

Viruses and interferon – 50 years on



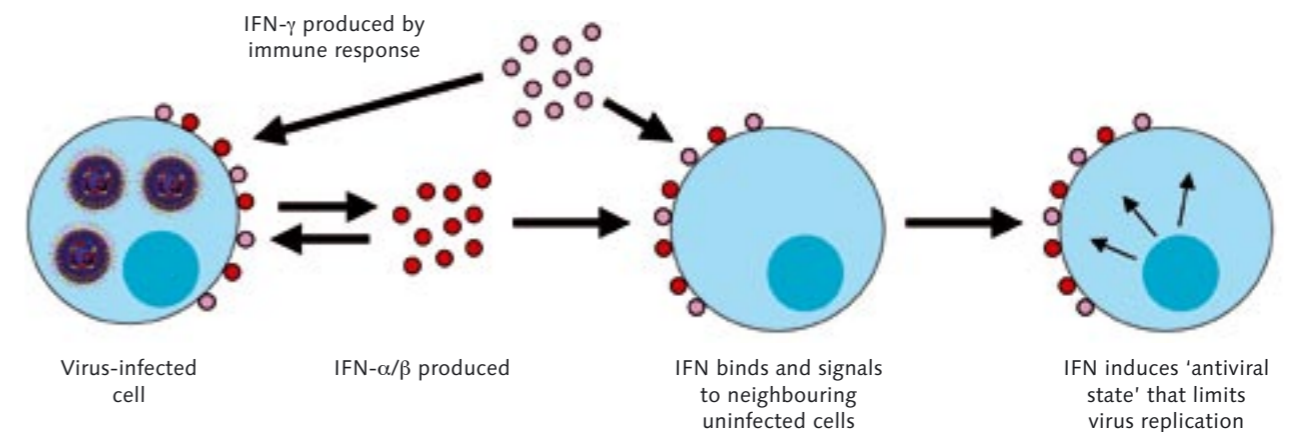
Although prior to 1957 scientists were studying the phenomenon of interference among animal viruses, it was 50 years ago that Isaacs and Lindenmann (working on influenza virus infection of chick chorio-allantoic membranes) first showed that virus-infected cells can release a substance, which they termed 'the interferon' (IFN), that when added to uninfected cells somehow interfered with subsequent virus infection (see Derek Burke's account on pp. 156–159).

Since then an enormous amount has been learnt about IFN and its importance in controlling virus infections. Indeed, when working correctly (which it rarely does due to virus countermeasures—see below), the IFN response is capable of

controlling most virus infections, even in the absence of an adaptive immune response. We now know that IFN works by inducing what is termed an 'antiviral state' in cells and does so by upregulating the expression of a large number of cellular genes (IFN-responsive genes), many of which have direct or indirect antiviral action (Fig. 1).

Examples of cellular genes upregulated by IFN with indirect antiviral activity include procaspases, which sensitize cells to undergo suicide (apoptosis) upon viral infection, and MHC molecules, that increase the chances of virus-infected cells being killed by the adaptive immune response (cytotoxic T cells); examples of proteins with direct antiviral activity include PKR and 2',5'-oligoadenylate synthetase (both of which inhibit virus protein synthesis)

Since its discovery in 1957 a huge amount has been learned about interferon and its importance in controlling virus infections. **Rick Randall** and **Steve Goodbourn** explain what's known now and what we still need to find out.



and Mx proteins (that have a number of antiviral activities). However, there are still many cellular proteins that are upregulated by IFN whose exact antiviral function is not yet known. Much has also been learnt about how IFN is induced and how it signals to upregulate the expression of these cellular genes. Indeed, the mechanisms of IFN induction and signalling have been paradigms of cellular gene expression.

