DEVELOPMENT OF NEW TREATMENTS AGAINST HEPATITIS C

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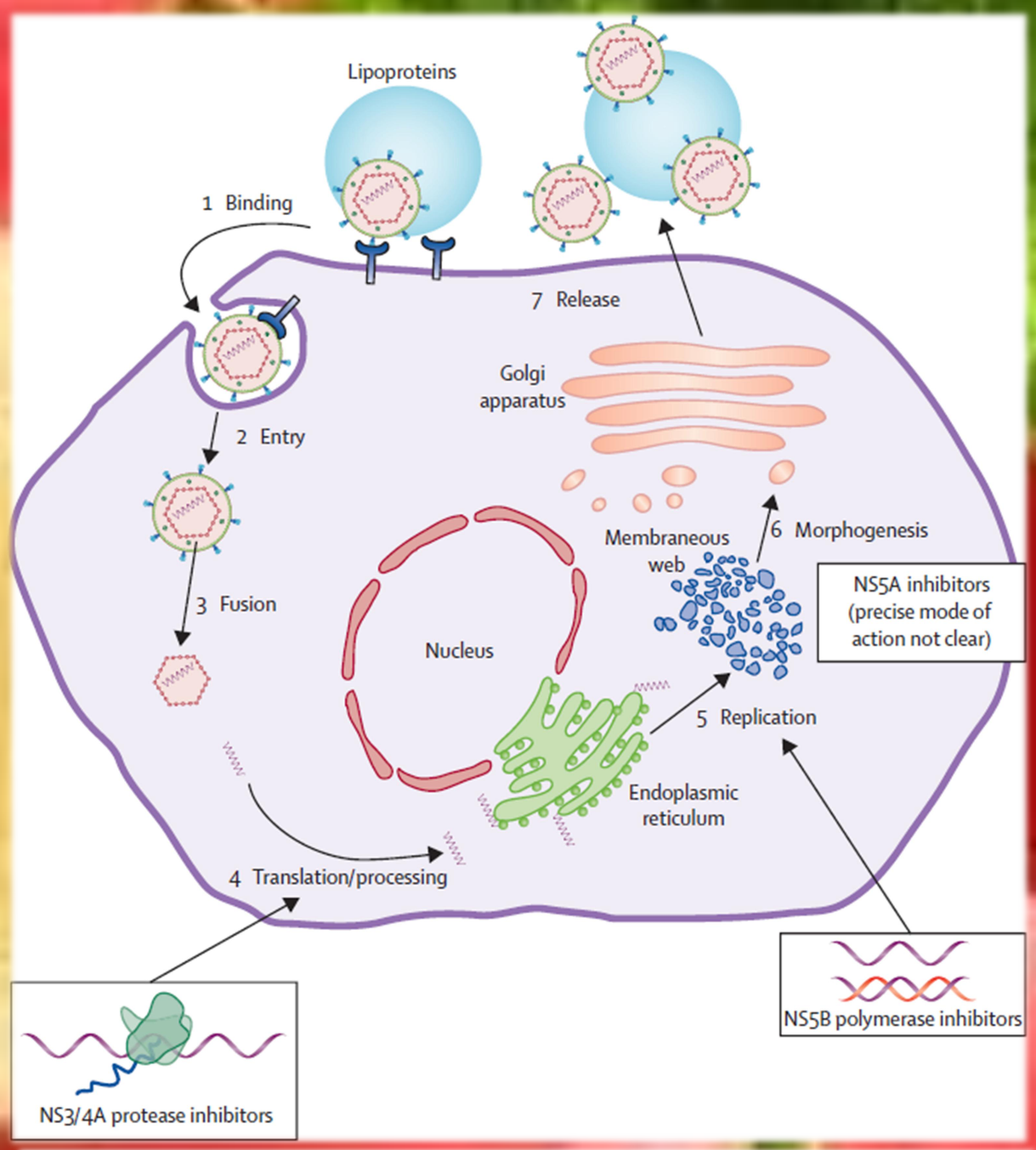
Introduction

Hepatitis C is an infectious disease, that affects the liver, caused by the hepatitis C virus (HCV). The infection is often asymptomatic.

