New Insights into Yellow Fever Liver Pathogenesis Using a Human Liver Organotypic Model

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Introduction

- Yellow Fever (YF) virus in humans is characterized by a strong liver involvement. Excessive production of inflammatory cytokines, in association with viral replication in hepatocytes, is believed to mediate severity of liver damages.
- Post-infection events elicited by wild-type YF Asibi or attenuated YF17D vaccine virus were studied here for the 1st time in human liver microtissues composed of primary human hepatocytes, Kupffer cells and other non-parenchymal cells.
- A transcriptomic approach (HTS) was used to investigate cellular responses elicited after infection by each strain. Differences were observed mainly in regulation of innate immune pathways.

Human Liver Organotypic model (InSphero AG)

YF Asibi and YF17D replicate in HliMt

Liver microtissues were infected by YF-17D at m.o.i. 1 (24 hpi) or by YF-Asibi at m.o.i. 10 (24 hpi). Detection of envelope protein E by confocal microscopy using specific OGG5 (E-YFV) and CD68 (Kupffer cells) monoclonal antibodies.

Data Summary and Conclusion

- Wild-type YF Asibi and attenuated YF17D were found able to productively infect liver microtissues. Both hepatocytes and Kupffer cells were infected.
- The 2 viruses were shown to elicit similar antiviral response but lowest transcription levels were observed after YF Asibi infection.
- Presence of Kupffer cells was shown to modulate cell death pathway.
- Early transcription factors previously associated with induction of neutralizing antibodies in 17D vaccinees (IRF7, STAT1, EIF2AK2), were identified here as part of the major canonical pathway activated by infection, but higher transcription levels were observed after infection by YF17D rather than by Asibi (confirmed by RT-PCR).
- The IFN response was dominated by type III/lambda and beta IFNs (17D>Asibi).
- Involvement. Excessive production of inflammatory cytokines, in association with viral replication in hepatocytes, is believed to mediate severity of liver damages.

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