The clear involvement of the interferon (IFN) system in the regulation of differentiation justifies the advanced IFN clinical trials in "differentiation therapy" of cancer. By employing this strategy, it may be possible to specifically reprogram the phenotype of a tumor cell by inducing its terminal cell differentiation and, thus, the loss of its tumorigenic potential. The effects of IFNs on erythroid differentiation and the related mechanisms are reported. Administration of highly purified preparations of murine IFN-alpha or -beta to Friend leukemia cells, induced to differentiate by dimethyl-sulfoxide, leads to a 100% increase of benzidine-positive cells. Both species of IFN induce a substantial increase in heme, hemoglobin and transferrin receptor levels. The results obtained suggest that in erythroid cells the intracellular heme level may represent a key regulatory factor in the hemoglobin synthesis pathway. It is postulated that IFN induces the enhancing effect on differentiation via a marked increase of heme synthesis and number of transferrin receptors which in turn leads to an enhancement of globin chain synthesis.

INTRODUCTION AND BACKGROUND

Interferon(s) (IFNs) are members of a network of substances (now called cytokines) that are all able to operate as regulatory molecules in the homeostatic control of cellular functions. Cytokines may be produced constitutively at low levels and exert multiple effects on virtually all cells. They are active participants in host defenses against viral or parasitic infections and tumors. It is now well accepted that IFNs affect normal cell division and many specialized cellular functions.

Research into IFN and cytokines is expanding markedly, and there are increasing therapeutic applications for cytokines. In fact, as reviewed below, the involvement of the IFN system in the regulation of differentiation has also led to significant advances in planning IFN clinical trials and cancer therapy. This alternative approach involves the use of agents which are not directly cytotoxic but modify tumor cell growth by inducing terminal cell differentiation, i.e., loss of proliferative capacity without a concomitant loss of cell viability. This strategy lies in the belief that neoplasia originates from the inhibition of cell differentiation. If this inhibition is overcome, a reprogrammed phenotype of a tumor cell, with possible loss of tumorigenic potential, would ensue. The ability to employ the above methodologies for cancer therapy requires the development of appropriate model
systems and the identification of both single and multiple agents capable of inducing terminal
differentiation of tumor cells. The present review will discuss how IFNs may function as regulatory
molecules and how they may alter cell differentiation by either inhibiting or inducing it, depending on
the target cells.

Although extensively studied, the relationships between the multiple effects of IFNs and their
pathways of action remain to be defined. For example, following the interaction of IFN with its
appropriate cell-surface receptor, the nature of the signal transduction mechanism mediating the
pleiotropic effects of IFN is not clear. Recent studies have shed some light on these early events
regarding both primary signal-transducing agents (i.e., protein kinases, phosphatidylinositol or
sphingomyelin turnover, etc.) and the activation of specific transcriptional changes in target cells (i.e.,
activation of latent transcription binding factors able to bind to the IFN-stimulated-response-element,
ISRE, an enhancer element inducible by IFNs for transcriptional activation). It is tempting to
postulate that some regulatory functions attributed to IFN are mediated through IFN-induced
enzymes, generally referred to as the IFN system, such as 2′-5′ oligoadenylate (2-5A) synthetase,
2-5A-activated RNase and double-stranded (ds) RNA-activated protein kinase.

**IFN IN DIFFERENTIATING AND DIFFERENTIATED CELL SYSTEMS**

Cell differentiation depends upon a program of ordered gene expression resulting in the production of
specific proteins, usually associated with a specific, terminally differentiated phenotype. IFN genes in
undifferentiated stem cells of teratocarcinoma (embryonal carcinoma cells) are refractory to virus
induction. In addition, these cells and those of early stage embryos are not sensitive to IFN action. In
this and other systems (Harada et al., 1990), genes responsible for the induction and action of IFNs are
in a repressed state and they become functional only after cell differentiation. Also IRF-genes (coding
for protein factors that specifically bind the IFN-alpha and -beta gene promoters, as well as the ISRE
of IFN-stimulated genes) are developmentally controlled (Harada et al., 1990). The effects elicited by
IFN on the complex biologic phenomena related to cell differentiation, i.e., either stimulatory or
inhibitory, depend not only on the cell system employed, but also on the type of IFN used (Rossi, 1985;
Rossi et al., 1987; De Maeyer and De Maeyer-Guignard, 1989; Romeo et al., 1989). Although the
reason for the differential effects of IFN on specific target cells is not known, the diverse responses to
IFN may reflect differences in the type of transmembrane signals elicited by different types of IFNs
following their binding to the appropriate cell membrane receptor and/or by the various target cells.

Several culture systems of differentiating or differentiated cells have been studied with respect to
the effects of IFNs. In general, these differentiation systems appear to be profoundly affected by
exposure to IFN. The effects have been highly specific, in that they are not accompanied by any
modification of overall cellular protein synthesis. This observation is important to dispel any residual
disbelief about the selectivity of IFN action.