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The intestinal microbiota and hepatocellular carcinoma

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Abstract: The microbiota and its collective genomes, i.e., microbiome, have recently attracted major interest in the scientific community. Especially the largest microbial community of the human body, the intestinal microbiota, is assumed to play a crucial role in many gastrointestinal, pancreatic and liver disorders. Several preclinical and clinical investigations have shown that liver diseases at various stages exhibit substantial changes in their microbiome compared to healthy controls, also defined as dysbiosis. The most profound changes have been observed in the stage of liver cirrhosis, and importantly, it is clinically well established that interference with the intestinal microbiota, e.g., rifaximin improves complications of liver cirrhosis, such as hepatic encephalopathy. It is currently unclear which factors drive the evolution of hepatocellular carcinoma (HCC), which usually appears in a cirrhotic liver. Pro-inflammatory signals, bacteria, and related metabolites might be involved. Several studies have recently assessed the role of the intestinal microbiota in HCC. Here, various reports could demonstrate that especially the abundance of pro-inflammatory intestinal communities, such as *Proteobacteria* and *Enterobacteriaceae* are increased. Furthermore, some studies in HCC have shown, that microbiome alterations are associated with decreased levels of butyrate-producing *Clostridiales* and species, known for their anti-inflammatory potential, like *Akkermansia muciniphila*. These strains could contribute to the overall pro-inflammatory phenotype of this malignancy. Furthermore, several preclinical studies could convincingly show that intestinal bacteria are involved in liver carcinogenesis. Overall, it can be concluded that the intestinal microbiota might play a crucial role in the pathophysiology of hepatic carcinogenesis.

Keywords: Inflammation, Liver cancer, Metagenomics, Metabolites, Microbiome.

INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive malignancy and almost exclusively develops in patients with chronic liver disease and cirrhosis. HCC is the third leading cause of worldwide cancer mortality, with growing incidence[1]. Predisposing factors differ between regions. While viral hepatitis, especially hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection represent the leading cause of cirrhosis and HCC in low income countries and Asia, alcoholic (ALD) and nonalcoholic fatty liver disease (NAFLD) are the main cause for developing cirrhosis and HCC in high income countries[2,3]. The pathogenesis of HCC is multi factorial, driven by a circle of liver injury, inflammation, and regeneration that typically spans decades.

Next to these predisposing factors, genome wide association studies (GWAS) changed our understanding of genetically associated HCC development essentially. These genetic associations can give us useful suggestions on signaling pathways which are important for tumor development[4]. But these studies give little evidence of the functional understanding of the disease as the presence of genetic risk factors alone does not cause the disease, thus, not every patient with polymorphisms in HCC associated genes develops disease. The current model of disease development is a combination of predisposing factors and genetic risk. Some studies point towards a key role of the bacterial microbiome in promoting liver diseases and the development of HCC[5]. Studies from the past decade have shed light on the important contributions of the gut microbiota to key

aspects of our health[6,7]. Although the gut microbiota provides substantial benefit to the host, in particular with respect to metabolism and immunity, there is also increasing recognition of the involvement of the gut microbiota in disease processes[8,9].

Next to predisposing factors, as already mentioned, increasing evidence points towards a key role of the bacterial microbiome and bacterial metabolites in the development of chronic liver disease (CLD). The intestinal microbiota promotes disease development not only *via* local effects, as in chronic inflammatory bowel diseases (IBD), but also at distant sites, such as the liver, heart, brain, and the hematopoietic system[10-12]. Likewise, there is accumulating evidence for an important contribution of the intestinal microbiota to carcinogenesis, such as in colorectal carcinoma, and even extraintestinal locations, such as melanoma or bronchial carcinoma[13-15]. Due to its anatomical connection *via* the portal vein, the liver is closely linked to the gut. Not only does the liver receive nutrient-enriched blood from the intestine, but it is also the first target of the intestinal microbiota and microbe-associated molecular patterns (MAMPs), which can elicit inflammatory responses *via* pattern-recognition receptors (PRRs) and microbial metabolites[16]. The multi-layer intestinal barrier ensures that hepatic exposure to pro-inflammatory MAMPs is minimal. However, a failing gut barrier and alterations of the gut microbiota in CLD may contribute to chronic inflammation and the progression of liver diseases, and thereby increase the risk of the development of HCC as the final stage of the disease process[17-20].

