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PERSPECTIVE ARTICLE

Monoamine oxidase B as a context-dependent metabolic switch in hepatocellular carcinoma

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Abstract

Monoamine oxidase B (MAO-B) is a flavin enzyme on the outer mitochondrial membrane that produces hydrogen peroxide during amine deamination and has been implicated as a pro-tumorigenic redox driver in several cancers. Hepatocellular carcinoma (HCC) represents a mechanistic exception: in hepatocytes, MAO-B also catalyzes the oxidation of geranylgeraniol to geranylgeranoic acid (GGA), an acyclic retinoid-like metabolite that, in experimental models, has been shown to eliminate premalignant hepatocyte clones via apoptosis, autophagy, or pyroptosis-like inflammatory cell death. It is hypothesized that the loss of MAO-B expression in aging and chronic liver disease may contribute to a state of relative "GGA insufficiency," only partially buffered by alternative oxidases, thereby enabling dysplastic hepatocytes to escape elimination and progress to HCC. This perspective reframes MAO-B as a context-dependent metabolic switch and outlines testable implications for biomarker development and chemoprevention in high-risk liver disease.

Keywords: Monoamine oxidase B; Hepatocellular carcinoma; Geranylgeranoic acid; Geranylgeraniol; Oxidative stress; Chemoprevention

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1. Introduction

Monoamine oxidase B (MAO-B) is a flavin-dependent enzyme on the outer mitochondrial membrane that catalyzes oxidative deamination of endogenous and xenobiotic amines, producing aldehydes, ammonia, and hydrogen peroxide (H_2O_2).[1] By coupling amine turnover to mitochondrial redox tone, MAO-B occupies a central position at the intersection of metabolism, reactive oxygen species (ROS) signaling, and cell fate. In oncology, this positioning has fostered a paradigm in which MAO-B can act as a pro-tumorigenic redox amplifier: sustained H_2O_2 generation may promote oxidative stress responses and reinforce transcriptional programs linked to invasion and therapy resistance in multiple malignancies.[2,3]

Hepatocellular carcinoma (HCC) remains a significant cause of cancer mortality, mainly because many patients are diagnosed at stages where curative options are limited, and current surveillance tools miss a substantial fraction of early disease.[4] Beyond improving detection, there is a parallel need to define metabolic pathways that shape risk and can be leveraged for prevention in high-risk chronic liver disease.[5,6]

Here, we revisit MAO-B through a liver-specific lens. Emerging evidence suggests that, in hepatocytes, MAO-B has an additional metabolic role as a geranylgeraniol oxidase that

sustains endogenous production of geranylgeranoic acid (GGA),[7,8] an acyclic retinoid-like metabolite that has been shown to eliminate premalignant hepatocytes through apoptosis,[9] autophagy, or pyroptosis-like inflammatory cell death in experimental systems.[10] It is hypothesized that declining hepatic MAO-B in aging and chronic liver injury may contribute to a state of GGA insufficiency, weakening an intrinsic chemopreventive barrier and facilitating clonal outgrowth toward HCC. This perspective frames MAO-B as a context-dependent metabolic switch with implications for biomarker development and chemoprevention (Figure 1).

2. The traditional view: Monoamine oxidase B as a pro-tumorigenic factor

The prevailing oncology framework has often portrayed MAO-B as a pro-tumorigenic redox enzyme in multiple cancer contexts. During the oxidative deamination of monoamines, MAO-B generates H_2O_2, a diffusible species that can influence signaling beyond the mitochondrion. Persistent MAO-B activity has therefore been proposed to promote oxidative stress and engage redox-responsive transcriptional programs, including nuclear factor kappa B cells and hypoxia-inducible factor 1-alpha (HIF-1α). In this view, MAO-B-derived ROS may help cancer cells sustain metabolic rewiring, tolerate hypoxia, and adapt to therapeutic pressure.[3,11]

