FOUND IN TRANSLATION

Escape from planned obsolescence: Hepatitis C, the cirrhotic liver, and clonal expansions

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Eliminating the burden of disease caused by hepatitis C virus infection is proving difficult, despite the availability of curative drug treatments. Progress will require innovations in healthcare delivery and a deeper understanding of how the liver and other vital organs survive damage caused by chronic injury.

Hepatitis C virus (HCV): Test, treat, and find a way to manage the damage left behind

HCV remains a public health threat even though direct acting antiviral (DAA) drugs can cure the infection in almost everyone. According to 2016 data, HCV caused about four deaths per 100,000 people in the US—roughly fourfold more than nonalcoholic fatty liver disease (Kim et al., 2019). HCV is often dismissed as a “solved problem”; however, newly diagnosed cases of HCV are spreading across widening sectors of the populace, and the US Preventive Services Task Force is considering a new advisory that would recommend HCV screening for everyone 18–79 yr of age. HCV cure prevents transmission and has nearly immediate benefits for the liver, reducing stiffness and decreasing serum levels of liver enzymes, a sign that liver injury has lessened. Treatment also reduces all-cause mortality and improves quality of life. Among patients with advanced disease, however, a cure cannot entirely erase the damage or remove the risk of liver decompensation or liver cancer, providing a strong impetus for early diagnosis and treatment.

Many health organizations have made HCV elimination a priority, but too often the “test and treat” paradigm gets stalled after the first step. In a study from a New York City Emergency Department, 80% of the people testing positive for HCV RNA (the definitive biomarker of infection) already had a positive HCV RNA test in their medical record (Torian et al., 2018). Importantly, ~70% of the HCV RNA–positive patients were born between 1945 and 1965 and thus are part of the baby boomer cohort (Torian et al., 2018). Most of them acquired HCV in the 1980s and 90s. During that time, there were ~300,000 new HCV infections every year—about sevenfold more than there are now. The livers of chronically infected baby boomers have suffered from decades of immune-mediated damage. New interventions are needed to mitigate the consequences. In 2016, ~70% of HCV-related deaths were due to cirrhosis (end stage liver disease/liver failure), with most of the remainder caused by hepatocellular carcinoma (HCC). Relatively little is known about gene expression or histology in the post-cure liver, which is a barrier to developing targeted therapies to stimulate repair. A paired-biopsy study performed during the era of interferon-based treatment showed portal inflammation in the majority of cases and no reduction in smooth muscle actin, a marker of myofibroblast activation, at a median follow up of five years (D’Ambrosio et al., 2012). The causes of the persistent abnormalities are unknown, although a recent study implicated epigenetic changes (Perez et al., 2019). An increase in National Institutes of Health-funded HCV research, which is disproportionately low (see Table 3 of Saab et al., 2018), could save lives by jump-starting efforts to find interventions for the millions of patients with post-cure HCV-related liver damage.

HCV is the leading underlying cause of HCC-related death in the US (Kim et al., 2019). Several studies have examined the impact of HCV cure on HCC risk and investigated whether the risk decreases over time. The results are inconsistent. HCC incidence is challenging to measure accurately because small HCCs are difficult to detect and patients often forego screening at regular intervals. Ultrasound, the recommended imaging modality, has low sensitivity for HCCs ≤ 2.5 cm. A change to a more sensitive method, e.g., magnetic resonance imaging, and/or a change to more frequent imaging, which may occur when patients are being worked-up for HCV treatment, could increase HCC detection rates, artificially raising the incidence. Conversely, if patients are screened just before starting DAs and those with suspicious lesions are excluded from follow-up analysis, the post-cure HCC incidence will be artificially lowered, causing an apparent treatment-related decrease that did not actually occur. As it stands, some HCC experts report that DAs increase HCC risk in the short term, because they “prime” tumor growth (Mariño et al., 2019), others report “a considerable reduction in the risk of HCC” (Kanwal et al., 2017), and others report no short-term impact (Mettke et al., 2018). A recent investigation showed that...
the incidence of HCC remained constant for ten years after interferon-based treatment, but decreased between the first and fourth years after DAA treatment (Ioannou et al., 2019). Future studies are needed to determine the precise impact of DAAs on HCC risk, but the bottom line is already clear: Patients who have significant liver damage remain at risk for HCC for many years (perhaps indefinitely) after they are cured, and those with an estimated annual risk of HCC exceeding $\sim 1.0\%$ will benefit from long-term twice-annual liver imaging to increase the chances of early detection and curative liver cancer therapy.