BACTERIAL DYSBIOSIS IN LIVER CIRRHOSIS

The pathogenesis of CLD is incompletely understood, but there is increasing evidence that the gut microbiota might play a key role in the development of CLD[21]. There exist several animal studies showing a clear association between CLD and microbiota dysbiosis. In one preclinical experimental model, adult mice with a certain microbiome were able to clear HBV within six weeks of infection. On the opposite, young mice without a differentiated microbiome or adult mice after gut sterilization for 6 to 12 weeks remained HBV positive[22,23]. In multiple other studies with NAFLD and ALD animal models, a clear association between the degree of liver disease and dysbiosis was detected[24-26]. Furthermore, beneficial bacteria like *Akkermansia muciniphila* can ameliorate alcoholic steatohepatitis (ASH) in mice[27].

In patients with liver cirrhosis, there is strong evidence that the progression of NAFLD, ALD, and chronic viral hepatitis is strongly associated with gut microbiome dysbiosis. These changes could be shown in patients suffering from HBV, where a decrease of *Bacteroidetes, Bifidobacteria*, and *Lactobacillus,* as well as an increase of *Enterococcus* and *Enterobacteriaceae*, could be detected[28-31]. There are only a few studies on microbiota and hepatitis C virus (HCV) infection: HCV patients show lower microbial diversity in comparison to those of healthy controls[32-34]. In patients suffering from alcoholic abuse and CLD, microbiome alterations were associated with decreased levels of butyrate-producing *Clostridiales* species order and increased levels of pro-inflammatory *Enterobacteriaceae*. *Bacteroidales* were reduced in patients diagnosed with cirrhosis[35-37]. Dysbiosis and NAFLD seem to create a complex network belonging one to each other, which is highlighted in multiple studies[38-42].

There are some studies demonstrating that the microbiome influences progression from pre-existing diseases into cirrhosis, pointing out a key role for dysbiosis in the development of end stage liver disease in murine models, as well as in human patients[25,26,43,44]. The gut microbiome of patients with advanced liver disease and cirrhosis is characterized by an increase in potentially pathogenic bacteria, along with reduced numbers of bacteria with beneficial properties[31,45]. Studies conducted so far on the gut microbiota in liver cirrhosis have pooled patients with different underlying liver diseases. At least some of the microbial alterations in cirrhosis are common to different etiologies, which suggests that alterations are driven by characteristic features of end-stage liver diseases. There are reduced bile output and changes in the intestinal secretion of antimicrobial peptides and immunoglobulin A (IgA)[43]. Key changes in the composition of the intestinal microbiota in cirrhosis include enrichment of *Veillonella* or *Streptococcus*, as well as decreased numbers from the order *Clostridiales*[31]. The gut microbiome of patients suffering from cirrhosis presented a relative reduction in *Bacteroidetes*, an increase in *Proteobacteria* and *Fusobacteria*, but changes in *Firmicutes* mimicked the microbiome from healthy individuals[32]. Furthermore, there were differences at the family level, with *Streptococcaceae* and *Veillonellaceae*. *Streptococcaceae* positively correlated with cirrhosis severity, while *Lachnospiraceae* negatively

correlated with disease activity. These differences were confirmed by another research group in a larger population of patients suffering from cirrhosis[32,46].

The majority of the patient's enriched species were of buccal origin, suggesting an invasion of the gut from the mouth in liver cirrhosis[31]. Buccal origin species in cirrhosis are associated with proton pump inhibitors (PPIs) use. PPIs modulate microbiota composition in patients with cirrhosis[47]. Furthermore, PPI intake is associated with a higher risk of hepatic encephalopathy and spontaneous bacterial peritonitis[48,49]. An association between HCC and PPI intake in patients with cirrhosis, due to hepatitis C or hepatitis B virus infection could not be found[50]. The finding that the intestinal microbiota of patients with compensated cirrhosis differs from that of patients with decompensated cirrhosis suggests that cirrhosis stage, rather than the underlying liver disease, drives gut microbiota changes[43]. In addition to alterations in bacterial composition, evidence demonstrates bacterial overgrowth in the upper gastrointestinal tract, which in turn is associated with increased circulating lipopolysaccharide (LPS) levels[51]. Bacterial translocation in the upper gastrointestinal tract is relevant for the development of liver disease owing to the anatomic connection of the small intestine to the liver. In the past few years, studies have demonstrated differences in the duodenal and salivary microbiota between healthy individuals and patients with cirrhosis, suggesting that there are also qualitative and quantitative changes in the upper gastrointestinal tract that might be linked to changes in the more distal microbiota and therefore contribute to the pathophysiology of CLD, as well as the development of HCC[52].