Glioma provides a clear exemplar of this paradigm. Glioblastoma cells show elevated MAO-B activity and higher basal H_2O_2 production than non-neoplastic astrocytes, and MAO-B substrate availability further augments peroxide generation.[12] Increased ROS can stabilize HIF-1α by inhibiting factor-inhibiting hypoxia-inducible factor and shifting the transcription factor balance (e.g., specificity protein 1 [Sp1]/Sp3), thereby reinforcing the expression of angiogenic and metabolic genes that support invasion and malignant fitness.[13] Consistent with these mechanistic links, higher MAO-B expression has been associated with advanced glioma grade and poorer outcomes, positioning MAO-B as both a marker of aggressiveness and a candidate therapeutic target.[13]

In prostate cancer, MAO-B has been implicated less as a cell-intrinsic driver and more as a stromal contributor to a permissive tumor microenvironment.[14] Stromal MAO-B has been reported to promote a reactive, tumor-supportive phenotype, consistent with increased ROS output and extracellular matrix remodeling, and to enhance tumor cell growth and invasion via paracrine chemokine signaling, notably the C-X-C motif chemokine ligand 12–C-X-C chemokine receptor type 4 axis.[14] Beyond these two settings, some datasets suggest correlations between higher MAO-B expression and advanced stage, epithelial–mesenchymal transition (EMT)-associated gene programs, or unfavorable prognosis in subsets of solid tumors, including colorectal cancer. Such associations align with evidence that ROS-dependent signaling can contribute to genomic instability and EMT-like plasticity.[15] Accordingly, irreversible MAO inhibitors, initially developed for neurodegenerative indications, have been explored in oncology settings as potential modulators of ROS-linked pathways and tumor–stroma metabolic fitness.[16]

Together, these observations have contributed to a canonical working model in which MAO-B is viewed as a mitochondrial ROS generator that can sustain oncogenic

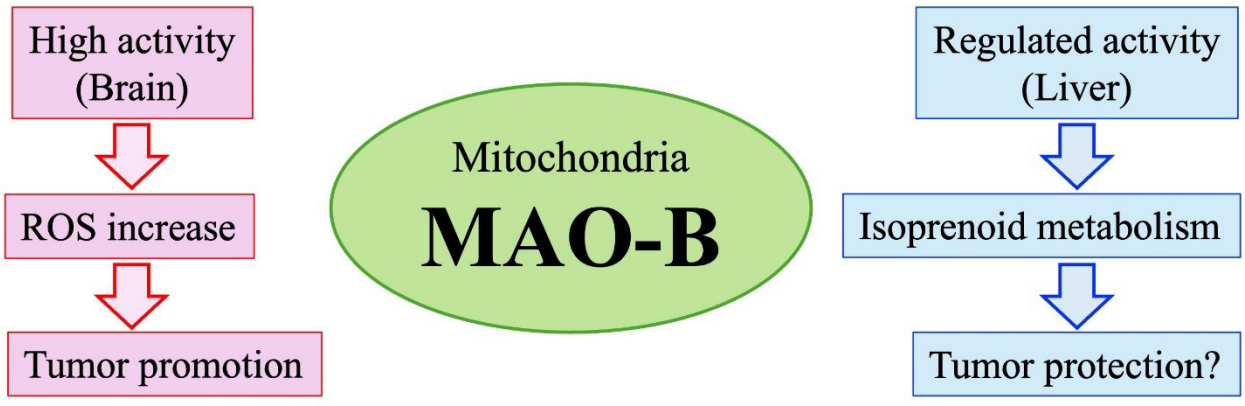


Figure 1. The Janus face of monoamine oxidase B (MAO-B) in oncology. Schematic representation of the context-dependent roles of MAO-B. In extrahepatic tissues, such as the brain (left), high MAO-B activity drives oxidative stress (ROS) and tumor promotion. Conversely, in the liver (right), MAO-B regulates isoprenoid metabolism to produce geranylgeranoic acid, potentially exerting a tumor-protective effect. This figure is original and was created by the author.

transcriptional programs, EMT-like transitions, and tumor–stroma interactions that promote progression and therapy resistance.

