Review

Aging-Dependent Shift in Hepatic GGA Biosynthesis: A Proposed Axis Involving MAOB and CYP3A4 in Liver Cancer Susceptibility

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Aging-Dependent Shift in Hepatic GGA Biosynthesis: A Proposed Axis Involving MAOB and CYP3A4 in Liver Cancer Susceptibility

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Abstract

Geranylgeranoic acid (GGA) is a naturally occurring acyclic isoprenoid with chemopreventive effects against hepatocellular carcinoma. In mammals, GGA is endogenously synthesized via the oxidative metabolism of geranylgeraniol by monoamine oxidase B (MAOB). However, MAOB activity decreases with age, leading to reduced hepatic GGA levels. Emerging evidence suggests that cytochrome P450 3A4 (CYP3A4) may compensate for this decline, providing an alternative oxidative pathway in MAOB-deficient conditions. This mini-review summarizes the current findings on GGA biosynthesis and metabolism in the aging liver, focusing on the MAOB-CYP3A4 axis and its relevance to age-related hepatic dysfunction. By discussing recent evidence on enzymatic compensation and age-dependent metabolic changes, this review highlights how the CYP3A4-GGA pathway may help unravel the complexity of hepatic aging.

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1. Introduction

Hepatocellular carcinoma (HCC) remains a global health burden, ranking as the third leading cause of cancer-related deaths worldwide[1]. Its development involves a complex interplay between genetic, metabolic, and environmental factors. In recent years, there has been increasing attention on metabolic regulators in the liver, particularly those involved in lipid metabolism and oxidative stress responses[2,3]. Among these, monoamine oxidase B (MAOB) has emerged as a noteworthy player due to its involvement in the endogenous synthesis of geranylgeranoic acid (GGA), a lipid mediator with potential tumor-suppressive properties[4,5]. GGA, an acyclic isoprenoid, has been shown to exert antitumor effects, particularly in the liver[6–8].

It is synthesized via the oxidation of geranylgeraniol by MAOB, highlighting the potential protective role of this enzyme. GGA induces pyroptotic cell death in precancerous hepatic cells via Toll-like receptor 4 (TLR4) activation[9,10]. This observation suggests a functional axis involving MAOB, GGA, and TLR4 in hepatic immune surveillance.

However, the role of MAOB in hepatic physiology appears temporally regulated. With aging, the expression and activity of MAOB decline, resulting in reduced hepatic GGA levels[4]. This reduction coincides with an increased risk of spontaneous hepatocarcinogenesis in certain mouse models, such as C3H/HeN mice[4]. The idea that age-dependent changes in MAOB and GGA may underlie the transition from a tumor-suppressive to a tumor-permissive hepatic microenvironment introduces a compelling paradigm for metabolic carcinogenesis. In this review, we explored the hypothesis that MAOB serves as a gatekeeper enzyme for hepatic tumor suppression by facilitating GGA production. We examined the metabolic shift that occurs with aging, its consequences for GGA availability, and the compensatory role of cytochrome P450 3A4 (CYP3A4), a hepatic enzyme that

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may partially substitute for MAOB in GGA synthesis[11] but also potentially promotes tumor progression[12]. By analyzing the MAOB–GGA–CYP3A4 axis, we aimed to highlight a critical yet underexplored dimension of liver cancer biology and propose experimental directions for future investigations.

2. MAOB and GGA: A Hepatic Tumor Suppressor Pathway

Geranylgeranoic acid (GGA) was initially synthesized as a potential pharmaceutical agent, and its antitumor properties, particularly its ability to induce cell death in hepatocellular carcinoma (HCC) cells, were recognized in the early stages of its development[7,8,13]. While it was initially approached as a synthetic compound, its biological significance broadened dramatically when Shidoji and Ogawa later discovered that GGA occurs naturally in certain medicinal plants, including turmeric[14]. This pivotal finding reframed GGA not only as a drug candidate but also as a naturally occurring bioactive lipid with potential physiological roles. Building upon this discovery, Shidoji et al. extended this investigation to mammals. We demonstrated that GGA is not only present in plant-derived foods but is also endogenously synthesized in mammals, including humans [15,16]. This was a major turning point, as it positioned GGA as a physiologically relevant metabolite, rather than an exogenous phytochemical.

