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INTRUÇÕES

1) As questões da prova deverão ser respondidas à caneta, cor azul ou preta, exclusivamente nas folhas de respostas fornecidas pela comissão de seleção.

2) **Não** é permitida a consulta de nenhum tipo de material bibliográfico ou anotações pessoais. **Não** será permitido o uso de aparelhos eletrônicos tais como telefone celular, tablets, notebooks ou similares.

3) A duração da prova será de 2 horas.

BOA PROVA!

**Drinking Causes Gut Microbe Imbalance Linked to Liver Disease
Scientific American, By Bob Roehr, on February 10th 2016**

Alcohol harms the liver in two ways, by damaging the organ's cells directly and by disrupting gut microbiota, which can scar the liver. Now researchers have figured out the mechanism behind the microbial imbalance due to drinking and could use the information to devise treatments for liver disease and a broad range of other medical conditions ranging from irritable bowel syndrome to autism.

"We've known for a very long time that patients with heavy drinking and alcohol use suffered an intestinal dysbiosis, where bacteria in the gut increase and they suffer from liver disease," says University of California, San Diego, research gastroenterologist Bernd Schnabl.

That curiosity led Schnabl and his research team to focus on antimicrobial molecules REG3B and REG3G and the genes (*Reg3b* and *Reg3g*) that produce them. The genes are only expressed in the intestines; the pair of peptides the genes generate are only produced in the gut and have broad-spectrum activity against gram-negative and gram-positive organisms, respectively.

Through a series of experiments, the researchers learned that administering alcohol downregulated the genes so that they produced significantly less of the antimicrobial molecules. Knockout mice lacking those genes developed more bacteria in their guts and more severe liver disease compared with normal wild-type mice.

One surprise was that the microbes in the lumen, the center of the gut, were essentially the same in all of the animals, regardless of how much REG3 they produced. Only when the scientists looked closer at the mucosa, the slimy area next to the gut wall, did they see a difference. "The bacteria in the mucosa just proliferated dramatically in the absence of these molecules," Schnabl says. The balance between microbes and immune defenses was upended and more bacteria were able to migrate through the gut wall into the body, eventually traveling through the bloodstream to the liver. T cells attacked the invaders and the resulting inflammation scarred the liver.

He believes the total amount of bacteria that translocates through the gut wall is the most important factor in causing disease. But it could be that specific types of bacteria also are important. Disease often depends not on the presence or the total amount of an organism in the gut but rather on location, which in this case is the gut mucosa. Location may be important in designing a therapeutic intervention. A product delivered to the middle of the gut may have little benefit; it may have to be packaged in a way to hone in on the mucosa. Potential treatments, however, are years if not decades away. Until then the best thing people can do is reduce alcohol consumption to lessen possible damage to the body.

"Intestinal REG3 Lectins Protect against Alcoholic Steatohepatitis by Reducing Mucosa-Associated Microbiota and Preventing Bacterial Translocation." Wang et al., *Cell Host & Microbe* 19, 1-13.