3. The paradox in liver: Monoamine oxidase B as a potential tumor suppressor

In contrast to its upregulation and pro-tumorigenic behavior reported in several extrahepatic malignancies, hepatic MAO-B expression appears comparatively low and tends to decline along hepatocarcinogenesis. Analyses of murine liver specimens consistently indicate that MAO-B is less abundant in malignant hepatocytes than in adjacent non-tumorous liver, and that its expression may further decrease with aging and with progression from chronic liver disease to overt HCC. This pattern diverges from glioma or prostate cancer, where higher MAO-B levels often track with aggressive phenotypes, and instead raises the possibility that the liver belongs to a subset of tissues in which MAO-B downregulation reflects, or contributes to, the loss of an intrinsic tumor-suppressive mechanism. From this perspective, reduced hepatic MAO-B is not merely a differentiation marker but a candidate indicator of impaired metabolic tumor surveillance.

A central liver-specific element is MAO-B's unique role in the biosynthesis of GGA,[7] an acyclic isoprenoid structurally related to retinoic acid. In hepatocytes, GGA can be generated from geranylgeraniol, a mevalonate pathway-derived alcohol, through stepwise oxidation of the terminal hydroxyl group; multiple lines of evidence identify MAO-B as a principal geranylgeraniol oxidase catalyzing this conversion.[7] Pharmacological inhibition or genetic suppression of MAO-B (e.g., small interfering RNA) markedly lowers intracellular GGA levels in hepatoma cell lines, supporting the view that MAO-B activity can be rate-limiting for endogenous GGA synthesis under relevant conditions. Although cytochrome P450 3A4 has been proposed to provide an alternative oxidative route, this compensation appears partial and context-dependent; importantly, it may be insufficient to sustain GGA at tumor-protective levels when MAO-B expression falls below a critical threshold.[7] Thus, in the liver, MAO-B can be considered not only as an amine oxidase producing H_2O_2, but also as a gatekeeper that links isoprenoid metabolism to endogenous isoprenoid-based chemopreventive capacity.

Geranylgeranoic acid itself has been extensively characterized as a chemopreventive agent against HCC, with the capacity to trigger cell death in hepatoma-derived cell lines at micromolar concentrations.[7] Early studies using synthetic GGA and related acyclic retinoids emphasized apoptosis and cell-cycle control, including modulation of growth-factor-associated pathways and the selective elimination of malignant or premalignant clones.[7] Subsequent work expanded the mechanistic landscape by showing that GGA can engage non-apoptotic death programs, including autophagic cell death and inflammatory, pyroptosis-like phenotypes, in association with endoplasmic reticulum stress responses and innate immune signaling modules, such as Toll-like receptor 4 activation and gasdermin D-dependent membrane disruption.[7] A recurring theme is selectivity: transformed or transformation-prone hepatocytes appear more susceptible than normal hepatocytes, consistent with the idea that GGA may function as a physiological metabolic sentinel that constrains clonal outgrowth before it becomes clinically apparent HCC.

Together, these observations support a paradoxical reinterpretation of MAO-B in the hepatic context. If MAO-B supplies a major oxidative flux from geranylgeraniol to GGA, then progressive loss or silencing of MAO-B in hepatocytes would be expected to reduce local GGA availability and weaken this endogenous chemopreventive barrier. Thus, it is hypothesized that aging and chronic liver injury, both characterized by sustained inflammatory and metabolic stress, may therefore create a state of GGA insufficiency, in which premalignant hepatocytes can more readily escape GGA-dependent apoptosis, autophagy, or pyroptosis-like elimination and accumulate additional oncogenic alterations.[7] This concept remains to be formally tested *in vivo*. While MAO-B downregulation could partly reflect dedifferentiation, the key conceptual shift is to view it as a metabolically meaningful event that can be permissive for hepatocarcinogenesis by dismantling a liver-specific MAO-B/GGA tumor-suppressive axis.[7]

In summary, the available hepatic data suggest that MAO-B may function as a tumor suppressor in HCC by sustaining endogenous GGA production and enabling continuous immune–metabolic surveillance of nascent malignant clones. Hence, it is proposed that when MAO-B expression is markedly reduced, intracellular GGA levels are likely to fall, GGA-responsive death pathways may be blunted, and the liver may become more permissive to carcinogenic progression. This liver-specific inversion of the MAO-B paradigm, pro-tumorigenic in multiple organs yet potentially tumor-suppressive in hepatocytes, suggests that MAO-B should be viewed not simply as a source of oxidative stress, but as a context-dependent metabolic node with potential relevance to HCC risk stratification and chemoprevention.

