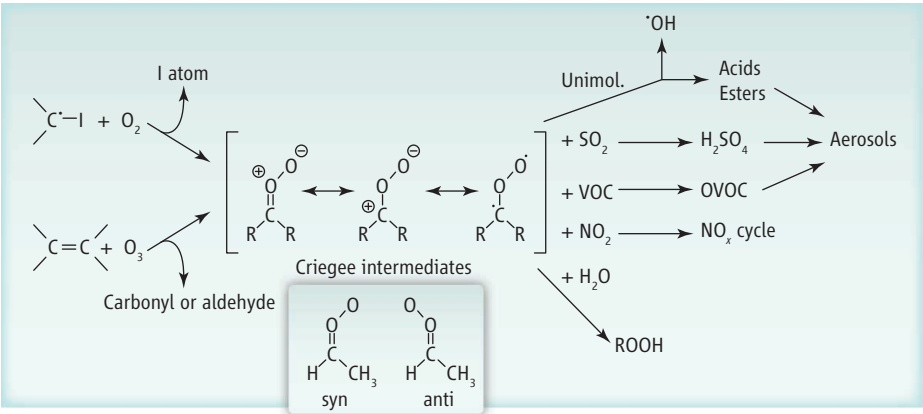
# An Interferon Paradox

Pamela M. Odorizzi and E. John Wherry

*Science* **340**, 155 (2013);
DOI: 10.1126/science.1237568




**Formation and reactions of CIs.** Criegee intermediates (CIs) formed from ozonolysis or iodoalkyl radicals have been difficult to observe. Su *et al*. (*2*) report the infrared spectroscopic detection of the smallest CI, $CH_2OO$. Kinetic measurements by Taatjes *et al*. (*3*, *12*) of their reaction with water, $SO_2$, $NO_2$, and volatile organic compounds (VOCs) suggest a specific role for CIs in the atmosphere. OVOC, oxygenated volatile organic compound. (**Inset**) *syn* and *anti* forms of $CH_3CHOO$.

pared to these rates, the $H_2SO_4$ formation rate from CI + $SO_2$ observed by Berndt *et al*. (*8*) is two orders of magnitude slower; Vereecken *et al*. (*11*) attributed this low yield to strong pressure dependence favoring other products.

The rate coefficient for the reaction of $CH_3CHOO$ with water was found to be much slower, but—given the high water concentrations in the troposphere—still fast enough to make it the dominant atmospheric sink for *anti*-$CH_3CHOO$ (*3*). Conversely, both *syn*-$CH_3CHOO$ (*3*) and $CH_2OO$ (*5*) react too slowly with water to measure, allowing other reactions to compete. These reactions include thermal decomposition of CI to form radicals (*5*, *8*, *10*) and the reaction of CI with different carbonyl compounds, for which fast reaction rates spanning two orders of magnitude were recently measured (*12*). All these observations, and their strong dependence on CI structure, are in agreement with theoretical predictions (*10*, *11*).

Inconsistencies remain, but the data discussed above suggest that CIs can play a role in the atmosphere well beyond their reaction with water. The reaction of CIs with $SO_2$ may be an important gas-phase source of low-volatility sulfuric acid, a key actor in the formation of atmospheric aerosols (*13*). The reaction of CIs with $NO_2$ may affect the $NO_x$ cycle, whereas their reaction with oxygenated hydrocarbons might be a source of aerosol precursors.

Theory-based analysis (*11*) of the impact of the CI structure on its atmospheric fate indicates that some smaller CIs will mainly react with water, but many others will partially react with other compounds or act as a source of free radicals. Additional experimental and theoretical studies are clearly needed on atmospherically relevant CIs. Atmospheric chemistry models will need to incorporate these new insights into CI chemistry.

**References**


1. R. Criegee, G. Wenner, *Justus Liebigs Ann. Chem.* **564**, 9 (1949).
2. Y.-T. Su, Y.-H. Huang, H. Witek, Y.-P. Lee, *Science* **340**, 174 (2013).
3. C. A. Taatjes *et al.*, *Science* **340**, 177 (2013).
4. C. A. Taatjes *et al*., *J. Am. Chem. Soc.* **130**, 11883 (2008).
5. O. Welz *et al*., *Science* **335**, 204 (2012).
6. J. M. Beames, F. Liu, L. Lu, M. I. Lester, *J. Am. Chem. Soc.* **134**, 20045 (2012).
7. E. P. F. Lee *et al*., *Chemistry* **18**, 12411 (2012).
8. T. Berndt *et al*., *J. Phys. Chem. Lett.* **3**, 2892 (2012).
9. A. Novelli ***et al.***, paper presented at the Atmospheric Chemical Mechanisms Conference, Davis, CA, 10 to 13 December 2012; see https://sites.google.com/site/atmoschemmech2012/.
10. L. Vereecken, J. S. Francisco, *Chem. Soc. Rev.* **41**, 6259 (2012).
11. L. Vereecken, H. Harder, A. Novelli, *Phys. Chem. Chem. Phys.* **14**, 14682 (2012).
12. C. A. Taatjes *et al*., *Phys. Chem. Chem. Phys.* **14**, 10391 (2012).
13. R. L. Mauldin III *et al*., *Nature* **488**, 193 (2012).