These alterations in the microbiome of patients with cirrhosis are not only demonstrated in feces, but also in serum, saliva, sigmoid colonic mucosa, small intestinal mucosa, ascites, and liver tissue[32,46,53,54]. It seems that the dysbiosis in cirrhosis causes holistic mucosal immune change or vice versa. Dysbiosis has also been associated with the main comorbidities going along with cirrhosis: spontaneous bacterial peritonitis, hepatic encephalopathy, organ failure, and death in patients with cirrhosis[43,46,55,56].

The most common components of the microbiota are bacteria, but evidence[57] points toward the important role of fungi, archaea, and viruses, especially bacteriophages. In a recent study fungal diversity in patients suffering from cirrhosis was linked to bacterial diversity and suggests that fungi can affect hospitalizations in conjunction with bacterial indices[58,59]. Further studies are needed to define the constituents of the entire microbiome in liver disease.

HCC AND MICROBIOTA: PRECLINICAL EVIDENCE

Many reports support a key role for dysbiosis in the development of liver disease and HCC. High circulating LPS-levels in mice models and humans with CLD and with HCC demonstrate the presence of an impaired intestinal barrier during multiple stages of CLD and hepatocarcinogenesis[60-62]. Functional experiments in germ-free toll like receptor (TLR)-deficient and LPS-treated mice have provided evidence[17] that a "leaky gut", *via* LPS and its receptor TLR4, makes essential contributions to hepatocarcinogenesis. In addition to causing characteristic infectious complications in end-stage liver disease, increased bacterial translocation also generates a chronic inflammatory state in the liver. The inflammatory responses in the liver are mediated *via* interaction between MAMPs and host PRRs, specifically the TLRs[63]. Accordingly, chronic infusion of low-dose LPS *via* osmotic pumps promotes HCC development in mice[17]. Likewise, disruption of the gut barrier by administration of dextran sulfate sodium, not only results in increased systemic LPS levels and increased liver fibrosis, but also promotes HCC formation in mice[64,65]. Conversely, inhibition of TLR4 signaling suppresses liver inflammation, fibrosis, and HCC formation in mice and rats[66,67]. TLR4 is present in multiple hepatic cell types, including Kupffer cells, hepatic stellate cells (HSCs), endothelial cells, and hepatocytes. TLR4 expressed on liver-resident cells, which include hepatocytes, HSCs and Kupffer cells is responsible for promotion of fibrogenesis and hepatocarcinogenesis[17]. LPS from the "leaky gut" seems to drive hepatocarcinogenesis *via* multiple cellular targets, including HSCs, the hepatocyte-tumor compartment and Kupffer cells. In HSCs, TLR4 activation leads to nuclear factor kappa B (NF-kB)-mediated upregulation of the hepatomitogen epiregulin (EPR)[17,68]. EPR is an epidermal growth factor family member with potent mitogenic effects on hepatocytes. Another key mechanism by which the LPS-TLR4 axis promotes HCC formation is the NF-kB mediated prevention of hepatocyte apoptosis[17]. Moreover, it has been demonstrated that activation of the LPS-TLR4 signaling pathways in Kupffer cells leads to tumor necrosis factor (TNF) dependent and interleukin (IL) 6 mediated compensatory hepatocyte proliferation, as well as reduced oxidative

stress and apoptosis[67]. In addition, TLR4 activation in HCC cell lines by LPS enhances their invasive potential and induces the epithelial mesenchymal transition[69]. Together, these data clearly show that an impaired intestinal barrier *via* MAMP-TLR mediated signals, contributes to hepatocarcinogenesis[70]. Dysbiosis and the impaired intestinal barrier are probably intimately linked. It is likely that intestinal dysbiosis contributes to an impaired intestinal barrier by multiple mechanisms, such as dysbiosis induced alterations of the intestinal barrier. Furthermore, there seems to be a shift to bacterial species with increase propensity to translocate[71].

