The sustained presence of high levels of alpha interferon was found in the circulation of people with AIDS in 1981. This interferon had an unusual instability in acid, resembling in this way the acid labile interferon that had been described in the circulation of people with systemic lupus erythematosus (SLE) and other autoimmune diseases. Interferon is present in the sera of most patients with AIDS and those with advanced AIDS related complex (Fig.1). Despite the early discovery of the AIDS associated interferon, as well as the early well supported proposal that its sustained presence contributes to the overall pathogenesis of AIDS, the nature of its inducer has not yet been definitively established nor has the cell of its origin been determined.

The possible role of HIV as the inducer of alpha interferon in people at risk for and with AIDS has not yet been adequately explored. There are reports that HIV does not induce interferon, that it inhibits interferon production in response to potent inducers, and that it induces low levels of interferon. On the other hand, HIV infected cells, even fixed infected cells, have been reported to be good inducers of interferon. We have explored the possible role of HIV in the induction of interferon by simultaneously performing interferon and HIV p24 antigen assays on sera of patients receiving azidothymidine (AZT, zidovudine).

Results

Fig.2 shows the effect of continuous AZT treatment (1200mg/day) on p24 and interferon levels in three ARC patients. Both p24 and interferon levels rapidly dropped on starting AZT.

Fig.3 shows results in an AIDS patient treated continuously (1200mg/day) and monitored for 40 weeks. This shows that
after an initial rapid drop, interferon levels begin to rise again after 9 weeks of therapy, followed by a recurrence of p24 antigen 24 weeks later.

Fig 4 shows results in two patients treated intermittently with AZT. These patients received AZT for periods of one week, separated by periods of one week. The rapid decline in interferon and p24 levels in response to AZT can be seen, as well as the rapid return of these markers on discontinuation of AZT.

The duration of the interferon lowering effect can be seen in Fig 5. Interferon levels began to increase 2-7 months after starting AZT.

The possibility that AZT interfered with the ability of the cell to produce interferon was excluded by experiments shown in Table 1. AZT had no effect on the induction of alpha, beta and gamma interferons.

There is a negative correlation between CD4 cell numbers and interferon levels. This is shown in Fig 6.

The appearance of interferon in the circulation of asymptomatic HIV infected homosexual men and hemophiliacs carries an adverse prognostic significance with respect to the development of an opportunistic infection. The prognostic importance of beta-2 microglobulin is well known. Interferon is a potent inducer of the synthesis and release of beta-2 microglobulin, which can probably be regarded as a surrogate marker for interferon. As expected, beta-2 microglobulin levels also decrease in response to AZT, undoubtedly as a consequence of lowered interferon levels.

An increase in serum IgA levels is also an adverse prognostic marker. Although interferon is most probably not responsible for IgA elevations, endogenous interferon levels correlate positively with serum IgA levels(Fig.7). As might be expected from data shown in Fig 6 and Fig 7, IgA levels show an inverse
correlation with CD4 counts\(^1\).

A further effect of interferon relevant to AIDS patients is its ability to impair hepatic mechanisms for drug detoxification. This has implications for those patients treated with exogenous interferon and those with endogenous interferon who also receive other medications.

Despite the strong possibility that interferon contributes to the overall pathogenesis of AIDS it is paradoxical that interferon clearly also has a place in the treatment of some AIDS patients

\(^{1}\) Note added in 2009:

It appears that interferon alpha can increase IgA production.
So can TGF beta, another cytokine

Effects of type I/type II interferons and transforming growth factor-beta on B-cell differentiation and proliferation. Definition of costimulation and cytokine requirements for immunoglobulin synthesis and expression. Immunology. 1998 December; 95(4): 604–611.

D M Estes, W Tuo, W C Brown, and J Goin

J. Stavnezer and J. Kang
The Surprising Discovery That TGF\{beta\} Specifically Induces the IgA Class Switch

Interferon alpha producing capacity is higher in individuals with IgA nephropathy,

Correlation between the severity of clinicopathological parameters and whole blood interferon-alpha production capacity in active phase IgA nephropathy patients.
Shirakawa K, Muso E, Nogaki F, Maeda M, Kawamura T, Ono T, Yoshimoto M, Uno K, Kishida T, Sasayama S.

Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto Japan.


Is IgA nephropathy induced by hyperproduction of interferon-alpha?
Wardie EN.

It is possible that interferon alpha is indeed connected with IgA elevations seen in HIV disease.
with Kaposi's sarcoma. The appearance of endogenous interferon is a late phenomenon, and as no clear biological differences have been reported between acid labile and conventional interferon there seems to be little justification to the administration of interferon to patients with low CD4 numbers who have high levels of endogenous interferon. In fact such patients may be refractory to the antiviral and possibly antiproliferative effects of interferon as prolonged exposure to interferon leads to a downregulation of cellular interferon receptors as well as abnormalities of interferon induced enzymes. Exogenous interferon has however clearly been shown to benefit patients with Kaposi's sarcoma who have higher CD4 cell numbers and no endogenous interferon, with respect to a reduction in tumor mass.

It is clearly important that studies be completed that will definitively identify the inducer of interferon in AIDS as well as its cell of origin. Furthermore it is important that studies be undertaken to more clearly define the potential role of endogenous interferon in contributing to some of the abnormalities associated with AIDS. It is possible that interventions that inhibit the production or action of the AIDS associated interferon may prove to be of clinical benefit.

Discussion

The above observations indicating that interferon production in AIDS is sensitive to AZT suggest a role for HIV as the interferon inducer. However, attempts to induce interferon with HIV have not been uniformly successful and HIV infection has even been shown to inhibit interferon induction by known potent interferon inducers. HIV infected cells on the other hand are good interferon inducers in vitro. If such cells were inducing interferon in vivo the sensitivity of interferon production to AZT would suggest that only newly infected cells played a role in this process. Since peripheral blood cells from AIDS patients cannot be induced to produce interferon, it is likely that it is synthesized and released in solid tissues where cell to cell contact is likely. The effect of AZT on interferon levels may also result from its inhibition of an infectious agent other than HIV.
Epstein-Barr virus is also inhibited by AZT and can induce interferon, and thus may play a role in interferon induction in AIDS.

The substantial reduction in alpha interferon levels following administration of AZT may account for some of the symptomatic improvement observed in treated patients. Specifically, fever and malaise are commonly observed in patients receiving exogenous interferon, and endogenous interferon is probably the cause of such symptoms during the course of viral infections. It is thus possible that improvement in these symptoms following AZT administration is mediated by its capacity to reduce interferon levels.

Interferon as a factor in AIDS pathogenesis

Many of the known effects of interferon resemble several features characteristic of AIDS. Interferon apart from causing fever and malaise can cause leucopenia, anemia and thrombocytopenia. It can selectively inhibit the proliferation of CD4 lymphocytes, modulate B cell activity and contribute to the increased production of immunoglobulins. Moreover, interferon can cause an increase in serum triglycerides as well as a lowering of tryptophan levels; high triglyceride and low tryptophan levels are characteristically seen in AIDS. Leucocytes of AIDS patients contain characteristic inclusions that are also seen in SLE and can be induced by interferon. It is even possible that interferon contributes to some cases of AIDS dementia. It is suggested that quinolinic acid may play a role in this manifestation of AIDS. Interferon induces an enzyme that degrades tryptophan and quinolinic acid is produced in the course of the degradation of tryptophan. Quinolinic acid levels are increased in the spinal fluid of some patients with AIDS dementia, as are levels of beta-2 microglobulin, an interferon induced protein.
CD4 COUNT AND SERUM INTERFERON

HIV seropositive homosexual men

CD4 COUNT (c.mm)

0
1-9
10-49
>50

(n=17)
(n=9)
(n=12)
(n=7)

SERUM INTERFERON (U/ml)

CRIA

Fig 1
Fig 3
Fig 4
Duration of AZT Effect

Interferon levels in 6 patients on AZT

MONTHS AFTER STARTING AZT

CRIA
Fig 5
## Interferon Titters in Stimulated Cell Cultures in the Presence or Absence of AZT

<table>
<thead>
<tr>
<th>Cell System</th>
<th>Stimulating Agent</th>
<th>Interferon Titer&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NO AZT</td>
</tr>
<tr>
<td>Normal Human Lymphocyte Culture</td>
<td>PHA</td>
<td>256 (gamma IFN)</td>
</tr>
<tr>
<td>Normal Human Lymphocyte Culture</td>
<td>HSV</td>
<td>192 (alpha + gamma IFN)</td>
</tr>
<tr>
<td>Human Fibroblast Culture</td>
<td>Poly-IC</td>
<td>64 (Beta IFN)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Expressed as reciprocal of dilution.

Table 1
SERUM IgA and SERUM INTERFERON

HIV seropositive homosexual men

serum IgA (mg/dl)

<table>
<thead>
<tr>
<th>Serum Interferon (U/ml)</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(n=22)</td>
</tr>
<tr>
<td>1-9</td>
<td>(n=21)</td>
</tr>
<tr>
<td>10-49</td>
<td>(n=27)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>(n=15)</td>
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</tbody>
</table>

CRIA
Fig 6
CD4 COUNT AND SERUM INTERFERON

HIV seropositive homosexual men

CD4 COUNT (c.mm)

<table>
<thead>
<tr>
<th>CD4 COUNT</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>1-9</td>
<td>9</td>
</tr>
<tr>
<td>10-49</td>
<td>12</td>
</tr>
<tr>
<td>&gt;50</td>
<td>7</td>
</tr>
</tbody>
</table>

CRIA

SERUM INTERFERON (U/ml)