De-bugging the system: could antibiotics improve liver transplant outcomes?

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Organ transplantation is now a preferred treatment for end-stage organ failure. Among the challenges for ensuring excellent clinical outcomes for transplant recipients is good initial allograft function at the time of organ implantation. This is determined in part by the functional status of the donor and donor organ, functional status of the recipient, and conduct of the operative procedure. Despite optimization of these variables, organ transplantation is still often plagued by substantial initial dysfunction, variably referred to as slow or delayed graft function, or in the most extreme cases, primary graft nonfunction necessitating urgent regrafting. In this issue of the JCI, Nakamura, Kageyama, Ito, Hirao, and colleagues investigate a potential role for the recipient’s microbiome in determining graft function after liver transplantation and demonstrate the benefits of antibiotic pretreatment in both a mouse model and in human patients.
De-bugging the system: could antibiotics improve liver transplant outcomes?

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Effect of the recipient’s gut microbiome on liver transplantation

Although many factors have been ascribed to poor initial graft function, ischemia-reperfusion injury (IRI) remains prominent among them (1). The causes of allograft IRI have usually been ascribed to poor donor organ quality, prolonged cold ischemia time, and suboptimal preservation technologies (2). Yet, even in optimal circumstances, IRI still occurs, so there must be other contributing events. In this issue, a team from the laboratory of Jerzy Kupiec-Weglinski, who have been leaders in the field of hepatic IRI for many years, assessed the potential role of the recipient’s gut microbiota as a driver of the initial IRI observed after liver transplantation (3).

The researchers focused on the gut microbiota because of its established role in the pathophysiology of liver diseases, including nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), and their progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma (4). It is also now apparent that the microbiome can be a causal agent in numerous metabolic, vascular, inflammatory, and neurohormonal events, with far-reaching consequences for disease pathophysiology (5). To evaluate the role of the gut microbiome in liver transplantation outcomes, the team first assessed the influence of oral antibiotic treatment on IRI severity in a clinically relevant murine allogeneic liver transplant model, with prolonged ex vivo cold storage at 4°C for 18 hours, which mimics extremely marginal human liver grafts. Recipient mice were treated for 10 days with oral amoxicillin prior to transplantation. Antibiotic treatment also increased hepatic EP4 functions and determine the development of IRI after transplantation (3).

Translating a mouse model to human patients

The limitations of this approach are that the murine recipients did not have cirrhosis, and longer-term consequences on hepatic function or recipient survival were not assessed. Thus, though the authors demonstrated an immediate effect of antibiotic therapy on IRI, this result might not translate into durable outcomes in...
metatranscriptomic sequencing — was performed. The antibiotic used, amoxicillin, is a moderate-spectrum β-lactam antibiotic targeting both Gram-positive and Gram-negative bacteria that are likely to exert broad effects on the gut microbiota. Previous studies have shown that treatment with amoxicillin increases the amount of aerobic Gram-positive cocci and enterobacteria in the gut, among other potentially significant shifts (9). Because of the lack of microbiota characterization, Nakamura et al. were unable to assess which specific bacterial group(s) might be responsible for the effects on IRI severity and whether some bacterial groups might have a beneficial impact (3).

It is also unclear whether the effects exerted by the microbiota on Cox2 gene regulation and PGE2 production were direct or indirect and what host cells and bacterial components were involved. Gut microbiota-mediated induction of the COX2 pathway, resulting in increased production of PGE2, has been previously demonstrated in obesity-associated liver cancer (9). In that study, it was shown that lipoteichoic acid, a Gram-positive gut microbial component, induced COX2 expression through a TLR2-mediated signaling pathway, facilitating tumor progression by suppressing antitumor immunity...
variable (13, 14). Further, the authors could not precisely analyze all the individual antibiotics used in the transplant patients and the associated effects of these antibiotics on recipient outcomes or microbiome structure. Taken together, it is difficult to conclude that an altered microbiota necessarily accounted for differences in IRI. Rather, the authors found that antibiotic use prior to liver transplantation informs short-term outcomes (long-term results were not assessed). Additional work needs to be done to tease out exactly why this may be the case.

The results might also seem contradictory to the generally accepted concept, borne from human microbiome studies over the past ten-plus years, that dramatic disruptions of the microbiota, such as those induced by antibiotic treatments, tend to have a negative impact on overall health. For example, the microbiota acts as a barrier against colonization and overgrowth of potentially pathogenic and opportunistic microorganisms in the gut (15, 16), and its disruption following antibiotic therapy has been associated with complications such as recurring *Clostridium difficile* infections (16). Gut microbiota dysbiosis has also been shown to be a major contributor to inflammatory bowel diseases, cardiovascular diseases, and even autism and Parkinson’s disease (17, 18). Previous studies have also suggested that antibiotic treatments can have long-lasting consequences, not only because of the risk of emergence and spread of antibiotic-resistant bacterial strains (19, 20), but also because microbiome dysbiosis can persist long after the treatment ends (13). Because the consequences of such permanent disruptions remain unknown, it will be important to follow this study with more in-depth analysis of the microbiota shifts in the treated transplant patients and identify the specific players and host factors involved in this response in order to potentially design a microbiota-based therapy for IRI that does not trigger unintended side effects.

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