Our studies further revealed that the biosynthesis of GGA in mammals involves monoamine oxidase B (MAOB), a flavin-dependent enzyme that is traditionally known for its role in neurotransmitter metabolism[17]. We previously showed that MAOB catalyzes the oxidative deamination of geranylgeraniol, an intermediate in the mevalonate pathway, to GGA[5]. This link between MAOB and GGA synthesis establishes the enzyme as a key metabolic node connecting lipid metabolism and cancer prevention. We further investigated the relationship between age-related changes in GGA metabolism and hepatocarcinogenesis using C3H/HeN mice, a well-established model of spontaneous HCC[4]. Our findings revealed that hepatic GGA levels markedly declined with age. Correspondingly, the expression of monoamine oxidase B (MAOB), a key enzyme responsible for GGA biosynthesis, also decreases in an age-dependent manner[4]. This decline coincided with the period during which the risk of hepatocarcinogenesis increased, suggesting that the reduction in GGA may create a “metabolic turning point” that permits the initiation of hepatic tumor formation.

Interestingly, a single oral administration of GGA or its 4,5-didehydro derivative during this metabolic turning point suppresses the progression of pre-neoplastic hepatocytes and significantly reduces the eventual development of liver tumors[4,18]. The antitumor effect was most pronounced when GGA was administered at 11 months of age, whereas administration at 8 or 13 months resulted in little to no effect[4,18]. These findings suggest that the tumor-suppressive function of GGA is temporally constrained and may specifically inhibit the silent progression of hepatocarcinogenesis during its early stages.

Furthermore, several studies, including ours, have reported that GGA induces hepatocellular carcinoma cell death through TLR4-mediated pyroptosis[10], highlighting a potential immune-mediated mechanism for eliminating abnormal hepatocytes. Therefore, the loss of GGA due to age-associated downregulation of MAOB represents not only a metabolic alteration but also a breakdown of the liver’s intrinsic tumor surveillance system.

While these findings underscore the tumor-suppressive role of GGA, they also raise an important question: how does the gradual decline in MAOB expression during aging establish the temporal vulnerability that permits tumor initiation? This question forms the basis of the next section, where we explore the dynamics of age-dependent MAOB reduction and its implications for hepatic carcinogenesis in greater detail.

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3. Age-Related Decline in MAOB and Its Implications for Hepatic Carcinogenesis

The expression and activity of monoamine oxidase B (MAOB) in the liver appear to be tightly regulated by age, with significant implications for hepatic tumor biology. Several studies, including ours, have demonstrated a marked decline in MAOB mRNA levels in murine liver tissues during aging[4,19]. This decline coincides with a reduction in geranylgeranoic acid (GGA) concentrations, as shown in longitudinal analyses of C3H/HeN mice, a strain prone to spontaneous hepatocarcinogenesis. Given that MAOB is the principal enzyme responsible for endogenous GGA biosynthesis, its downregulation represents a pivotal event in the loss of hepatic tumor-suppressive capacity. The onset of spontaneous hepatocellular carcinoma (HCC) in aging C3H/HeN mice temporally aligned with this decline in MAOB expression. In particular, the period between 9 and 13 months of age appears to be a vulnerable phase, during which hepatic GGA levels fall below the threshold required for effective tumor surveillance. This vulnerable phase, which we have termed the "metabolic turning point," marks a shift in the hepatic microenvironment from tumor resistance to tumor permissiveness. During this interval, hepatocytes that have accumulated genetic or epigenetic alterations may escape immune-mediated clearance because of insufficient GGA production.

Our experiments have shown that a single oral administration of GGA at 11 months of age, precisely within this turning point, can significantly suppress the development of spontaneous liver tumors[4]. In contrast, GGA administration at 7 or 17 months of age failed to confer the same protective effect. These findings suggest that early neoplastic lesions are established silently during this narrow window of MAOB insufficiency and that timely GGA supplementation is required to prevent their progression[4]. Similar results were reported in experiments with the 4,5-didehydro derivative of GGA[18].

It is important to note that the decline in MAOB is gradual rather than abrupt, which may explain the narrow temporal effectiveness of the GGA intervention. This gradual decrease allows for a transient phase of metabolic insufficiency, during which GGA biosynthesis is reduced to sub-protective levels without being completely abolished. The implications are profound: liver tumorigenesis may not solely result from external carcinogenic insults or genetic mutations but also from an intrinsic failure of the liver's metabolic immune surveillance machinery.

Taken together, the age-associated reduction in MAOB and its downstream metabolite GGA constitutes a fundamental mechanistic link between aging and hepatocarcinogenesis. The metabolic turning point identified in this model represents a novel target for preventive intervention and may inform strategies for early diagnosis and chemoprevention in aging populations. In addition to the age-related decline in MAOB and GGA, other changes, such as increased expression of pro-inflammatory cytokines (e.g., IL-1β) or increased fibrogenic markers (e.g., Col1a1)[20,21], have been reported in aged liver tissue. Although these phenomena are not directly linked, they may act synergistically to shape the tumor-permissive hepatic microenvironment.