There are two types of IFN, namely IFN- α/β (a group of IFNs sometimes referred to as type I IFNs) that are released by virus-infected cells and specialist immune cells (including plasmacytoid dendritic cells), and IFN- γ (type II IFN) that is released by subsets of lymphocytes during an immune response. Cells which secrete IFN- α/β have a variety of receptors that recognize patterns of molecules (termed PAMPs), such as double-stranded RNA (dsRNA), which are characteristic of pathogens as they are not normally present in the absence of infection. These PAMP receptors, once stimulated by their appropriate ligands, activate intracellular signalling cascades that lead to the induction of genes that encode IFN- α/β . Once released, IFN- α/β binds to the IFN- α/β receptor on neighbouring uninfected cells (as well as on

▲ Fig. 1. Antiviral action of IFN. Rick Randall

◀ A glass vial of IFN. Here, the crystal form of IFN is seen; it is made soluble when used as an injection. James King-Holmes / Science Photo Library

the initial infected cell) and activates an intracellular signalling cascade, known as the JAK/STAT pathway, leading to the upregulation of IFN- α/β -responsive genes. IFN- γ binds to a different receptor and activates a slightly different signalling pathway that leads to the upregulation of IFN- γ -responsive genes (there is some, but not complete, overlap between the sets of genes upregulated by IFN- α/β and IFN- γ).

Viruses counteract the interferon response

The recognition that IFN could inhibit the replication of many viruses soon led to the hope that it could be used as a general treatment for virus infections as an early 1960s 'Flash Gordon' cartoon illustrates (Fig. 2). However, we now know that one reason why IFN treatment of virus infections has not lived up to its early promise, and why in nature IFN is not always



▲ Fig. 2. Flash Gordon cartoon depicting the 'first' human use of interferon (1960).
Reproduced with permission of King Features Syndicate Inc.

effective in controlling virus infections, is because viruses all have strategies for circumventing the IFN response. Usually this involves viruses making products that specifically prevent the IFN response from working correctly. Indeed, the general importance and potential power of the IFN response in controlling virus infections can be judged from the fact that even simple RNA viruses, with limited genetic capacity, nevertheless produce proteins that specifically antagonize the IFN response. Interestingly, the way in which viruses circumvent the IFN response varies and these different modes of action must be one of the major factors influencing the type of disease a particular virus causes.

Some viruses (e.g. poliovirus and some strains causing influenza) have a blunderbuss approach in which they globally block host cell gene expression/and or protein synthesis, thus preventing the cell from either producing or responding to IFN. Whilst extremely effective, such an approach has the major disadvantage that the infected cell will die fairly rapidly, thereby limiting the time in which the virus can complete its replication cycle. In addition, with such a strategy it may not be possible for viruses to manipulate cells

to their own advantage, e.g. by inducing the cell cycle so that enzymes are produced that might be required for virus replication. Furthermore, these viruses will not be able to establish latent or persistent infections in cells in which cellular protein expression has been blocked.

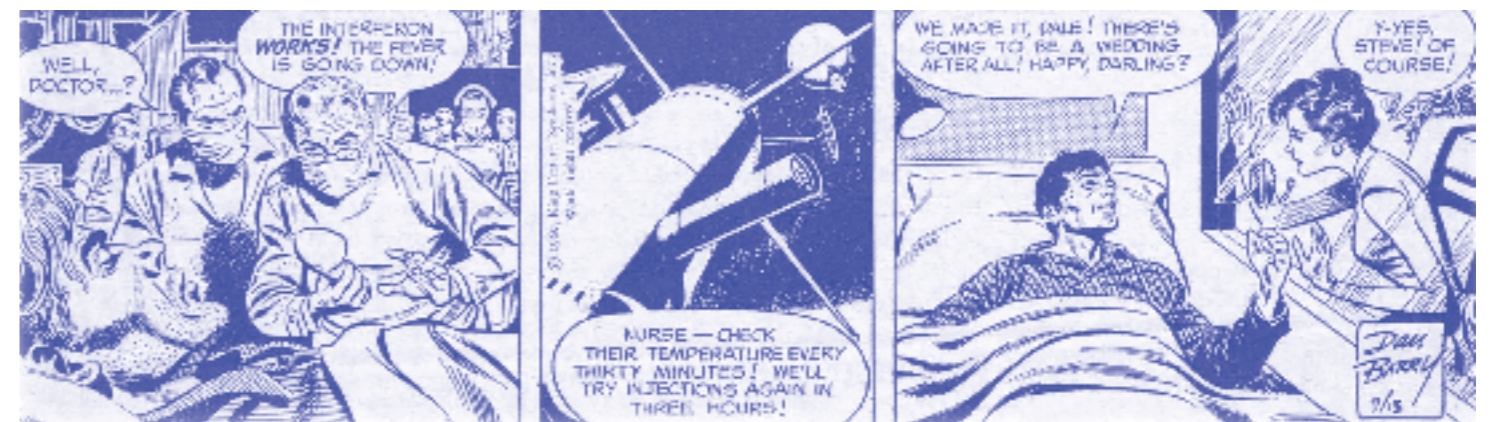
As a result, many viruses have more subtle ways of circumventing the IFN response that include: specifically interfering with the cellular pathways that lead to the induction of IFN (e.g. hepatitis C virus, rotaviruses, herpesviruses), blocking the ability of IFN to signal in virus-infected cells (e.g. poxviruses, paramyxoviruses, rabies, dengue), inhibiting the activity of IFN-induced enzymes which have antiviral activity (e.g. influenza viruses, herpesviruses, poxviruses) or having a replication

