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International Society for Interferon & Cytokine Research

April 2009 - Volume 16, No. 1

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ISICR WWW Site

www.ISICR.org

ISICR Business Office

ISICR@faseb.org

TEL: 301-634-7250

FAX: 301-634-7420

ISICR Newsletter Editors

Howard Young

younghow@mail.nih.gov

Hannah Nguyen

hannah.nguyen@mcgill.ca

Seng-Lai (Thomas) Tan

tsltan@yahoo.com

The History of Interferon: Some personal thoughts and experiences in the early years of Interferon research

Joseph Sonnabend

In 1964, the world of interferon research was much different and really just beginning to blossom. There was no molecular biology and the tools available for research were much more primitive. Thus research into interferons required a thought process about the biology of the experimental systems being investigated. The following is a recollection from Dr. Joseph Sonnabend, one of the pioneers in Interferon research, accompanied by a reproduction of some thoughts he circulated for discussion at that time.



I probably wrote this in the room I shared with Alick Isaacs. It was written in response to Joyce Taylor's experiment with actinomycin suggesting that interferon's antiviral action required cell RNA synthesis. Joyce and I were the only members of the virology division using biochemical techniques at that time and I was quite close to the work she was doing, and of course Bob Friedman and I were to work together.

When Joyce first saw her results, we thought that an inactive preparation of interferon had been used. I believe I was probably the first to realize the implications of the actinomycin sensitivity of interferon action. One must remember that this was an incredibly exciting time; the time of Jacob and Monod, of derepression - in bacterial systems; the role of ribosomes in protein synthesis had just been worked out, and Sidney Brenner confirmed the Jacob/ Monod idea of the role of mRNA, I think in that same year- 1964. These were the issues that Joyce, Bob Friedman, some biochemists - particularly

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(History of Interferon, cont. from page 1)

Ted Martin, and I talked about. It was also a time when virologists were venturing into biochemical approaches. However not our division, as we had no high speed centrifuge or spectrophotometer let alone a scintillation counter. Joyce and I, and then Bob, had to use equipment in other divisions. So I recognized that this was the first indication (at least to me) that maybe something similar was happening in eukaryotic systems as in bacterial systems, which was then a topic of great interest. That is, the induced synthesis of specific proteins. Alick Issacs was completely disinterested in these discussions at that time.

I wrote the few pages in this state of enthusiasm. Joyce and Bob read it - it reflected what we were

It was not intended for publication, but we sent it to interferon labs, those we knew, which may have been

talking about.

Of course I also showed it to Alick for any comment, he made the few annotations you can see - particularly adding Jean Lindenmann's name (which was so characteristic of him). I'm sure I also discussed it with Ted Martin and maybe others in the biochemistry division. Joyce left around this time.

Not only was there no comment at the time from those I sent it to, but Joyce herself had forgotten about it when I showed it to her a few years ago.

Just out of interest I did later write a kind of devil's advocate alternative interpretation of the need for RNA synthesis (Sonnabend, J. A., I. M. Kerr, and E. M. Martin. 1970. Development of the antiviral state in response to interferon, p. 172-183. In *Interferon*. Little, Brown & Co., Boston).



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INTERFERON : PRODUCTION AND MECHANISM OF ACTION

and history
Since the early reports of Isaacs in 1957 on the release of a non-viral interfering agent by virus infected cells, a large number of observations have accumulated on the production and action of Interferon. A model will be presented which will attempt to correlate these observations. Essentially, both Interferon production and Interferon action will be viewed as involving a specific participation of the host genome; Interferon will be viewed both as an inducer and, itself, an induced protein.