There are an estimated 170 million people worldwide infected with hepatitis C (corresponding 3% of world population), and more than 350 000 people die every year due to hepatitis C-related liver diseases.

The transmission of HCV can occur by different ways:

- By intravenous drug use (IDU) : one of the most important risk factors for hepatitis C transmission.
- By methods for blood transfusions or unsafe medical procedures : reusing needles and syringes, poorly sterilized surgical equipment, etc.
- By being tattooed (with contaminated material), or by sharing personal hygiene items (such toothbrush), or by sexual and vertical transmission (if there are bloody injuries).



Life cycle of the hepatitis C virus and mode of action of the three main classes of directly acting antivirals in phase 3 trials. NS5B polymerase inhibitors seem to be the most promising.

Conclusions

- New drugs have a major efficiency on difficult genotypes to treat.
- If we combine peginterferon and ribavirin treatment with new drugs, there will be interferon side effects too.

References

- Manns, M.P; Cornberg, M. **Sofosbuvir: the final nail in the coffin for hepatitis C?** *The Lancet Infectious Diseases*, Vol 13:5 (378-379), 2013.
- Yang, P.L; Gao, M; Lin, K; Liu, Q; Villareal, V.A. **Anti-HCV drugs in the pipeline**. *Current Opinion in Virology*, Vol 1 (607-616), 2011.

Hepatitis C virus (HCV)

It is a small, enveloped, positive single-stranded RNA virus.

When the virus replicated, the positive-stranded RNA virus generated a polyprotein, from an open reading frame (ORF), and then is processed by proteases to 10 active proteins.

It has been described 7 genotypes of HCV, due to a great antigenic variability and a different geographical zone distribution. Also, it has been found that there are different subtypes of each genotype.

Genotypes 1a-b, 2a-b, 3a, 4a, and 6a are the most frequently identified.

Old treatments

Interferon α

It was the first and only drug available to treat chronic hepatitis C.

The results were poor, only 15-20% of patients were cured (no virus RNA presence). The great majority did not respond to treatment.

Pegylated interferon and ribavirin

Pegylated interferon is a new molecule obtained from the union between polyethyleneglycol and recombinant interferon α. Its functions are to delay elimination, prolong its activity and improve efficiency. The biggest problem were the side effects (stomach pain, vomiting, weight loss, baldness, immune reactions, difficulty to sleep and concentrate, etc).

Ribavirin is an antiviral drug (it is a nucleoside analogue). Its functions are prevent the virus to spread throughout the body and improve the capacity of pegylated interferon (also named peginterferon). It presented side effects too (anemia, skin rashes, miscarriages in women, etc).

The rate of response to treatment had improved significantly compared with the other treatment, but there were differences between genotypes (genotype 1 did not make a good response).

New treatments – Directly Acting Antivirals

These antivirals act directly on the virus. They act on NS3/4A protease, NS5B polymerase and NS5A protein, promoting an inhibition.

- Boceprevir and telaprevir are two drugs that inhibit NS3/4A protease. They work on a combinatorial treatment with peginteron and ribavirin.
- Protein NS5A specific function is not know yet, but there are some drugs that are being studied in clinical trials, as daclatasvir.
- Polymerase NS5B is highly conserved among different viral genotypes, so their inhibitors seem to be the most promising. There are two types, nucleoside inhibitors and non-nucleoside inhibitors. One of these drugs, still in a clinical trial, is sofosbuvir.

New treatments – Host-targeting Antivirals

They are antivirals that interfere with host factors to facilitate viral replication.

Cyclophilin (CypS) are peptidyl-propyl cis-trans isomerases (PPlases), and its function is to catalyze the transformation of the position of peptide bonds. They are necessary for the HCV replication. Some CyPs interact with NS5A (or NS5B). It is needed drugs as inhibitors that cause the viral protein do not fold well and are not transported to the replication complexes. One of these drugs is alisporivir (in a clinical trial).