In a murine HCC model, the depletion of host microflora after antibiotic treatment was able to suppress tumor formation with a significant reduction of the number and size of HCC nodules in treated mice compared to untreated mice[67]. Furthermore, dysbiosis can promote the development of HCC by altering bile acid metabolism. In a model of NASH-associated HCC induced by a high-fat diet rich in saturated fatty acids and cholesterol (STHD-01), given to specific pathogen free (SPF) C57BL/6J mice, the accumulation of cholesterol and secondary bile acids caused hepatic inflammation and injury, which might contribute to enhanced carcinogenesis[72]. In a mouse model of HCC, tumor growth could be significantly reduced by administering probiotics thus decreasing the Th17 cell level and the production of interleukin (IL)-17. Probiotic treatment also slowed down tumor growth and again reduced tumor size by decreasing the Th17 cell level and the production of IL-17 in a mouse model of HCC[73].

In carcinogenesis, inflammation plays a key role and dysbiosis can create a proinflammatory environment, which favors carcinogenesis and HCC development. Regulatory T cells (Tregs) reflect a specialized subpopulation of T cells that act to suppress immune response, and also produce anti-inflammatory IL-10. Their number was associated with an increase of *Alistipes, Butyricimonas, Mucispirillum, Oscillibacter, Parabacteroides, Paraprevotella*, and *Prevotella*. *Parabacteroides* have proven to inhibit inflammation by restraining inflammatory cytokines secretion and by promoting the release of anti-inflammatory cytokines like IL-10[73,74]. Such changes are found in the feces of the specific pathogen-free (SPF) mice with a normal spectrum of commensal microorganisms, but not in microbiota-deficient mice that were treated with broad-spectrum antibiotics (AVNM) or in germ-free (GF) mice[73]. In a murine model of streptozotocin-high fat diet (STZ-HFD) induced NASH-HCC and the species *Akkermansia muciniphila, Bacteroides fragilis, Parabacteroides distasonis,* and *Alistipes shahii* were also significantly enriched[75,76]. *Alistipes shahii* tends to modulate the gut by ablating tumor growth and *Bacteroides fragilis* acts by stimulating Treg cells *via* induction of IL-10[77].

HCC AND MICROBIOTA: HUMAN EVIDENCE

There are only a few clinical trials correlating microbiota and HCC (Table 1). These trials show different alterations of the gut microbiota in patients with HCC. In one study, the presence of HCC in cirrhotic patients was associated with increased fecal counts of *Eschericha coli*. Intestinal overgrowth with *Escheria coli* could contribute to the process of hepatocarcinogenesis[78]. In a more recent study, patients suffering from HCC with HBV/HCV harbored more potential pro-inflammatory bacteria (*Escherichia, Shigella, Enterococcus*) and reduced the levels of *Faecalibacterium, Ruminococcus*, and *Ruminoclostridium*, resulting in a decrease of potentially anti-inflammatory short-chain fatty acids[79]. Patients with NAFLD-related cirrhosis and HCC (21 patients), NAFLD-related cirrhosis without HCC (20 patients), and healthy controls (20 patients) were also compared. Plasma levels of interleukin 8 (IL-8), IL-13, chemokine ligand (CCL) 3, CCL4, and CCL5 were higher in the HCC group and associated with an activated status of circulating monocytes. The fecal microbiota of the whole group of patients with cirrhosis showed higher abundance of *Enterobacteriaceae* and *Streptococcus* and a reduction in *Akkermansia*. *Bacteroides* and *Ruminococcaceae* were increased in the HCC group, while *Bifidobacterium* was reduced[20]. In another study 75 patients with early HCC were compared with 40 patients with cirrhosis and 75 healthy controls. In this investigation, fecal microbial diversity was increased from cirrhosis to early HCC with cirrhosis. The phylum *Actinobacteria* was increased in early HCC compared to patients with liver cirrhosis. Correspondingly, 13 genera including *Gemmiger* and *Parabacteroides* were enriched in early HCC versus cirrhosis. The microbiota pattern showed an increase in LPS producing species, such as *Parabacteroides* and a decrease in the butyrate-producing species, such as *Actinobacteriae* compared to healthy individuals. Therefore, current evidence[80] suggests that a specific microbiota pattern for patients with HCC might exist (Table 1).

