**CCL5 is upregulated and secreted by HDV independently of the IFN response**

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Liver cancer is the sixth most common cancer and third most common cause of cancer-related deaths worldwide. It is predicted that the number of new cases of liver cancer per year will increase by 55% by 2040. The main causes of liver cancer are hepatitis viruses. Among them, HBV and HCV are considered as oncogenic viruses, but the role of HDV in hepatocarcinogenesis is still unknown. HDV is known to accelerate liver disease progression and increase HCC incidence. Thus, it is crucial to understand how HDV is oncogenic and the mechanisms underlying HDV-induced malignant hepatocellular transformation. In our single-cell RNAseq data, mono-HDV or HBV/HDV co-infected HepaRG cells are clearly separated from non-infected and HBV-infected cells. Pathway analysis in these populations revealed these differences in the strong inflammatory response associated with HDV infection, particularly IFN signaling. Additionally, the alteration of molecular and metabolic is in hepatocytes by HDV is mostly induced by IFN signaling, not by the virus itself, according to our bulk RNA-seq data. But interestingly, the mono-HDV infected sub-cluster showed a strong upregulation of CCL5, which is induced by HDV infection independently of IFN signaling. Furthermore, CCL5 produced in response to HDV infection was detected in the supernatant of HepaRG cells and PHH. These results are of potential relevance in the context of liver disease development, as CCL5 is expressed in a wide variety of myeloid and lymphoid populations within the liver microenvironment, and that increased levels of CCL5 have been implicated in the progression of chronic liver disease towards HCC. We currently showed that conditioned medium from HBV/HDV co-infected hepatocyte induced CCL5 and activated LX-2 cells. We have previously shown that HDV infection, but not S/L Ag expression, induced CCL5, suggesting that RNA sensing mechanisms are involved. Thus, we are exploring the mechanisms in vitro (CRISPR/Cas9), we will validate these data in biopsies and investigate CCL5 cytokine and receptor expression patterns by IHC in resections. Our study reveals a yet unknown upregulation and secretion of chemokine CCL5 induced by HDV mono-infection, and it could, may explain the excessive inflammation phenotype of HDV infected liver and accelerated progression of HDV related fibrosis and HCC.