Uptake and Degradation of Bacteriophages by Liver Sinusoidal Endothelial Cells

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Abstract:

Bacteriophages (briefly, "phages") are viruses which target bacteria, and are non-infectious to eukaryotic cells. It is estimated that more than 30 billion phages cross into the human body from the gut each day[1], and eventually need to be cleared from the blood circulation. The liver plays a central role in pathogen clearance, and liver sinusoidal endothelial cells (LSECs), which form the lining of the numerous capillaries in the liver, are therefore on the front lines for this removal process. However, despite their strategic location and efficiency in removing small (<200 nm) particles[2], LSECs have historically been poorly studied in terms of removal of phages.

We hypothesized that LSECs play a critical role in the removal of phages from the bloodstream through endocytic uptake and lysosomal degradation, and used GFP-labeled T4 bacteriophages as a model system to study this clearance process. Uptake and trafficking of phages in primary cultured LSECs was monitored by deconvolution microscopy on both short (1 hour) and long (24 hours) term timescales, and structured illumination microscopy was used to confirm the identity of the LSECs using their unique, sub-diffraction scale morphological features: tiny holes called fenestrations. After being taken up by the cells, the phages were rapidly transported to late endosomes/lysosomes, as confirmed by colocalization studies with an LSEC-specific lysosomal vital marker. Challenging the LSEC cultures with radiolabeled phages for up to 24 hours showed that the phages were degraded about 4h after being taken up by the cells, with degradation products being increasingly released to the spent medium up to about 18h after uptake. In conclusion, our novel finding that LSECs internalize and degrade bacteriophages lends support to the hypothesis that LSECs play an important role in the clearance of blood borne phages.

References:

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