4. CYP3A4 and Its Dual Role in the Aging Liver

As the age-dependent decline in MAOB compromises endogenous GGA production, the liver may attempt to compensate through alternative oxidative enzymes[11]. One such candidate is cytochrome P450 3A4 (CYP3A4), a member of the cytochrome P450 superfamily that plays a pivotal role in xenobiotic metabolism, cholesterol homeostasis, all-*trans*-retinol oxidation and oxidative biotransformation[22–24]. Although CYP3A4 is primarily known for its involvement in drug metabolism, emerging evidence suggests that it may contribute to the residual synthesis of GGA from geranylgeraniol under MAOB-deficient conditions[11].

Previous biochemical studies have demonstrated that CYP3A4 enzymes can catalyze oxidation reactions of isoprenoid alcohols such as farnesol and geranylgeraniol, producing corresponding acids including geranylgeranoic acid. Our study demonstrated that in MAOB-knockout cells, the hepatic

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synthesis of GGA was not completely abolished, and that the expression of CYP3A4 (or its murine orthologs) was upregulated, indicating a compensatory role of this enzyme in GGA biosynthesis under MAOB-deficient conditions[11].

Therefore, in the context of MAOB depletion due to aging, CYP3A4 (or its murine orthologs such as Cyp3a11) may serve as a secondary route for GGA biosynthesis.

In our own studies, the hepatic GGA levels in C3H/HeN mice between 6 and 13 months of age were maintained at approximately 60% of the peak values observed in younger mice, suggesting that CYP3A4 may partially sustain GGA synthesis during this period[4].

However, this residual GGA production appears to be insufficient to exert robust tumor-suppressive effects, implying that CYP3A4-mediated compensation may operate below the functional threshold required for effective chemoprevention. While CYP3A4 may serve as a compensatory pathway for residual GGA synthesis, this benefit is counterbalanced by its potentially deleterious effects in the aging liver. CYP3A4 generates reactive oxygen species (ROS) as byproducts of its enzymatic activity, particularly during the metabolism of xenobiotics[25] and endogenous lipids[22]. Chronic ROS production can induce DNA damage[26], lipid peroxidation[27], and cellular senescence[28], which collectively promote hepatocarcinogenesis[29]. Moreover, CYP3A4 plays a critical role in the metabolic inactivation of various chemotherapeutic agents, including sorafenib[25] and other tyrosine kinase inhibitors widely used in the treatment of liver cancer[30]. This metabolic activity may reduce the therapeutic efficacy and contribute to drug resistance in hepatocellular carcinoma. In this context, elevated CYP3A4 expression in the livers of aged or diseased individuals may inadvertently support tumor progression rather than suppression. The dual role of CYP3A4 as both a metabolic backup for GGA production and a pro-oncogenic enzyme raises important questions regarding its net impact on liver tumorigenesis. It is plausible that the timing and extent of CYP3A4 upregulation dictate whether its effects are beneficial or detrimental to the host. In the early stages of MAOB decline, limited CYP3A4 expression might sustain sufficient GGA to maintain immune surveillance. However, as aging progresses and CYP3A4 expression further increases, this balance may tip toward oxidative damage and tumor promotion. Therefore, understanding the temporal dynamics of CYP3A4 expression and function in the aging liver is essential. Future studies should investigate whether a "CYP3A4 threshold" exists, beyond which its tumor-promoting activities outweigh its compensatory benefits in GGA biosynthesis. Identifying this tipping point could provide a valuable biomarker or therapeutic window for preventing age-related liver carcinogenesis.

5. Future Perspectives and Research Directions

The findings of this review open new avenues for exploring the metabolic and molecular mechanisms underlying age-associated hepatocarcinogenesis. Central to our hypothesis is the functional axis involving MAOB, GGA, and CYP3A4, which together define a metabolic landscape that transitions from a tumor-suppressive to a tumor-permissive state during aging. Understanding the dynamic interplay among these factors is essential for developing diagnostic biomarkers and preventive strategies for hepatocellular carcinoma (HCC), especially in aging populations.

One of the most urgent research directions is to elucidate further the compensatory role of CYP3A4 and its murine orthologs (e.g., Cyp3a11) in GGA biosynthesis. While our previous studies suggest that CYP3A enzymes maintain residual GGA levels under MAOB-deficient conditions[11], the exact enzymatic efficiency, substrate specificity, and regulatory mechanisms remain unclear. The quantitative assessment of Cyp3a11 expression in aging liver tissue, particularly across a critical age window (e.g., 6–15 months in C3H/HeN mice), would be an important first step. These data could help determine whether a “CYP3A4 threshold” exists, beyond which the enzyme’s pro-oxidative and pro-oncogenic activities outweigh its GGA-synthesizing potential.

