupted the Shh-IL6-RANKL signalling axis in the tumor microenvironment \[33\]. All these results implicate MAO-A as a potential therapeutic target in prostate cancer. A recent report suggested that pargyline and phenelzine, the two potent small molecule inhibitors of MAO-A, significantly reduced neuroendocrine differentiation (NED) and autophagy activation of prostate cancer cells which again identified MAO-A as a potential therapeutic target in prostate cancer. A recent report provided evidence that Th-2 lymphocyte derived cytokines IL-4/IL-13 can induce expression/activity of MAO-A in A549 lung epithelial cancer cells which is associated with enhanced level of migration, invasion and the aggressiveness of these cells and targeting MAO-A by selective inhibitors like Moclobemide or Clorgyline can suppress the aggressiveness of these cancer cells (unpublished observations) suggesting MAO-A as a potential target in lung cancer therapy. Moreover, several lung cancer tissue samples were analyzed by bioinformatics analysis and many differentially expressed genes (DEGs) were identified. One of the upregulated DEGs associated with lung cancer was identified as MAO-A, suggesting MAO-A as potential target for lung cancer diagnosis and treatment \[35\].
MAO-A inhibitors and their effect on the aggressive behaviour of cancer cells

Increased expression of MAO-A is associated with high grade prostate cancer and inhibition of MAO-A activity by Clorgyline, an irreversible MAO-A inhibitor, is believed to be an important contributor in promoting the process of differentiation of cultured primary prostatic epithelial cells into secretory cells and reverse the aggressive behaviour of high grade prostate cancer \[36\]. Anti-oncogenic and differentiation-promoting effects of MAO-A inhibitor Clorgyline has also been reported on high grade aggressive prostate cancer (PCa) suggesting the potential application of Clorgyline as therapeutic PCa drug \[37\]. Moreover, Clorgyline treatment showed substantial inhibitory effect on the growth and downregulated several oncogenic pathways in a model of advanced prostate cancer (PCa), VCaP cells. Clorgyline treatment in VCaP mouse xenograft model also slowed down the tumor growth and showed its anti-oncogenic effects and thereby identified as a target of MAO-A for the treatment of advanced prostate cancer \[31\]. In a recent study, effect of MAO inhibitors, pargyline and tranylcypromine on the survival of prostate carcinoma (LNCaP-LN3) cell was investigated. The results of this study showed that pargyline inhibited cellular proliferation and induced cell cycle arrest (at the G1 phase) in a dose-dependent manner and increased the cell death rate by promoting apoptosis, thereby suggesting pargyline as a potential drug for prostate cancer therapy \[38\]. Recent evidence suggested that a conjugate of near-infrared dye and MAO-A inhibitor clorgyline (NMI) selectively inhibited MAO-A with low IC50 and thereby suppressed prostate cancer cell proliferation, migration and invasion. These results implicate NMI as an efficient anti-cancer agent with high tumor-targeting specificity \[39\]. Bioactive phytochemical Curcumin is another compound that showed attenuation of cancer-associated fibroblasts (CAFs)-induced invasion and EMT and also abrogated ROS production in prostate cancer cells by inhibiting MAO-A/mTOR/HIF-1α signalling and hence suggested the potential therapeutic efficacy of Curcumin in prostate cancer \[40\]. Our studies in A549 and H1299 lung cancer cells and in HCT116 colorectal cancer cells provide evidence that MAO-A specific inhibitors Clorgyline and Moclobemide abrogate cellular proliferation, migration, invasion and ROS generation and support the idea that pharmacological inhibitors that target MAO-A might be useful for cancer therapy (unpublished observations by our group).

Conclusion

MAO-A is constitutively present in many cancer cells like prostate cancer cells, human glioblastoma cells, lung epithelial cancer cells and in colorectal cancer cells. Elevated expression of MAO-A was further confirmed in high grade prostate cancers and in renal cell carcinoma. Based on these findings it can be suggested that MAO-A expression in high grade tumors may play a crucial role in promoting aggressive behaviour of cancer cells. MAO-A degrades monoamine neurotransmitters by oxidative deamination and produces ROS. Increased level of ROS generation can mediate tumorigenesis, progression and metastasis in high grade cancers. Hence enhanced level of MAO-A expression and aggressive behaviour of cancer cells may be correlated in advanced grade of cancer. From the studies on different type of cancer that are discussed here, it can be concluded that MAO-A may serve as a diagnostic biomarker and can also be applied as a therapeutic target in the treatment of cancer. This review also investigated the potential contribution of MAO-A selective inhibitors in controlling aggressive behaviour of all types of cancer cells and suggests new application of primarily known anti-depressant drugs in cancer prevention.

Conflicting interests

The authors have declared that no conflict of interests exist.

Acknowledgments

Studies mentioned in this article were supported by the research grant of Ramalingaswami fellowship awarded to Ashish Bhattacharjee by the Department of Biotechnology, Govt. of India and by the research grant from SERB, Govt. of India (SERB/SR/SO/HS-093/2013).

Abbreviations

MAO-A: monoamine oxidase A; PHD: Prolyl hydroxylase; ROS: reactive oxygen species; EMT: epithelial to mesenchymal transition; CRC: colorectal cancer; HCC: hepatocellular carcinoma.

References


Ou XM, Chen K, Shih JC. Monoamine oxidase A and repressor R1 are involved in apoptotic signaling pathway. Proc Natl Acad Sci USA 2006; 103: 10923-10928.


36 Zhao H, Nolley R, Chen Z, Reese SW, Peehl DM. Inhibition of monoamine oxidase A promotes secretory differentiation in basal prostatic epithelial cells. Differentiation 2008;76:820-830.


