Nature Reviews Immunology | AOP, published online 12 July 2013; doi:10.1038/nri3500

VIRAL IMMUNITY

Arms convoy

A recent study in *Nature Immunology* sheds further light on the mechanisms by which type I interferons (IFNs) promote antiviral immunity. Li *et al.* report that IFNα induces cells that are resistant to virus infection to release exosomes that are loaded with antiviral molecules — these are taken up by susceptible neighbouring cells, thereby enabling the transmission of viral resistance.

Type I IFNs are released in response to virus infection and promote the expression of a set of genes that help to establish an antiviral state in cells. IFNα is also known to induce the transfer of viral resistance from cells in which a virus cannot replicate to cells that permit viral replication. Li *et al.* hypothesized that such resistant cells might use exosomes — small membrane vesicles that originate in the late endosomal compartment — to transfer antiviral proteins to neighbouring cells. To investigate this, they studied hepatitis B virus (HBV) infection. This virus exclusively infects hepatocytes (the parenchymal cells of the liver) and does not infect the non-parenchymal cells of the liver, such as macrophages, lymphocytes and liver sinusoidal endothelial cells (LSECs). Of further interest, although IFNα is an approved treatment for chronic HBV infection, the direct treatment of HBV-infected hepatocytes with this cytokine does not efficiently inhibit HBV replication.

> “IFNα induces cells that are resistant to virus infection to release exosomes that are loaded with antiviral molecules”

In *in vitro* studies using a transwell system to prevent direct cell contact, the authors found that IFNα only limited HBV replication in cells from a human hepatocyte cell line when these permissive cells were co-cultured with macrophages or LSECs. Further experiments in which signal transducer and activator of transcription 1 (STAT1) expression was knocked down confirmed that IFNα signalling in macrophages and LSECs, but not in hepatocytes themselves, is necessary to suppress HBV replication in hepatocytes. To investigate whether exosomes could be involved in transferring protection, the authors treated macrophages with inhibitors of exosome biogenesis prior to stimulation with IFNα. Notably, this blocked the ability of these cells to transfer viral resistance to heptocytes *in vitro*. Furthermore, blockade of exosome release *in vivo* limited the antiviral effects of IFNα in a mouse model of HBV infection.

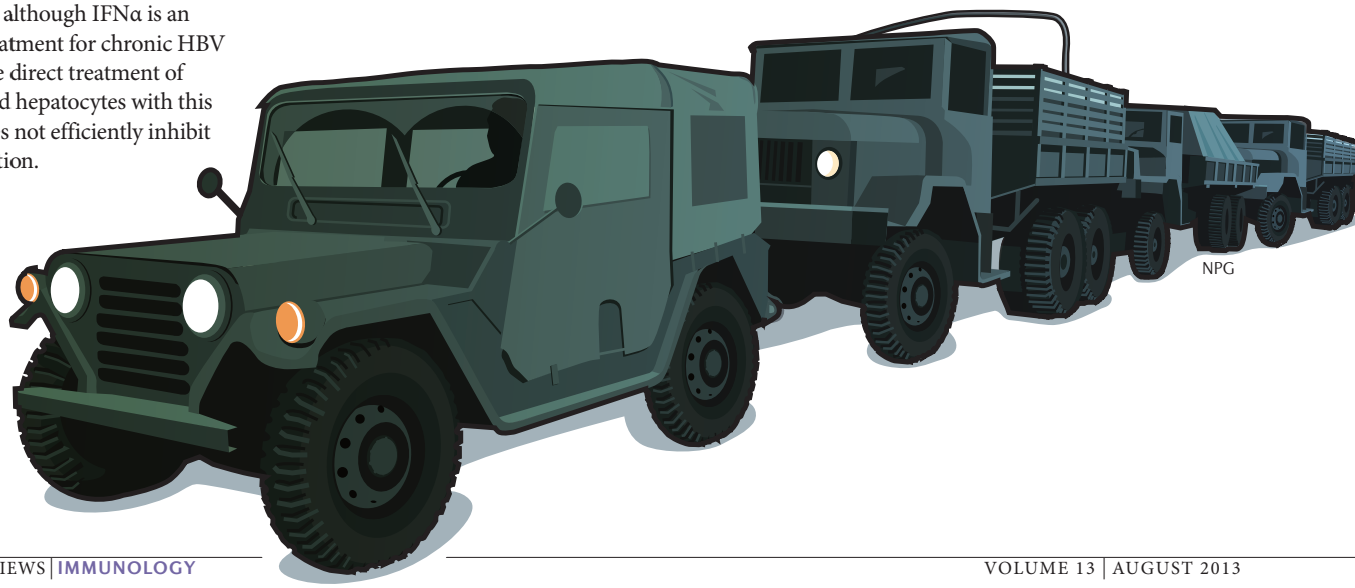
The authors next used immunoblot and microarray analysis to compare the contents of exosomes from IFNα-treated and untreated macrophages. They found that IFNα induced the selective sorting of the antiviral molecule APOBEC3G and a range of mRNAs and microRNAs into exosomes. The knockdown of APOBEC3G expression, the inhibition of mRNA translation or the blockade of microRNA function in exosomes from IFNα-stimulated macrophages markedly impaired their antiviral activity. In addition, the transfection of hepatocytes with vectors containing mRNAs or microRNAs that were selectively enriched in IFNα-induced exosomes suppressed the replication of HBV in these cells.

Finally, the authors addressed whether IFNα-induced exosomes can suppress the replication of viruses other than HBV. Blocking exosome release in mice infected with mouse hepatitis virus A59 led to higher viral titres, and experiments using neutralizing antibodies confirmed that type I IFNs were necessary for exosome-mediated protection in this model. Exosomes also contributed to IFNα-mediated antiviral immunity in a mouse model of lung infection with adenovirus, which indicates that exosomes promote antiviral responses in other tissues as well as in the liver.

IFNα is currently approved for the treatment of chronic hepatitis, but some patients do not effectively respond to this therapy and others experience severe side effects. The authors suggest that the delivery of antiviral mediators via exosomes could therefore be a safer and more effective treatment option during chronic infection with HBV or with other viruses.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Li, J. *et al.* Exosomes mediate the cell-to-cell transmission of IFN-α-induced antiviral activity. *Nature Immunol.* http://dx.doi.org/10.1038/ni.2647 (2013)



NPG

ONLINE ONLY

Subject categories: cytokines, infection, innate immunity

Web summary: IFNα-induced exosomes transfer antiviral mediators to surrounding cells.