Reviewer #1: This topic is interesting. As it is stated in the paper that in-depth known structure mapping of the 3'X-region will give us a better understanding of the virus and lead to additional means to control it. Whereas, it is now the direct anti-virus drugs are effective for us in controlling the virus and eventually clear it. I wonder whether it is indispensable to exploit new drugs based on this region of HCV.

First of all, we would like to thank the reviewer for a positive recommendation. Recently, a big progress in hepatitis C treatment has been made and new, efficient drugs have been established. However, HCV as an RNA virus, which undergoes dynamic changes in its genome in every replication cycle and could easily escape any drug provided separately in quite a short time. The most conserved region, the 3'X region, is the best target in antiviral research to prevent viral escape into mutations. We think that research against RNA viruses should never stop in order to have ready solutions in case the virus gains resistance to currently used treatment.

Reviewer #2: Manuscript No: 39588 Title: Form confers function: The case of the 3'X region of the hepatitis C virus genome Manuscript Type: Review Dr. Dutkiewicz M et al. This is an interesting and informative review. Minor; In lines 4-8, page 8, 'In fact, genotype 1 (1a and 1b) is more virulent and resistant to medical treatment than others, including genotype 2a. This indicates how virus virulence and drug response is significantly influenced by the long-range kissing interactions, which likely cause changes in the base-pairing character of the very 3' terminal nucleotides.' should be revised. First of all, there was no reference in the sentences. According to clinical reports, genotype 1 was resistant to interferon-based therapy. However, in interferon-free therapy, genotype 3 is more resistant than genotype 1. In addition, what meant virulence? Authors should add the referred reports about virulence.

We would like to thank the reviewer for a positive recommendation. HCV subtype-1b has been described as most virulent since it is associated with more severe liver disease symptoms and longer time of infection in comparison with other genotypes (Irshad 2013, Carter et al. 2017). We have changed the indicated sentence and have included additional references.

lines: 1-5, page 8 - after changes: 'In fact, subtype 1b is more virulent and resistant to interferon-based therapy than other genotypes, including subtype 2a[29,34]. This suggests how virus virulence and drug response is significantly influenced by the long-range kissing interactions, which likely cause changes in the base-pairing character of the very 3' terminal nucleotides.

*lines 13-15, page 16 - '**Carter LDB, Aronsohn A**. Overcoming injustice: A roadmap to improve access to hepatitis C virus therapy for our medicaid patients. Hepatology 2017; **65**: 1735-1740 [PMID: 28160311 DOI: 10.1002/hep.29095]*
*in reference list: lines 30-32, page 16 - '**Irshad M, Mankotia DS, Irshad K**. An insight into the diagnosis and pathogenesis of hepatitis C virus infection. World J Gastroenterol 2013; **19**: 7896-7909 [PMID: 24307784 DOI: 10.3748/wjg.v19.i44.7896]'*

Reviewer #3: In this study, the author reviews the several different secondary structure models of the 3'X region of HCV have been proposed. It is likely that the 3'X region adopts more than one structural form in infected cells and that a specific equilibrium between the various forms regulates several aspects of the viral life cycle. The author summarizes current knowledge of the structure and function of the 3'X region of hepatitis C genomic RNA, reviews previous opinions, presents new hypotheses and summarizes the questions which need further investigation.

Thank you for a positive recommendation.

Reviewer #4: Authors, in ordr to give feadres a more comprehensive view of the topic, mainly those outside this specific field of research, should further emphasise the extra-hepatic role of HCV, maimnly at immune system localization, with very long-lasting effects, which are extremely difficult to treat, as evident in....Successful and Safe Long-Term Standard Antiviral Therapy in a Patient with "Explosive" Immune Response in Course of HCV-Related Liver Cirrhosis. Int J Mol Sci. 2015 Jun 19;16(6):14075-85.

Thank you for a positive recommendation and valuable comments. We have added information about extra-hepatic role of HCV as well as the indicated reference to the revised manuscript:
lines: 15-17, page 3 - 'Sometimes HCV enters cells of the immune system, leading to very long-lasting effects which are extremely difficult to treat effectively[8].'
*in reference list: lines: 3-6, page 14 - **Conca P, Cafaro G, De Renzo A, Coppola A, Cimino E, Tarantino G**. Successful and Safe Long-Term Standard Antiviral Therapy in a Patient with "Explosive" Immune Response in Course of HCV-Related Liver Cirrhosis. Int J Mol Sci 2015; 16: 14075-14085 [PMID: 26101866 DOI: 10.3390/ijms160614075]*