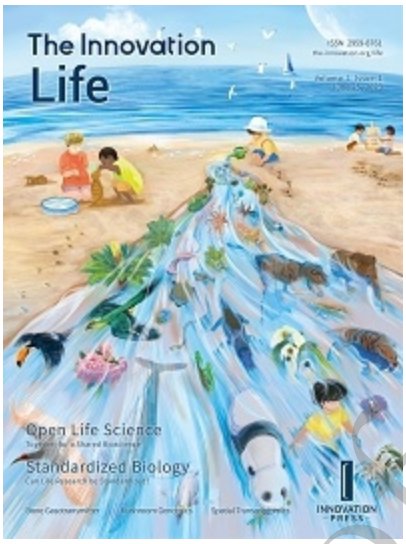

Beyond carrier design: The gut microbiota–serotonin axis modulates systemic delivery in mouse models

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Beyond carrier design: The gut microbiota–serotonin axis modulates systemic delivery in mouse models

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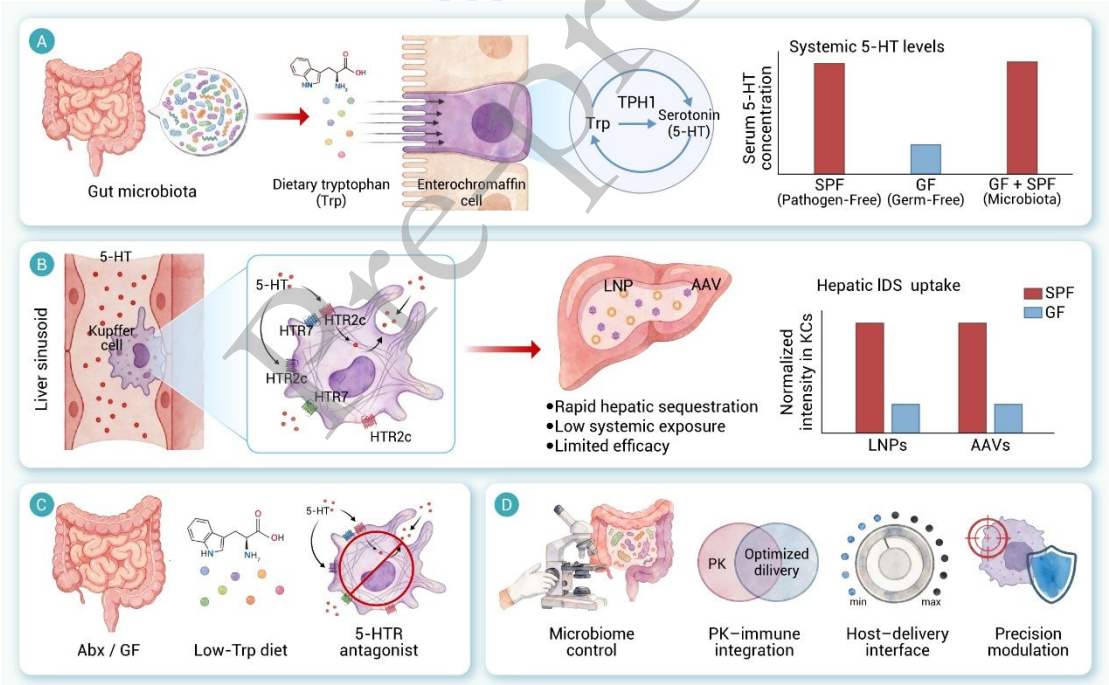

Figure 1. The gut microbiota–serotonin axis regulates systemic in vivo delivery

(A) Microbiota–EC cell signaling and serotonin production. Gut microbiota promote serotonin (5-hydroxytryptamine, 5-HT) biosynthesis from dietary tryptophan (Trp) in intestinal enterochromaffin (EC) cells via tryptophan hydroxylase 1 (TPH1). Systemic 5-HT levels are high in specific-pathogen-free (SPF) mice, low in germ-free (GF) mice, and restored upon microbiota reconstitution (GF + SPF microbiota).

(B) Liver-specific clearance mechanism via Kupffer cells. Circulating 5-HT activates hepatic

Kupffer cells (KCs) via two 5-HT receptors, 5-hydroxytryptamine receptor 2C (HTR2C) and 5-hydroxytryptamine receptor 7 (HTR7), thereby enhancing hepatic clearance and reducing both systemic circulation and target-tissue delivery of exogenous carriers. Consequently, hepatic uptake of lipid nanoparticles (LNPs) and adeno-associated viruses (AAVs) is elevated in SPF mice but attenuated in GF mice.

(C) Host-directed strategies. Three representative interventions—antibiotic treatment or germ-free conditions (Abx/GF), low-Trp diet, and 5-HTR antagonists—suppress the microbiota–5-HT axis and reduce Kupffer cell–mediated hepatic clearance.

(D) Future perspectives. A next-generation framework for precision delivery, integrating microbiome control, pharmacokinetic–immune integration, host–delivery interface, and precision modulation.

