Hepatitis C Virus

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Summary (1000 characters including spaces)

Hepatitis C virus (HCV) is an enveloped, RNA virus transmitted through blood to blood contact. It infects humans only and primarily targets liver cells. HCV evades innate and adaptive immunity and establishes chronic infections in 70% of cases. If untreated, 20% of patients develop liver cirrhosis and a fraction of these progress to hepatocellular carcinoma. Annually 400,000 patients die due to HCV infection. Direct acting antivirals (DAAs) are licensed and target three viral proteins: The NS3-4A protease needed for processing of the viral polyprotein, the NS5A phosphoprotein that regulates RNA replication and virus assembly, and the viral RNA dependent RNA polymerase (NS5B) that catalyzes genome replication. Combination therapies cure more than 95% of treated patients. Approximately 71 million people are chronically infected and 1.7 million new infections occur annually.

Treatment induced cure does not protect from viral re-infection. A prophylactic vaccine is under development.

Key Facts: (together up to 1450 character including spaces)

The HCV genome is 9.6 kb and encodes a single polyprotein, which is cleaved by cellular and viral enzymes into ten mature proteins.

The three structural proteins comprise the viral particle while the nonstructural proteins are involved in viral replication.

Viral strains differ by up to 30% at the nucleotide level and are classified into 7 genotypes.

The viral NS3-4A protease targets innate immune signaling molecules, facilitating immune evasion.

Incorporation of host lipoproteins into virions contributes to antibody escape and facilitates binding to liver cells.

HCV evolves as a quasispecies within infected patients.

Disease Facts:

HCV is parenterally transmitted. Unsafe use of needles and high risk sexual behavior are risk factors for transmission. Screening of blood products has reduced transmission rates.

Chronic infection causes fibrosis, cirrhosis and hepatocellular carcinoma. Two thirds of patients develop extra-hepatic manifestations like cryoglobulinemia vasculitis.

Virus replication dysregulates metabolic processes facilitating liver steatosis and inflammation.

Combination DAA therapies achieve cure rates greater than 95%.

In patients failing therapy, viruses develop drug resistance. However salvage therapies with modified drug combinations currently cure most patients upon re-treatment.

Viral re-infection is possible and occurs frequently in populations at high risk of HCV exposure.

Taxonomy and Classification:

Genome: Single-stranded positive sense RNA

Family: *Flaviviridae*

Genus: *Hepacivirus*

Genotypes: Seven

Literature

[1-10]

- [1] Bartenschlager R, Baumert TF, Bukh J, Houghton M, Lemon SM, Lindenbach BD, et al. Critical challenges and emerging opportunities in hepatitis C virus research in an era of potent antiviral therapy: Considerations for scientists and funding agencies. *Virus Res* 2018;248:53-62.
- [2] Walker CM. Designing an HCV vaccine: a unique convergence of prevention and therapy? *Curr Opin Virol* 2017;23:113-119.
- [3] Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. *Gastroenterology* 2015;149:1345-1360.
- [4] Pawlotsky JM, Feld JJ, Zeuzem S, Hoofnagle JH. From non-A, non-B hepatitis to hepatitis C virus cure. *J Hepatol* 2015;62:S87-99.
- [5] Rehermann B. Pathogenesis of chronic viral hepatitis: differential roles of T cells and NK cells. *Nature medicine* 2013;19:859-868.
- [6] Bartenschlager R, Lohmann V, Penin F. The molecular and structural basis of advanced antiviral therapy for hepatitis C virus infection. *Nat Rev Microbiol* 2013;11:482-496.
- [7] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. *Hepatology* 2014;59:318-327.
- [8] WHO. Global hepatitis report, 2017. 2017.
- [9] WHO. Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection 2018.
- [10] Mitchell JK, Lemon SM, McGivern DR. How do persistent infections with hepatitis C virus cause liver cancer? *Curr Opin Virol* 2015;14:101-108.