Currently, use is associated with a small

Technology, Development

Currently, treatment of chronic Hepatitis B Virus (HBV) infection includes using either interferon type I (IFN?) therapy or the administration of nucleoside/nucleotide analogs to inhibit virus replication (Include a citation).

While these treatments can improve HBV disease outcomes, they also have significant side effects or treatment limitations. For example, while Lamivudine has negligible side effects, it is associated with high rates of drug resistance (Include citation Given). Alternatively, adefovir dipivoxil has a low rate of drug resistance but long-term use is associated with a small risk of nephrotoxicity (Include citation Given). Further, high doses of IFN? treatment can induce neuropsychiatric adverse effects, including an acute confusional state.

As such immune modulatory therapies which present with minimal adverse effects have received increasing interest recently in the treatment of chronic HBV infection (Cite the paper you presented here). T cells play the center roles in control viral infection. With these limitations, alternative immune approaches have been advanced for the treatment of chronic HBV infection. Several studies have reported the severely depression of antiviral response, especially dysfunction of virus-specific CD8+ T effector cells in chronic HBV patients. Thus, restoring functional of effector T cells is a promising approach in clinical. Fisicaro et al characterized the distinct transcriptomic profile of HBV-specific CD8 T cells in the context of chronic HBV infection.

The study showed that in chronic patients CD8+ T cell lost their functions due to the mitochondria’s gene downregulation compared to resolved patients. Treatment of mitochondria in exhausted T cells with antioxidants

MitoQ or MitoTempo is very effective to retain multi-functions of mitochondria as well as effector T cells. This research provided the potential use of those compounds as drugs in functional restoration of HBV-specific CD8 T cells in chronic HBV infection (5). Chronic hepatitis C virus infection (HCV) is a noteworthy general medical issue, influencing up to 177. 5 million individuals all over the world (17). There is a small proportion of people can spontaneously resolve the infection, the others develop chronic disease in the liver, and leads to the development of cirrhosis and hepatocellular carcinoma at late stage (HCC) (8).

The progression to HCC is a serious problem for chronic patients because of asymptomatic during the course of infection. It is noticeable only the pathological processes become relatively advanced. Several studies have been published regarding the functional impairment of HCV-specific CD8 T cells in chronic HCV infection (19, 20, 23, 26), and different mechanisms have been proposed to interpret this defective function included insufficient generation of memory T cell and continuous exposure to antigen (10, 19, 24, 25), virus mutated to create poorly immunogenic antigen to escape from T cell surveillance (4, 21, 22). In addition, the increase expression of co-inhibitory molecules such as PD-1 on HCV-specific CD8 T cell and intrahepatic cells has been published in chronically patients, may contribute to virus-specific CD8 T cells apoptosis and dysfunction (11, 18).

The mechanisms responsible for CD8+ T cell failure to control virus infection are not completely understood. Better understanding the functional defects and mechanisms behind the defective is important to develop therapeutic

strategies for restoration of exhausted T cells. It is necessary to find additional molecular targets to enhance functional restoration effect in chronic patients. There is no report characterizing transcriptional gene expression profile of HCV-specific T cells in chronic patients so far.

Because of the essential functions in clearance of viral infection, many research groups approached to recover exhausted T cell in chronic patients. First, PD-1 and other inhibitory molecules were chosen as blockage targets in vitro (3, 13). These studies showed to increase functional activity of virus-specific T cell in peripheral blood.

However, blockage PD-1 alone is inefficient to restore T cell function in intrahepatic cells isolated from liver biopsies (14). Subsequently, they demonstrated to retain HCV-specific T cell function in chronic liver's patients required combination blockage of several inhibitory molecules (9, 13). Nakamoto et al (2009) reported that in PD-1+ T cells increase expression of the inhibitory receptor cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) from the liver of chronic HCV patients and in blood of cute infection. Combination blockade of PD-1/CTLA-4 in vitro leads to the restoration of HCV-specific CD8 T cells (13). Second, in vivo experiments were conducted in chimpanzees (6) and humans (7) with chronic HCV using anti-PD-1 antibodies to block PD-1 signaling. In the chimpanzee experiments, they observed a significant increase in HCV-specific CD8 T cell responses but reduction in the copy numbers of HCV in blood was achieved only one of three animals (6). In the patient's study, 11% of patients showed a greater than 0.

5log10IU/ml reduction in the number of HCV RNA after single dose PD-1 blocking antibody administration. Increasing antibody dose to 10mg/kg they obtained a more than 4log10IU/ml reduction in HCV RNA titer in 15% of patients. The suppression of HCV replication sustained more than 8 weeks post administration in most of the patients (7).

Direct-acting antivirals (DAA) are treatment therapies with the same direction to rescue exhausted CD8 T cell by affecting the function of various HCV proteins related in HCV replication such as NS3/NS4 protease, NS5B polymerase and NS5A (15). Some studies showed DAA combinations result in getting rid of HCV infection (2, 12), but it is unclear whether the treatment could eliminate HCV or restore full HCV-specific cytolytic T function. Interferon and ribavirin (RBV) regimens were chosen as standard chronic HCV treatment for many years.

However, it gave low cure rates and came along with frequent side effects. The available treatment of HCV currently relies on a novel combination of PegIFN-?, viral protease inhibitors and ribavirin, which help to sustain antiviral response rate of up to 70% (1), but side effects and high cost are the major drawbacks in this antiviral therapy. New therapeutic treatment approaches need to be established to help clearance of target viral infection and enhance rescuing multi-functions of dysfunctional CD8 T cells.