4. Future perspectives

The dichotomous behavior of MAO-B across cancers,

pro-tumorigenic in glioma[12] and prostate[14] cancer, yet potentially tumor-suppressive in HCC, raises a central question: what determines whether MAO-B biology is dominated by H_2O_2-driven redox output or by production of isoprenoid metabolites such as GGA? One plausible explanation is tissue-specific substrate routing.[17] In neural and prostatic contexts, amine catabolism may predominate, linking MAO-B-associated H_2O_2 to HIF-1α, related programs, EMT-like plasticity, and microenvironmental remodeling. It is hypothesized that MAO-B can act as a geranylgeraniol oxidase, supporting GGA generation that may preferentially eliminate transformation-prone clones via apoptosis, autophagy, or pyroptosis-like inflammatory cell death. Alternative oxidases (including CYP3A4-dependent routes) may further shape this balance when MAO-B expression declines.

This framework yields testable predictions. First, MAO-B expression alone may be insufficient to infer function; instead, informative readouts include (i) the dominant substrate pool, (ii) local GGA availability, and (iii) downstream transcriptional and cell death signatures. Pan-cancer analyses integrating transcriptomics with pathway-level proxies (e.g., mevalonate/isoprenoid activity, oxidative stress programs, EMT signatures) could help distinguish contexts in which MAO-B aligns with redox-associated invasion versus those in which it aligns with isoprenoid-dependent tumor suppression.[18] Second, single-cell and spatial profiling may clarify whether MAO-B's pro-tumorigenic associations are primarily stromal (as suggested in prostate cancer), while hepatocyte MAO-B is linked to epithelial-intrinsic defense programs.[19] Third, functional perturbation in organoids and patient-derived models could separate "ROS-driven" versus "GGA-driven" MAO-B dependencies by combining MAO-B suppression with rescue strategies (exogenous GGA, geranylgeraniol supplementation, or modulation of compensatory oxidation routes) and tracking endoplasmic reticulum-stress- and pyroptosis-like responses.

Clinically, if GGA insufficiency indeed represents a permissive state for hepatocarcinogenesis, maintaining the hepatic MAO-B/GGA axis could be explored as a chemopreventive concept in high-risk chronic liver disease. At present, however, there is no prospective clinical evidence that targeting this axis prevents HCC, and key issues such as long-term safety, inter-individual variability in MAO-B and CYP3A4 activity, and optimal dosing or timing remain unresolved. Rather than broadly deploying retinoids, approaches that preserve endogenous GGA availability by increasing precursor availability, stabilizing hepatic MAO-B expression, or enhancing compensatory oxidation when MAO-B is low could be evaluated alongside established surveillance. Establishing robust biomarkers of the MAO-B/GGA axis status will be essential to stratify patients and to test whether restoring this pathway can suppress clonal outgrowth toward HCC. In future studies, close collaboration with clinical hepatology and liver transplant centers will be crucial to validate these concepts and experimental observations in well-characterized cohorts of patients with HCC and assess their potential impact on early diagnosis and therapeutic decision-making.

5. Conclusion

This perspective reframes MAO-B as a context-dependent metabolic switch rather than a purely unidirectional source of oncogenic oxidative stress. In glioma and prostate cancer, MAO-B-associated H_2O_2 output can support redox signaling programs linked to invasion and progression. In the liver, however, it is hypothesized that declining MAO-B may weaken an intrinsic defense pathway by limiting endogenous GGA production, thereby contributing to a state of GGA insufficiency in which premalignant hepatocytes can more readily escape elimination and evolve toward HCC. Defining when MAO-B biology is predominantly ROS-driven versus GGA-driven, and establishing biomarkers of MAO-B/GGA axis status, will be essential steps toward translating this paradox into risk stratification and rational chemopreventive strategies for high-risk liver disease.

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