INTERFERON ACTION

The important observations which any scheme must take into account are :-

- No direct anti viral action
- Active on both RNA and DNA viruses
- Greater protection afforded by pretreatment of cells
- Species specificity of action
- No gross effects on host cell metabolism - as far as this has been studied
- Recovery of Sensitivity to viruses
- Inhibition of virus specific RNA synthesis
- Actinomycin sensitivity of Interferon action

From the absence of a direct antiviral action, and the observation that protection is greater if infection is delayed following a period of pretreatment, it is likely that some additional step or steps are required in the acquisition of viral resistance. These steps may involve -

- (1) Interferon
- (2) The Cell

The first possibility means that Interferon is in some way already activated so that it can express its antiviral activity only intracellularly.

It is the second possibility, namely, that the antiviral action of Interferon results from some change that it induces within the cell, that would seem to be most consistent with the observations. It is evident from the actinomycin sensitivity of Interferon action that host cell RNA synthesis is required for an expression of its action. Recent results suggest a similar dependence on protein synthesis. It is suggested that Interferon induces the synthesis of a specific messenger RNA determining the synthesis of a protein having antiviral activity.

Thus, resistance to viruses would increase with pretreatment.

Two further observations are explained on this basis :

The persistence of protection despite removal of the Interferon, and the failure to recover Interferon from treated cells which are protected.

The Antiviral Agent and its Mode of Action

Interferon inhibits both RNA and DNA viruses. A common point of action would be on RNA synthesis. An important observation is that Interferon does not seem to inhibit the messenger function of virus nucleic acid. Thus, in the mengovirus L cell system, viral induced cut off of host cell RNA and protein synthesis is not affected, and although no new virus is produced, the cells die. It might be anticipated that the virus induced RNA-RNA polymerase is also produced. It is less likely that the action of this enzyme is inhibited, since Interferon is active on DNA viruses. It is suggested that the antiviral activity of Interferon results from the induced synthesis of an enzyme by the host cell which degrades newly synthesized

synthesized/

RNA. From the preservation of the messenger function of the viral RNA referred to above, it is necessary to specify that it is newly synthesized RNA that is susceptible. One would also anticipate an effect on host cell RNA synthesis, and this will be returned to later.

The antiviral agent is apparently not present in crude preparations of Interferon, since the action of these preparations is sensitive to actinomycin. This implies an instability to the various treatments that Interferon preparations are subjected to to remove virus, or to the fact that it does not penetrate the cell membrane.

Species Specificity

If Interferon is viewed as an inducer, specificity of action might reside at the point of induction: in other words, only Interferon of appropriate specificity can induce the synthesis of the antiviral agent.

Action on the Host Cell

On the basis of the above model, one might predict an effect on host cell RNA synthesis. As far as this has been studied, it is clear that there is no gross effect at levels of Interferon which afford considerable protection against viruses.

It is suggested :

- (1) That the action of Interferon is self limiting
- (2) That bulk (ribosomal) RNA synthesis is unaffected
- (3) It is newly synthesized messenger RNA, both viral and cellular, that is susceptible to the degradative enzyme. If this enzyme is unstable, a basis is provided for a self limiting effect

The dependence of Interferon action on continued host cell RNA and protein synthesis leads to the prediction that viruses that inhibit these cellular functions would be less sensitive to the action of Interferon added with the virus; a period of pretreatment before challenge would be expected to protect the cells.

SUMMARY

It is suggested that Interferon induces the synthesis of an unstable enzyme which degrades newly synthesized RNA, both viral as well as host cell M-RNA.

This outline suggests the following work :

- (1) Attempts to isolate an RNA degradative enzyme from Interferon treated cells. An approach may be to look for increased activity of enzymes known to have this effect. (polynucleotide phosphorylase).
- (2) The effect of Interferon on cell RNA synthesis.
 - (i) The effect on overall RNA synthesis
 - (ii) The effect on specific molecular species of RNA
- (3) The demonstration that Interferon action depends on continued protein synthesis. There are already supportive preliminary results.

J.A. Sonnabend

R.M. Friedman

Joyce Taylor.

National Institute for Medical Research
The Ridgeway, Mill Hill, London. N.W. 7

April, 1964.