Additionally, it is important to investigate whether pharmacological or genetic modulation of CYP3A4 activity alters the incidence or progression of spontaneous liver tumors in MAOB-deficient or aging animal models. For example, selective inhibition of CYP3A4 during advanced age may

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reduce oxidative stress and prevent drug resistance, whereas its early phase activation may help maintain GGA production. These dual roles suggest that therapeutic interventions targeting CYP3A4 must be precisely timed and tailored to individual metabolic profiles.

Another promising area of research involves validating of the MAOB–GGA–CYP3A4 axis in human liver tissue. Post-mortem liver samples or biopsy specimens from patients of different age groups could be analyzed for MAOB and CYP3A4 expression, GGA concentration, and markers of liver inflammation and fibrosis. Integrating these data with clinical outcomes, such as tumor incidence or drug responsiveness, may provide a translational bridge between experimental models and patient care. Furthermore, high-throughput technologies, such as single-cell RNA sequencing and spatial transcriptomics, can be employed to map MAOB and CYP3A4 expression across different hepatic cell populations. These techniques may reveal cell-type-specific regulation of GGA metabolism and help identify the liver cell types that are most critical for tumor surveillance. Such data would refine our understanding of the contribution of the hepatic microenvironment to carcinogenesis.

Finally, the concept of a "metabolic turning point" introduced in this review may extend beyond the scope of liver cancer. Similar age-related declines in lipid-derived mediators and compensatory enzyme systems may occur in other tissues and tumor types as well. Exploring this concept in a broader oncological context could lead to the discovery of common metabolic vulnerabilities that arise with aging.

In summary, future research should focus on quantifying and manipulating the MAOB–GGA–CYP3A4 axis in animal models and human tissues to establish a foundation for age-adapted preventive and therapeutic strategies against HCC.

6. Conclusions

Hepatocellular carcinoma (HCC) remains a formidable challenge in oncology, particularly in aging populations, where hepatic metabolic capacity undergoes significant alterations. This review explored the interplay between age-related metabolic shifts and liver tumorigenesis, focusing on the MAOB–GGA–CYP3A4 axis as a novel regulatory pathway in hepatic carcinogenesis.

We demonstrated that MAOB plays a critical role in maintaining hepatic homeostasis by catalyzing the endogenous biosynthesis of geranylgeranoic acid (GGA), a lipid mediator with tumor-suppressive properties. The age-dependent decline in MAOB expression and GGA production observed in models such as C3H/HeN mice suggests a vulnerability window during which the liver loses a key component of its intrinsic tumor surveillance system. This "metabolic turning point" is temporally associated with increased susceptibility to spontaneous hepatocarcinogenesis and provides a mechanistic framework linking aging with cancer risk.

We also discussed the immunological role of GGA, particularly its capacity to induce pyroptotic cell death in pre-malignant hepatocytes via TLR4 activation. This reinforces the concept that GGA is not merely a metabolic byproduct but a functional mediator of hepatic immune defense. The loss of GGA due to MAOB decline thus represents a dual threat of metabolic and immunological deregulation.

To compensate for the loss of MAOB, the liver appears to upregulate alternative oxidative enzymes, such as CYP3A4 and its murine orthologs, which partially sustain GGA biosynthesis. However, this compensatory mechanism may have a cost. Elevated CYP3A4 activity is associated with increased production of reactive oxygen species (ROS)[29] and enhanced metabolism of chemotherapeutic drugs[22,25], both of which can accelerate hepatic tumorigenesis. Thus, CYP3A4 acts as a double-edged sword, mitigating the loss of GGA while contributing to tumor-promoting conditions.

Taken together, the findings reviewed here position the MAOB–GGA–CYP3A4 axis as a central player in the age-associated transition from hepatic health to hepatic carcinogenesis. This axis offers novel insights into the intersection of metabolic aging and cancer biology and may serve as a strategic target for preventive and therapeutic interventions. Identifying critical windows of metabolic

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vulnerability, such as midlife decline in MAOB, may inform timing-based strategies for chemoprevention.

Although this review focused on endogenous pathways, future studies may benefit from exploring the potential of exogenous GGA supplementation, whether dietary or pharmacological, as a means to restore immune surveillance and prevent early neoplastic progression. A deeper understanding of the temporal dynamics and tissue specificity of CYP3A4 expression may offer new opportunities to balance its dual roles in liver physiology and pathology.

In conclusion, the age-dependent modulation of the MAOB–GGA–CYP3A4 axis represents a promising frontier in the prevention and understanding of hepatocellular carcinoma, with important implications for both basic science and clinical applications.

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