10.1126/science.1236475

IMMUNOLOGY

# An Interferon Paradox

Interferons must balance antiviral actions against immunosuppressive effects during acute and chronic infections.

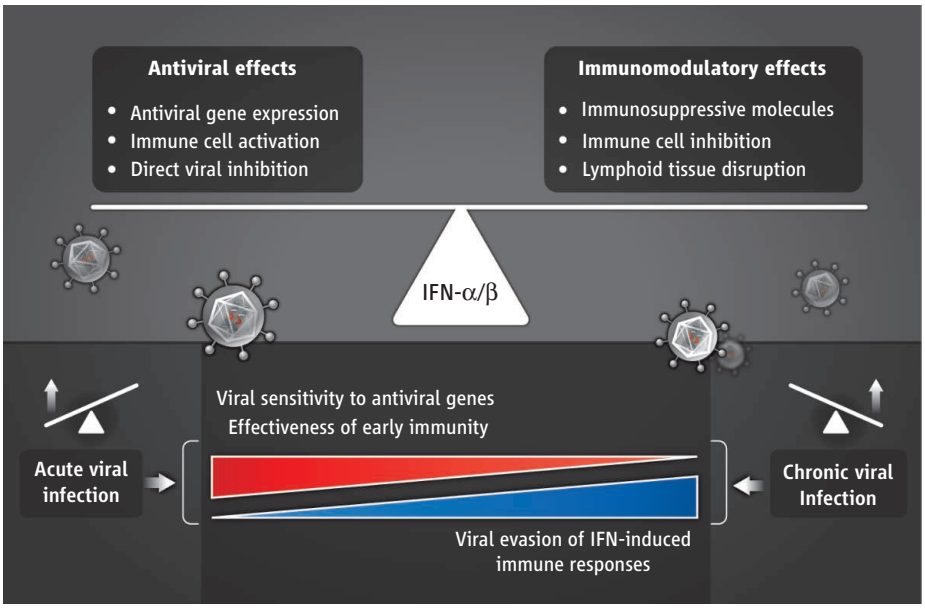
**Pamela M. Odorizzi and E. John Wherry**

Type 1 interferons (IFN-α/β) are a major first line of host defense against viral infection. Because of this potent antiviral activity, IFN-based therapies have been developed for chronic infections with hepatitis B and C viruses, as well as for HIV. However, a poorly understood phenomenon has been the persistence of virus despite induction of antiviral immune responses by type 1 IFNs. On page 207 and 202 in this issue, Teijaro *et al*. (*1*) and Wilson *et al*. (*2*) address this long-standing question and find that IFN-α/β can also suppress the immune system in ways that promote viral persistence. This paradoxical finding should spur a reassessment of the fundamental roles of IFN-α/β during chronic infections.

In the early stage of viral infection, recognition of pathogen-associated molecular patterns (PAMPs) through molecular sensors in the body, such as Toll-like receptors, leads to rapid production of type 1 IFNs by various cell types (*3*, *4*). IFN-α/β acts in both an autocrine and paracrine manner to induce the expression of IFN-stimulated genes that limit viral replication and spread (*4*, *5*). Importantly, loss of IFN-α/β signaling in animal models usually leads to uncontrolled viral replication (*6*). Chronic viral infections can result in sustained IFN-α/β signaling, presumably due to ongoing recognition of viral PAMPs (*7*). It has been unclear, however, why this ongoing IFN-α/β signaling during chronic infections does not lead to viral control.

Teijaro *et al*. and Wilson *et al*. used a mouse model of chronic infection with either of two strains of lymphocytic choriomeningitis virus (LCMV)—the Armstrong strain, which is associated with T cell–mediated viral control, and the clone 13 strain, which induces broad immune dysfunction, including T cell exhaustion (gradual decrease in T cell function). Both strains trigger robust,

Institute for Immunology and Department of Microbiology, University of Pennsylvania Perelman School of Medicine, 421 Curie Boulevard, Philadelphia, PA 19104, USA. E-mail: wherry@mail.med.upenn.edu




**Balancing dual roles.** Type 1 interferons (IFN-α/β) may control viral replication and spread through two mechanisms. Antiviral responses include the expression of antiviral genes and the activation of specific immune cells. Immunomodulatory responses include the expression of immunosuppressive molecules, immune cell inhibition, and cell death. The balance of these responses may shift, with enhanced antiviral actions during acute infections and greater immunomodulatory effects during chronic infections.

but transient, IFN-α/β production; however, the expression of many IFN-stimulated genes persists during chronic infection. In these studies, the removal of IFN-α/β signaling in animals through genetic deletion of a subunit for the type 1 IFN receptor, or antibody-mediated blockade of the IFN receptor before infection, increased viral replication and acute LCMV infection was no longer controlled. Surprisingly, inhibiting IFN-α/β signaling also reduced the expression of immunosuppressive molecules, such as the regulatory cytokine interleukin-10 (IL-10) and the inhibitory receptor ligand programmed death ligand 1 (PD-L1). The IL-10 and PD-1 pathways promote viral persistence and T cell exhaustion during many chronic viral infections (*8*). Despite an initial increase in virus, blocking IFN-α/β during chronic LCMV infection led to a substantial reduction in viral titers by 2 months after infection. Therapeutic blockade of IFN-α/β signaling with an antibody against the IFN receptor after the establishment of chronic infection also enhanced viral control. Both studies observed improved virus-specific $CD4^+$ T cell responses and preserved lymphoid tissue organization in the absence of IFN-α/β signaling.