In vivo delivery systems (IDSs) have become essential tools in modern biomedicine, enabling the transport and targeted delivery of exogenous molecules such as nucleic acids, proteins, and therapeutic drugs. Recent advances in viral vectors, exemplified by adenoviral vectors (AdVs) and adeno-associated viruses (AAVs), as well as synthetic carriers such as lipid nanoparticles (LNPs), have accelerated the development of gene therapy and mRNA therapeutics.[1] However, efficient *in vivo* delivery remains a major challenge, as high vector doses are often required and may lead to dose-related toxicities.[2] A major barrier is the rapid clearance of administered carriers by the mononuclear phagocyte system (MPS), particularly liver-resident Kupffer cells, which limits their accumulation in target tissues.[3] Although current strategies focus on optimizing carrier properties to improve circulation and biodistribution, delivery efficiency remains inconsistent and the mechanisms underlying liver-dominated clearance are not fully understood. These limitations suggest an important role for host-regulated processes in shaping delivery outcomes. In a recent study published in Science, Wang et al. identified a gut microbiota–serotonin signaling axis that modulates hepatic phagocytic activity, revealing a previously unrecognized host mechanism controlling systemic *in vivo* delivery efficiency (Figure 1).[4]

In contrast to conventional material-centered strategies, this study highlights host physiological regulation, particularly the gut microbiota, as an important factor influencing systemic delivery efficiency. Using antibiotic-treated and germ-free mouse models, microbiota depletion significantly enhanced the performance of multiple delivery platforms, including albumin nanoparticles (NPs), liposomes, LNPs, and gold nanoparticles (AuNPs), as well as viral vectors such as AAVs, AdVs, and lentiviruses (LVs). This effect was associated with reduced hepatic sequestration of administered carriers, thereby prolonging systemic circulation

and increasing their accumulation in target tissues. Consequently, therapeutic efficacy was markedly improved across diverse applications, with approximately 3-fold enhancement in chemotherapy and oncolytic virotherapy, and 5–15-fold increases *in vivo* genome editing and mRNA delivery. Collectively, these findings identify the gut microbiota as a previously underappreciated host factor that modulates systemic *in vivo* delivery.

The mechanistic basis underlying this host regulation was further delineated as a gut–liver signaling axis linking microbial activity to hepatic phagocytic function. Microbial sensing in the intestinal epithelium, rather than direct interaction with hepatic immune cells, was required for regulating carrier clearance, indicating a cross-organ communication pathway. Disruption of microbiota-derived signaling altered the functional state of Kupffer cells and reduced their phagocytic activity, thereby decreasing hepatic uptake of diverse delivery systems (Figure 1, Panel B). This shift in Kupffer cell behavior ultimately improved systemic distribution of administered carriers, supporting a role for the microbiota-driven gut–liver axis in modulating systemic delivery efficiency. These findings highlight the intestinal epithelium as a critical relay linking microbial signals to hepatic immune regulation. Such cross-organ communication suggests that hepatic clearance of delivery systems is dynamically shaped by systemic host physiology rather than being solely determined by intrinsic carrier properties.

Within this cross-organ regulatory framework, serotonin was identified as the key mediator of gut–liver communication. The gut microbiota regulated tryptophan metabolism in intestinal epithelial cells, thereby controlling serotonin production (Figure 1, Panel A). Circulating serotonin subsequently acted on Kupffer cells through HTR2C and HTR7, activating ERK signaling associated with cytoskeletal remodeling and phagocytosis. Disruption of serotonin signaling reduced Kupffer cell uptake of both synthetic nanoparticles and viral vectors, indicating that this pathway contributes to the regulation of hepatic clearance. These findings support serotonin as an important molecular link connecting gut microbiota activity to Kupffer cell function and provide a mechanistic explanation for microbiota-dependent modulation of systemic *in vivo* delivery. Notably, this mechanism connects microbial metabolism with immune-mediated clearance, revealing how metabolic signals derived from the gut can directly influence the pharmacokinetics of therapeutic delivery systems.

Beyond mechanistic insights, the microbiota–serotonin axis provides new opportunities for improving systemic *in vivo* delivery. Modulation of gut microbiota composition, pharmacological inhibition of serotonin signaling, or transient dietary regulation of tryptophan availability may reduce hepatic clearance and enhance delivery efficiency without altering carrier design. Such host-directed strategies could benefit applications requiring high systemic

exposure, including gene therapy, mRNA therapeutics, and *in vivo* genome editing. Furthermore, combining host modulation with vector engineering may enable more precise and controllable delivery, for example by integrating microbiota regulation with tissue-targeted nanoparticles or engineered viral tropism. The microbiota–serotonin axis may therefore provide a framework for developing host-guided strategies that complement conventional carrier optimization (Figure 1, Panel C). However, the influence of the microbiota–serotonin axis may vary among delivery platforms, and carrier-specific physicochemical properties and immune interactions remain important determinants of biodistribution and clearance.

Although this study reveals a new regulatory mechanism, the current evidence is mainly derived from mouse models, and the relevance of the microbiota–serotonin axis to humans requires further characterization. Moreover, the temporal window and magnitude of host modulation required for optimal delivery enhancement have yet to be defined. Future studies integrating microbiome manipulation with pharmacokinetic and immunological analyses may help establish controllable strategies for improving systemic delivery. From a translational perspective, safety and specificity will also need careful evaluation, given the pleiotropic roles of serotonin in multiple physiological processes.[5] Achieving transient and reversible modulation of this axis will be important for minimizing systemic effects while maximizing delivery efficiency. Evaluating this strategy in clinically relevant disease models and large-animal systems will further determine its feasibility for therapeutic applications.

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AUTHOR CONTRIBUTIONS

X. Y. and B.L. conceptualized the manuscript, drafted the initial manuscript and prepared the figure; B.L. supervised the work and revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest.