

Fifty years of interference

To the editor:

This year marks the 50th anniversary of the discovery of 'inhibitory factor', which is now recognized as interferon¹. During the past half-century, a vast body of evidence has accumulated that demonstrates the crucial involvement of the interferon family in various phases of host defense, including antiviral and anticancer immune responses. I salute the two groups that initially identified the inhibitory factor, or interfering reagent, which one of them named interferon. Their achievements were independent and used very different experimental systems with a common context of viral interference.

Back in 1954, Japanese virologists Yasu-ichi Nagano and Yasuhiko Kojima of the Institute for Infectious Disease (now the Institute of Medical Science) at the University of Tokyo published a report² in French that described an inhibitory factor derived from tissue suspensions of vaccinia virus-infected rabbit skin or testis. At that time Nagano and Kojima were studying vaccination with vaccinia virus inactivated by ultraviolet irradiation. They noticed that a few hours after intradermal inoculation of rabbits with the inactivated virus, the rabbit skin showed resistance to a challenge at the same site with live vaccinia virus. They

hypothesized that the quick inhibition of virus multiplication must be due to the presence of some "*facteur inhibiteur*"² (inhibitory factor). That 1954 paper demonstrated that the activity could be separated from the virus particles sedimented by ultracentrifugation and was found in the supernatant. The authors, however, were not able to reconcile the antiviral activity shown in the rabbit skin experiments with the fact that intraperitoneal injection of mice with the supernatant elicited the production of virus-neutralizing antibodies. This ambiguity was later ascribed to the presence of small amounts of virus remaining in the supernatant after centrifugation. Indeed, by 1958 Nagano and Kojima had accumulated evidence, with thrice-centrifuged supernatant, that the inhibitory factor was distinct from both virus particles and immune serum against virus³. The features of the inhibitory factor coincided with what is now classified as type I interferon.

Another landmark paper⁴, by Scottish virologist Alick Isaacs and Swiss researcher Jean Lindenmann, working at the National Institute for Medical Research of the Medical Research Council, was published in 1957 and named 'interferon' as the interfering reagent

in the study of viral interference of influenza virus. Isaacs and Lindenmann found that heat-inactivated influenza virus, when added to chick chorioallantoic membrane fragments, could induce the formation of an 'interfering' reagent that inhibited growth of live influenza virus when added to fresh membranes. This interfering reagent is now also classified as type I interferon.

Those initial investigations into the nature of host responses to viruses have grown into an enormous literature on interferons. It is a credit to the insight of the original investigators that a term coined 50 years ago is still in use today and that the field of inquiry they started remains a burgeoning and active area of research.

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