The path to planned obsolescence: Cell turnover, somatic mutation, telomere shortening, and cellular senescence

Because most people who die of liver disease have cirrhosis, it is essential to understand how this type of organ damage develops. Pathogenesis appears to involve hepatocyte injury, cell turnover, somatic mutation, and telomere shortening in most cases. Telomeres are hexameric DNA repeats that protect the ends of linear chromosomes. They shorten with each division cycle in most somatic cells in humans because the telomere repair machinery is inactivated. When telomeres shorten below a critical length, replication is blocked, and cells become primed for apoptosis and/or senescence. Importantly, germline mutations in the telomerase pathway increase the risk of cirrhosis, presumably because they reduce the length of telomeres in adult hepatocytes and thereby limit the number of daughter cells each hepatocyte can produce. Highlighting the importance of telomere shortening in liver pathogenesis, a recent study showed that one-fifth of patients with advanced cirrhosis who were awaiting liver transplantation had telomere-related germline mutations (Chiu et al., 2019). Murine models could provide mechanistic insights into the link between telomere shortening and cirrhosis, but the current model is prohibitively expensive and cumbersome. It requires telomerase-deficient mice to be passed through three to six generations to create progeny with short telomeres and increased susceptibility to cirrhosis (Rudolph et al., 2000). A short-telomere strain, i.e., a parental line with telomeres the length of those in adult human cells (which are far shorter than those of wild-type murine cells), would be useful.

A surprising escape: Everything old is new again

Because telomere shortening leads to cell cycle arrest, this process, which likely protects against carcinogenesis, would seem to carry a significant risk of precipitating liver failure as patients and their hepatocytes age. Stunning new data reveal that the functional life span of vital organs may be increased through a phenomenal process: the liver and other organs may remain viable by expanding selected clonal populations of somatically mutated cells (Martincorena et al., 2018; Ikeda et al., 2014; Zhu et al., 2019; Brunner et al., 2019). As illustrated in the figure, DNA analysis of histologically normal esophagus revealed that mutated cells comprise nearly all of the tissue in donors $>55$ yr of age (Martincorena et al., 2018). Expansion of somatically mutated cells appears to be a consistent feature of aging tissues and may be an essential component of tissue maintenance. Mutations in cancer driver genes, including TP53, were common. These findings shine a new and more favorable light on mutations in cancer driver genes and suggest that they may confer a survival advantage to patients with aged and damaged organs. Who knew?

Clonal populations also arise in the liver (Ikeda et al., 2014; Zhu et al., 2019; Brunner et al., 2019). The leptin receptor is the most frequently mutated gene in HCV-infected cirrhotic liver (Ikeda et al., 2014). Leptin receptor mutations could plausibly help hepatocytes compensate for the changes in lipid metabolism and insulin sensitivity caused by HCV infection. Similar to the esophagus, several of the most frequently
mutated genes in the liver are commonly mutated in liver cancer, including APOB, ALB, ARIDIA, TP53, and ARID2 (Zhu et al., 2019); however, the clonally expanded cells rarely harbor TERT promoter mutations (Brunner et al., 2019), distinguishing them from HCCs. Increasing numbers of somatically mutated clones are associated with higher levels of fibrosis, inflammation, and damage (Zhu et al., 2019). Importantly, the somatic mutations increased clonal fitness and promoted regeneration when tested in murine models of liver injury (Zhu et al., 2019). Going forward, it will be critical to learn how cells in the clonal populations originate and expand. Do they have short telomeres and mutations that override the shortened-telomere block to replication, or do they have long telomeres?

From the therapeutic perspective, it will be important to determine whether different types of stress select for different somatic mutations. If so, these mutations might provide a blueprint for targeted drug discovery: mutations in the liver of patients with nonalcoholic fatty liver disease could identify the pathways hepatocytes use to protect themselves from toxic fatty acids and adipokines, guiding the search for drugs to combat fatty liver disease. Even if the somatic mutations are not specific to particular types of injury/stress, they are well-worth studying because they may identify genes that enable hepatocytes to survive in the cirrhotic liver and forestall liver failure.

**All’s well that ends well**

President Nixon’s War on Cancer galvanized public support and led to the National Cancer Act. This act included a special bypass to the traditional budget approval process and empowered the National Cancer Institute (NCI) Director to directly submit the NCI budget to the President and Congress. It pulled all cancers under one umbrella and helped NCI support the research that has led to life-saving breakthroughs in cancer therapy. Similar to cancer, end organ diseases (cirrhosis, emphysema, renal failure, heart failure, osteoporosis, vision and hearing loss, and neurocognitive disorders) have pathogenic pathways in common with each other, and collectively they have devastating effects, which are increasing as the population ages. A concerted effort is needed to first understand how the somatic mutation/clonal expansion process works and then to reengineer it for organ renewal. End organ disease research would benefit from having a scientific and administrative home modeled after the NCI.

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