TABLE 1. SEVERAL HUMAN STUDIES AS OUTLINED HERE HAVE INVESTIGATED THE COMPOSITION OF THE INTESTINAL MICROBIOTA IN HCC.

Publication	Patients			Microbiome changes			
	HCC	Cirrhosis	Healthy	Phylum	Taxa	Family	Genus
Ren et al[80]	75	40	75	Actinobacteria↑↑ Verrucomicrobia↓			Klebsiella↑ Haemophilus↑ Gemmiger↑ Parabacteroides↑ Paraprevotella↑ Alistipes↓↓ Phascolarctobacterium↓↓ Ruminococcus↓↓
Ponziani et al[20]	21	20	20	Bacteroidetes↑↑		Streptococcaceae↑↑ Enterococcaceae↑↑ Gemellaceae↑ Ruminococcaceae↑ Verrucomicrobiaceae↓ Bifidobacteriaceae↓	Phascolarctobacterium↑ Enterococcus↑ Streptococcus↑ Gemella↑ Bilophila↑ Adlercreutzia↓ Collinsella↓ Akkermansia↓ Bifidobacterium↓ Dialister↓
Liu et al[79]	57		33	Bacteroidetes↑ Firmicutes↑ Proteobacteria↑	Enterobacteriales↑ Clostridiales↑ Bacteroidales↑ Selenomonadales↑		Escherichia↑ Escherichia↑ Shigella↑ Enterococcus↑ Buchnera↑ Bacteroides↑ Prevotella↑ Megamonas↑ Faecalibacterium↑ Faecalibacterium↓ Ruminococcus↓ Pseudobutyrivibrio↓ Lachnoclostridium↓ Prevotella↓ Alloprevotella ↓ Phascolarctobacterium ↓ Ruminoclostridium↓
Grat et al[78]	15	15				Enterobacteriaceae↓	Escheria coli↑↑ Clostridium↑ Enterococcus↓ Lactobacillus↓ Bacteroides↓ Bifidobacterium↓

↑↑ indicates a significant increase in HCC *vs* control group(s)
↑ indicates an increase in HCC *vs.* control group(s)
↓↓ indicates a significant decrease in HCC *vs.* control group(s)
↓ indicates a decrease in HCC *vs.* control group(s)

HCC AND BACTERIAL METABOLITES: PRECLINICAL EVIDENCE

There is evidence that the effects of dysbiosis on the development of liver disease and HCC are mediated by bacterial metabolites[81-84], possibly in a disease-specific manner[85]. Most tumors have an aberrantly activated lipid metabolism that enables them to synthesize, elongate, and desaturate fatty acids to support proliferation[86]. However, only particular subsets of cancer cells are sensitive to approaches that target fatty acid metabolism and, in particular, fatty acid desaturation. This suggests that many cancer cells contain an unexplored plasticity in their fatty acid metabolism[87]. In a recent study it was shown, that some cancer cells can exploit an alternative fatty acid desaturation pathway. In murine hepatocellular carcinomas and in primary human liver carcinomas, palmitate was found to desaturate to the unusual fatty acid sapienate, hence, to support mem-

brane biosynthesis during proliferation. Accordingly, sapienate biosynthesis enables cancer cells to bypass the known fatty acid desaturation pathway that depends on stearoyl-CoA desaturase[88]. In a mouse model for NAFLD, HCC development was triggered by treatment with the combination of 1,3-dimethylbutylamin (DMBA) and ferredoxin (FD). A strong increase in Gram-positive bacterial strains, in particular specific Clostridium clusters, was also observed[18]. Simultaneously, this treatment led to increased serum levels of deoxycholic acid (DCA), a secondary bile acid whose production depends on dihydroxylation of primary bile acids by the bacterial microbiota, notably *Clostridium* clusters. The key role of DCA in hepatocarcinogenesis was further demonstrated in experiments that showed increased HCC development in mice after supplementing diets with DCA[18].

