Journal Scan

A small-molecule inhibitor of hepatitis C virus infectivity

One of the most challenging goals of hepatitis C virus (HCV) research is to develop well-tolerated regimens with high cure rates across a variety of patient populations. Such a regimen will likely require a combination of at least two distinct direct-acting antivirals (DAAs). Combining two or more DAAs with different resistance profiles increases the number of mutations required for viral breakthrough. Currently, most DAAs inhibit HCV replication. We recently reported that the combination of two distinct classes of HCV inhibitors, entry inhibitors and replication inhibitors, prolonged reductions in extracellular HCV in persistently infected cells. We therefore sought to identify new inhibitors targeting aspects of the HCV replication cycle other than RNA replication. We report here the discovery of the first small-molecule HCV infectivity inhibitor, GS-563253, also called HCV infectivity inhibitor 1 (HCV II-1). HCV II-1 is a substituted tetrahydroquinoline that selectively inhibits genotype 1 and 2 HCVs with low-nanomolar 50% effective concentrations. It was identified through a high-throughput screen and subsequent chemical optimization. HCV II-1 only permits the production and release of noninfectious HCV particles from cells. Moreover, infectious HCV is rapidly inactivated in its presence. HCV II-1 resistance mutations map to HCV E2. In addition, HCV-II prevents HCV endosomal fusion, suggesting that it either locks the viral envelope in its prefusion state or promotes a viral envelope conformation change incapable of fusion. Importantly, the discovery of HCV II-1 opens up a new class of HCV inhibitors that prolong viral suppression by HCV replication inhibitors in persistently infected cell cultures.

Comment

HCV can lead to chronic liver disease causing cirrhosis, hepatocellular carcinoma and end-stage liver disease among 5-20 per cent of infected persons. The standard of care for HCV patients over the past decade has been treatment with pegylated interferon combined with ribavirin. Recent addition of HCV NS3-4A protease inhibitors, teleprevir and boceprevir to this regime have improved the sustained virologic response. However, poor tolerability to treatments containing pegylated interferon has been a major issue. The authors have discovered this entry inhibitor molecule, HCV II-1 which is predicted to reduce viral load in a monophasic manner reflecting the slow death rate of infected hepatocytes (t1/2 = 2 to 70 days) and the protection of naive, uninfected cells from HCV infection in contrast to replication inhibitors which are predicted to reduce viral load in a biphasic manner. Combination of HCVII-1 with HCV replication inhibitors led to a prolonged reduction in extracellular HCV levels and HCV-infected cells over a 3-week time course can be more beneficial compared to HCVII-1 monotherapy. The findings of this study suggest that an infectivity inhibitor could be a useful component in a treatment regimen also containing a robust replication inhibitor. Also, HCV II-1 or its derivative might be useful both during a liver transplant and after such a transplant to prevent the new liver from being infected.

Bush CO, Pokrovskii MV, Saito R, Morganelli P, Canales E, Clarke MO, Lazerwith SE, Golde J, Reid BG, Babaoglu K, Pagratis N, Zhong W, Delaney WE 4th,Paulson MS, Beran RK. A small-molecule inhibitor of hepatitis C virus infectivity. Antimicrob Agents Chemother. 2014 Jan;58(1):386-96. doi: 10.1128/AAC.02083-13. Epub 2013 Oct 28.

Genomic variation landscape of the human gut microbiome

Whereas large-scale efforts have rapidly advanced the understanding and practical impact of human genomic variation, the practical impact of variation is largely unexplored in the human microbiome.We therefore developed a framework for metagenomic variation analysis and applied it to 252 faecal metagenomes of 207 individuals from Europe and North America.

Online access

http://svimstpt.ap.nic.in/jcsr/apr- jun 14_files/js214.pdf

Using 7.4 billion reads aligned to 101 reference species, we detected 10.3 million single nucleotide polymorphisms (SNPs), 107,991 short insertions/deletions, and 1,051 structural variants. The average ratio of non-synonymous to synonymous polymorphism rates of 0.11 was more variable between gut microbial species than across human hosts. Subjects sampled at varying time intervals exhibited individuality and temporal stability of SNP variation patterns, despite considerable composition changes of their gut microbiota. This indicates that individual-specific strains are not easily replaced and that an individual might have a unique metagenomic genotype, which may be exploitable for personalized diet or drug intake.

Comment

Gut microbiota has been shown to be associated with various diseases including chronic gastrointestinal diseases like Crohn's disease, diabetes, obesity and malnutrition. Alterations in gut microflora as a result of genomic variations can lead to phenotypes with altered metabolism, nutrition and immune response. This can require personalized care or treatment of the host. The findings of the present study support the hypothesis that a healthy individual retains specific strains for extended periods of time and this profile could be unique even in very large cohorts. This could help to screen in-silico for many pathogenic or antibiotics resistance variants in the population. The concept of altering gut flora by microbial intervention in an attempt to improve GI health is the burning topic and this study could pave way for new interventions to remove harmful microbes.

Schloissnig S, Arumugam M, Sunagawa S, Mitreva M, Tap J, Zhu A, Waller A, Mende DR, Kultima JR, Martin J, Kota K, Sunyaev SR, Weinstock GM, Bork P. Genomic variation landscape of the human gut microbiome. Nature. 2013 Jan 3;493(7430):45-50. doi: 10.1038/nature11711. Epub 2012 Dec 5.

The animal food supplement sepiolite promotes a direct horizontal transfer of antibiotic resistance plasmids between bacterial species

Animal fodder is routinely complemented with antibiotics together with other food supplements to improve growth. For instance, sepiolite is currently used as a dietary coadjuvant in animal feed, as it increases animal growth parameters and improves meat and derived final product quality. This type of food additive has so far been considered innocuous for the development and spread of antibiotic resistance. In this study, we demonstrate that sepiolite promotes the direct horizontal transfer of antibiotic resistance plasmids between bacterial species. The conditions needed for plasmid transfer (sepiolite and friction forces) occur in the digestive tracts of farm animals, which routinely receive sepiolite as a food additive. Furthermore, this effect may be aggravated by the use of antibiotics supplied as growth promoters.

Comment

Massive amounts of antimicrobials are used as growth promoters along with food additives in livestock fodder. Sepiolite, a food additive was authorized by the European Union in 1990 and registered as a technological additive for animal feed (E-562), which is widely as a food additive to broiler chickens and pigs, among other types of livestock since it increases animal growth and improves quality of meat and other products. The results of the present study show that sepiolite may induce the transfer of resistance determinants through a direct genetic material exchange among different strains and species in the digestive tracts of farm animals. This should raise the alarm bells since use of antibiotics and food additives if not regulated may further aggravate the problem of antibiotic resistance. This study should encourage scientific community working on antibiotic resistance to start studying this phenomenon *in vivo*, undertaking the appropriate experiments in livestock.

Rodríguez-Beltrán J, Rodríguez-Rojas A, Yubero E, Blázquez J. The animal food supplement sepiolite promotes a direct horizontal transfer of antibiotic resistance plasmids between bacterial species. Antimicrob Agents Chemother. 2013 Jun;57(6):2651-3. doi: 10.1128/AAC.02363-12. Epub 2013 Mar 25.

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