The studies by Teijaro *et al*. and Wilson *et al*. highlight an unappreciated dual nature of IFN-α/β signaling during chronic viral infections (see the figure). Type 1 IFNs limit early viral replication through multiple direct molecular mechanisms, including inhibition of viral transcription and translation, as well as degradation of viral nucleic acids (*5*). The production of IFN-α/β early upon infection also serves as an activation signal for immune cells by promoting lysis of infected cells by natural killer cells, enhancing antigen presentation–T cell priming by dendritic cells, and sustaining proliferation and activation of T cells (*3*–*5*). However, IFN-α/β also has regulatory effects that suppress immune responses. For example, IFN-α/β can trigger programmed cell death of activated T cells and increase production of immunosuppressive molecules, including IL-10, PD-L1, and indoleamine (2,3)-dioxygenase (*4*, *9*). Thus, although early antiviral effects of IFN-α/β are critical, the potential immunoregulatory roles of IFNs later in chronic infection could explain paradoxical clinical observations using IFN-based treatments. For example, strong basal IFN-α/β signatures (increased expression of IFN-stimulated genes) correlate with poor responses to IFN-α therapy during chronic hepatitis C virus infection (*10*, *11*). Such signatures are also associated with disease progression during chronic HIV and pathogenic SIV infections, as well as during active versus latent *Mycobacterium tuberculosis* infection (*12*–*14*).

Why might IFNs elicit direct antiviral effects while concurrently boosting immunoregulatory responses that prevent robust adaptive immune responses to infections? One possibility is that the immunoregulatory functions of IFN-α/β may have evolved to limit immune-mediated pathology during infections where viral persistence is inevitable. In these settings, the IFN-α/β pathway may sense the level of ongoing viral replication and bolster immune suppression to avoid damaging immunopathology, such as a "cytokine storm" (uncontrolled cytokine production and immune cell activation), meningitis, or immune-mediated tissue destruction. An essential next step will be determining how this balance is influenced by pathogen virulence and the strength of the immune response. In addition, the ability of IFN-α/β to efficiently control early viral replication, and the capacity of different viruses to evade this response, may dictate the importance of these immunoregulatory effects.

How might these findings improve IFN-based treatment strategies? There are several issues to be addressed. Identifying the molecular basis for the antiviral versus immunomodulatory effects of IFN-α/β will be necessary to selectively manipulate these opposing activities. It will also be critical to determine how the balance between antiviral and immunoregulatory effects varies from virus to virus or during a single viral infection over time. The studies of Teijaro *et al*. and Wilson *et al*. suggest that patients currently on IFN therapy could be monitored for the induction of antiviral versus immunoregulatory effects, allowing physicians to modify treatment strategies accordingly. It also may be possible to further improve the antiviral therapeutic potential of IFNs and perhaps exploit the immunoregulatory properties of this pathway for nonviral diseases.

**References**


1. J. R. Teijaro *et al*., *Science* **340**, 207 (2013).
2. E. B. Wilson *et al*., *Science* **340**, 202 (2013).
3. A. Iwasaki, R. Medzhitov, *Science* **327**, 291 (2010).
4. J. M. González-Navajas, J. Lee, M. David, E. Raz, *Nat. Rev. Immunol.* **12**, 125 (2012).
5. A. G. Bowie, L. Unterholzner, *Nat. Rev. Immunol.* **8**, 911 (2008).
6. U. Müller *et al*., *Science* **264**, 1918 (1994).
7. L. N. Lee, S. Burke, M. Montoya, P. Borrow, *J. Immunol.* **182**, 7178 (2009).
8. E. J. Wherry, *Nat. Immunol.* **131**, 492 (2011).
9. A. Boasso, A. W. Hardy, S. A. Anderson, M. J. Dolan, G. M. Shearer, *PLoS ONE* **3**, e2961 (2008).
10. P. M. George, R. Badiger, W. Alazawi, G. R. Foster, J. A. Mitchell, *Pharmacol. Ther.* **135**, 44 (2012).
11. M. Sarasin-Filipowicz *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **105**, 7034 (2008).
12. J. -P. Herbeuval *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **103**, 7000 (2006).
13. B. Jacquelin *et al*., *J. Clin. Invest.* **119**, 3544 (2009).
14. M. Berry *et al*., *Nature* **466**, 973 (2010).


10.1126/science.1237568

CREDIT: Y. HAMMOND/*SCIENCE*