HCC AND BACTERIAL METABOLITES: HUMAN EVIDENCE

There are some human metabolomics studies, suggesting that integrating metabolomics in HCC diagnostic work up can increase the predictive value in the diagnosis of HCC. In a recent study 11 serum metabolites and three clinical factors showed a better prediction of HCC than alpha-1 fetoprotein, a serum marker for HCC, alone[89]. These results could be confirmed by others in a bigger cohort study of patients, where metabolites showed a higher sensitivity than alpha-1-fetoprotein in differentiating HCC patients from patients suffering from cirrhosis[90]. Additionally, some more studies investigated biomarkers highly sensitive for HCC[91-93]. Urine and serum analyses were performed in a rather small group of patients suffering from HCC compared to healthy controls. In the urine samples the significantly affected pathways were bile acid biosynthesis, citric acid cycle, tryptophan metabolism, and urea cycle pathway, whereas in the sera of HCC positive patients, acetylcarnitine seemed to be a diagnostic biomarker for HCC patients. The link between dysbiosis, alterations of the intestinal barrier, and bacterial metabolites that lead to increased risk of HCC is not investigated in full yet and further studies are eagerly awaited.

CONCLUSIONS

The intestinal microbiota is strongly associated with chronic liver disease, by supporting a hepatic milieu that favors the progression of liver inflammation and development of HCC. There exist diverse mechanisms how the gut microbiota influences HCC development (Figure 1). Dysbiosis leads to an impaired intestinal barrier, both mechanisms driving TLR-mediated chronic liver inflammation. Furthermore, dysbiosis promotes altered bacterial metabolites, including pro-carcinogenic metabolites. Currently it remains unclear whether altered bacterial metabolites or chronic inflammation associated with the translocation of MAMPs from the impaired intestinal barrier are key players in hepatocarcinogenesis. It is most likely that these mechanisms

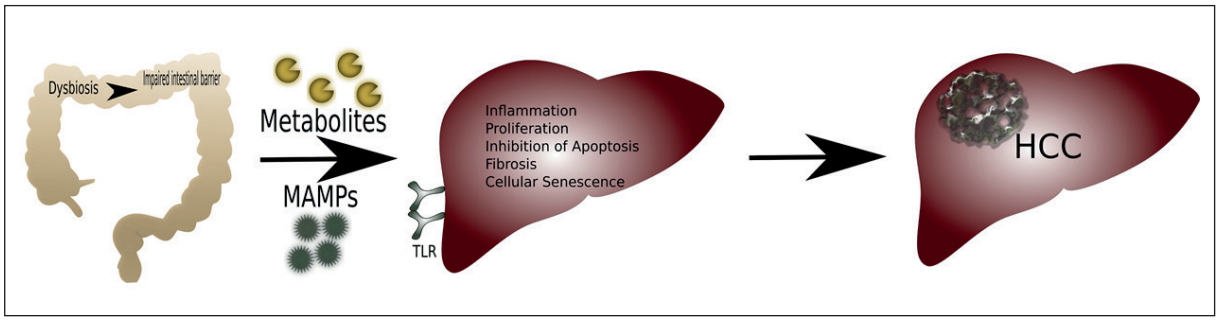

Figure 1. Contribution of the gut microbiota to hepatocarcinogenesis. Progression of liver disease and development of HCC is modulated by dysbiosis and impaired intestinal barrier *via* multiple different mechanisms. The dysbiotic microbiota promotes cellular senescence and cancer-promoting metabolites boost hepatic inflammation, fibrosis, and inhibition of apoptosis. An increased hepatic exposure to gut-derived microbe-associated molecular patterns (MAMPS) promotes *via* TLR (Toll-like receptor) hepatic inflammation, fibrosis, and inhibition of apoptosis as well.

work synergistically in the development of HCC. There is increasing evidence that HCC might be associated with a certain gut microbiome signature. There is still a lack of knowledge on how the gut microbiota and its alterations affect development of chronic liver disease and finally HCC. The knowledge and understanding of the dysbiosis-chronic liver inflammation HCC axis is currently mainly based on preclinical models and assessment of fecal samples from patients suffering from liver diseases. Thus, many tailored human microbiome studies are urgently needed in well-designed trials to further strengthen a potential role for certain commensals in the pathophysiology of HCC. Such studies could form the basis for new intervention studies targeting this highly lethal human disease.

Conflict of Interest

The authors declare that they have no conflict of interest.

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