HCV are its genetic variability and the diverge courses of hepatitis C progression in patients. To assess whether intra-genotypic HCV variations affect the triggering of host innate immunity, we stimulated human primary plasmacytoid dendritic cells (pDC) with crude preparations of different cell culture-derived genotype 2a HCV variants. These experiments revealed that parental JFH1 did not induce IFN-a, whereas the intra-genotypic chimera Jc1 triggered massive IFN-a responses. Furthermore, efficient virus particle formation, but not virus infectivity, determined the magnitude of IFN-α responses. Notably, co-culture of pDC with HCV infected hepatoma cells retrieved the capacity to induce IFN-a, while Jc1 infected cells still triggered stronger responses than JFH1 infected ones. Recently, within the IFN-α locus several single nucleotide polymorphisms (SNP) were detected. One of these, rs12979860, showed high linkage disequilibrium with a SNP that reconstituted IFN-α4 gene function. Analysis of pDC derived from rs12979860 CC/CC (major allele) or TT/TT (minor allele) donors revealed that the genotype did not affect IFN-α responses against Jc1. On the contrary, hepatoma cells infected with Jc1 triggered strong IFN-α responses only in CC pDC, but not in TT ones. These results are striking since TT/TT patients with chronic HCV infection respond less efficiently to IFN-α2 / ribavirin therapy than CC/CC patients.

P116
The Impact of obesity-related hormones on the HCV life-cycle
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Obesity is associated with increased viral load during HCV-infection and non-response to IFN/Ribavirin-based therapy. Fat tissue is known to produce a variety of cytokines and hormones leading to increased levels of pro-inflammatory markers in sera of obese individuals. In this study we assessed the impact of several adipokines on cell-culture derived full-length HCV life cycle.

A few tested hormones showed moderate antiviral activity in vitro (IL-6, TNF-α). However, a promising effect was observed for the adipokine Chemerin.

Chemerin is a hormone that is mainly expressed by fat-tissue and the liver. It is elevated in obese compared to lean individuals, with serum levels of ~300 to ~200 ng/mL respectively, and has been recently described for the first time. By binding to its main receptor - the G-protein-coupled Chemokine-like receptor 1 (CMKLR1) -, which is mainly expressed by macrophages, pDCs/mDCs and NK-cells, Chemerin serves as a chemo-attractant. However, little is known about its impact on non-immune cells.

In cell-culture derived full-length HCV screen we observed a dose-dependent antiviral effect of this hormone (IC50 at 1000 ng/mL). We excluded a modulation of HCV-entry and confirmed an inhibition of replication with sub-genomic replicons of two different HCV genotypes (1a, 2a).

Treatment of the target cells with Chemerin prior and post infection with HCV caused a robust inhibition of viral replication. Modulation of CMKLR1 did not alter the inhibition of viral replication by Chemerin in Huh-7.5 cells. Transcriptomic analysis of Chemerin-treated Huh-7.5 cells revealed an upregulation of distinct ISGs and also non-ISGs. A pathway analysis showed no clear correlation to already described antiviral pathways, pointing to an unique mode of action of this hormone. Chemerin was also able to inhibit propagation of Coronavirus in Huh-7.5 cells, although to a lesser extend.

We proofed that Chemerin acts antiviral in primary human hepatocytes and confirm induced expression levels for IFI-6 and ISG-15 in these cells by real-time PCR.

In conclusion we describe for the first time an antiviral activity of Chemerin in hepatoma- as well as primary human hepatocytes. The precise mechanism and signaling pathways of Chemerin are currently further evaluated in more detail.

P117
Hepatitis C Virus mediates NRG1-dependent down-regulation of ErbB3, thereby modifies ErbB receptor family composition at the cell surface
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BACKGROUND: Recently, both EGF receptor and EGF- dependent signalling have been shown to play a role in HCV entry and replication. However, to what extent HCV also may interfere with expression of other ErbB receptor family members is still unknown. In this study we analyzed the influence of HCV on ErbB3 expression and the consequences for surface expression of other ErbB receptors.

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