strategy which is largely insensitive to the actions of IFN (e.g. retroviruses). However, it is important to note that many viruses employ more than one of these mechanisms to circumvent the IFN response and, within these categories, different viruses achieve the same general outcomes using different molecular means.

Vaccines, antiviral drugs and oncolytic viruses

Although viruses encode products that block different arms of the IFN response, and whilst in general IFN has not been the hoped for 'wonder drug' in treating virus infections, nevertheless it has been successful in treating certain chronic/persistent infections, such as hepatitis C (although even here the success rate is only ~50–70%).

By understanding at the molecular level how viruses counteract the IFN response, new medicines and new ways of combating infections may be developed.



Nevertheless, by understanding at the molecular level how viruses counteract the IFN response, new medicines and new ways of combating infections may be developed. For example, it is clear that if a virus fails to circumvent the IFN response it will be attenuated *in vivo*. Consequently, attenuated virus vaccines may be developed by specifically isolating viruses that are unable to circumvent the IFN response. This may be achieved either by genetically engineering viruses to knock-out their IFN antagonists, or by selecting mutants that are sensitive to IFN. The fact that most viruses encode specific IFN antagonists also raises the possibility that novel antiviral drugs may be developed which block the activity of the viral antagonists.

There is also a great deal of interest in using oncolytic viruses, which may be defective in terms of their ability to circumvent the IFN response, for cancer therapy. Such an approach may be useful in treating cancers in which the tumour cells are in some way deficient in their IFN response as IFN-sensitive viruses may be able to replicate and kill tumour cells, but not normal cells with an intact IFN response. Furthermore, the study of viral interactions with the IFN response has led to a deep understanding of the mechanistic details of IFNs and their actions. Since it now appears that IFNs play additional roles in the control of certain cellular/immune functions in the absence of virus infections, new cellular targets are being identified for drugs to control cell functions in a variety of conditions.

The future

Although a great deal has been learnt about how viruses interact with the IFN response in the last 50 years, the story is not over. The molecular events involved in IFN induction and signalling are not yet completely understood, much

has still to be learnt about how many viruses block the IFN response and about the consequences that particular molecular methods employed by given viruses have for both the virus and host, and there are many opportunities of using the knowledge gained from such studies to improve human and animal health.

Richard E. Randall

Professor of Molecular Virology, University of St Andrews, School of Biology, BMS Building, The North Haugh, St Andrews KY16 9ST, UK (t 01334 463397; e rer@st-and.ac.uk)

Steve Goodbourn

Professor of Biomolecular Science, Division of Basic Medical Sciences, St George's, University of London, London SW17 0RE, UK (t 0208 725 5942; e s.goodbourn@sgul.ac.uk)

Further reading

- Isaacs, A. & Lindenmann, J. (1957). Virus interference: I. The interferon. *Proc R Soc Lond Ser B Biol Sci* 147, 258–267.
- Randall, R.E. & Goodbourn, S. (2008). Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. *J Gen Virol* (in press).