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Interferon

Clyde Schultz*

Department of Biology, University of Calgary, Calgary, Alberta, Canada

Abstract

Interferon (IF) is an anti-viral protein that is somewhat unstable when introduced into the body by normal intermuscular injection. It was originally discovered in the late 1950's and was once believed to be a magic bullet for the treatment of cancer. This has since given way to more practical uses as part of a combination therapy regimen especially for cancer patients.

Introduction

Interferon (IF) was discovered in 1957 by Issacs and Lindenman while studying the effects of inactivated influenza virus on the replication of active influenza virus in fragments of chick chorioallantoic membrane [1]. When virus free fluids from membranes exposed to inactivated virus were incubated with fresh membranes and inoculated with active influenza virus replication was inhibited. The inhibitor was a soluble substance with a molecular weight of about 32,000 Daltons, was resistant to pH 2 in the cold, and was not inactivated at 56 C for 1 hr; and was not sedimented at 100,000 x g.

IF is an anti-viral protein produced in living cells. The interferon system is species specific in that it will protect cells against virus only in the same or closely related animal species in which it was produced. Interferon produced in rabbit cells will not protect mouse cells, but human interferon can protect monkey cells from some viral attack [2]. IF can be detected in blood within two hours after virus infection making it one of the first lines of defense against virus dissemination. IF is a cytokine or in its essential function is a chemical messenger [3]. The molecule was named as such because of its ability to disrupt viral replication, which was how it was originally discovered. Since the time of Issacs and Lindenman, IF has been shown to have other functions as well including immune cell activation and increase in the expression of the major histocompatibility complex (MHC).

Structure and types

There are at least 20 different IF genes and proteins that have been identified. They are divided by class or type. Interferon structure is related to type and this is one of the ways of discriminating the two. There are two sub-types of interferon, alpha and beta. They comprise Type I interferon. Type I IF bind to a receptor complex IFNAR that is comprised of two genes, IFNAR 1 and 2. Type I interferon activates when the body detects an invading virus [4]. Type 1 binds to specific receptors on target cells, once released by fibroblasts and monocytes. The monocytes may occur in the spleen or lymph nodes. Upon forming the receptor complex, proteins are released that will prevent at least in part viral entry into target host cells. Type I interferon is monomeric and is composed of one chain and two different receptor chains. It has five alpha helices.

Type II interferon has a single member, interferon gamma [5]. It is known as immune interferon and is known to be induced by Interleukin-12. It may also be released by cytotoxic T cells and by T helper cells. IF Type II will block or inhibit T-helper type 2 cells, which further enhance Type I cells.

One other more recently discovered IF type is Interferon Type III [4]. It is important in the prevention of viral and fungal infections. It works through a receptor complex consisting of IL10R2 and IFNLR1. Types I and III can be induced by almost all categories of virus including SARS-CoV-2. Type II IF is almost always induced by cytokines especially IL-12.

Induction

Interferons do not reside at low levels in an animal body like complement components do. They are induced by the presence of a pathogen, often a virus and expressed by lymph cells other types of immune cells [6]. Mitogens or other cytokines such as IL-2 and tumor necrosis factor can also induce IF production. IF can, by interactions with specific receptors activate signal transducer and activator complexes that will activate or regulate immune genes. These complexes are induced by both IF Type I and II.

Function

As mentioned, IF has two main functions, viral protection and immune regulation. All interferon types are involved to a greater or lesser degree with these two functions. The viral protection effect occurs not because of direct interaction with the virus but because of its effect on surrounding cells. When a virus interacts with an uninfected cell, it penetrates the cell. This penetration causes the release of interferon and thus interaction of the interferon with receptors on the surface of neighboring cells. This in turn leads to inhibition of viral replication. Also, other additional interferon as well as other cytokines are produced. The key is interaction of interferon with cell membranes of un-infected cells [7].

Correspondence to: Dr. Clyde Schultz, Department of Biology, University of Calgary 2500 University Drive, Calgary, Alberta, Canada T2N 1N4, Tel: 403-220-5278; E-mail: schultzc@ucalgary.ca

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Administration of Type I IF in animals has been shown to inhibit tumor cells growth [8]. This effect has not been replicated in humans to a significant degree as in animals. Cellular responses to IF stimulation involve the production of dozens of proteins. The most significant being protein kinase R. This enzyme phosphorylates eIF-2 in response to the infection. This forms, in a cascade fashion (similar to complement) a complex with eIF2B. This downregulates cellular protein synthesis. RNAse L destroys intracellular RNA which also reduces protein synthesis. These actions inhibit both cellular and viral activity in the cell. In un-infected cells there is no trace of IF. The gene is depressed.

The other major function of IF is in immune regulation [9]. IF will up-regulate the major histocompatibility molecules MHC I and MHCII. MHC I dependent antigens are enhanced. This leads to increased presentation of viral proteins from cancer cells to cytotoxic T cells with effects that these proteins are neutralized or inactivated. Higher MHC II expression increases presentation of immunoproteasome to helper T cells, these releasing increased levels of cytokines.

IF activates the signal transducer activator transcription processes (STAT) [10]. STATs are actually a group of transcription factors that are activated by Types I and II IF. In this way the Janus kinase (JAX) STAT (JAX-STAT) signaling pathway is activated. Following the association of JAX with IF receptors there is phosphorylation of both STAT 1 and 2. IF stimulated gene factor forms and is then removed to the interior of a cell nucleus. Inside the nucleus IFN stimulated response elements are bound; the ISGF3 complex formed from JAX-STAT in association with another transcription factor IRF9, binds to specific IF response promotors. As a result, ISG genes transcribe mRNA.

Viral resistance

Virus blocks IF action primarily by interfering with receptor activity [11]. This action may take a couple of different forms, or put another way be nuanced. Downstream signaling events are blocked once the receptor is bound, thus preventing initiation of the protective cascades. Some herpes viruses such as KSHV and dengue type 2 are examples of this. Other viral proteins will inhibit signaling in a more direct fashion, such as the Epstein Bar Virus. HIV has been reported to block the synthesis of interferon. Some of the pox viruses will produce proteins that interact with the IF receptor homologues, thus preventing attachment. Protein production can also be prevented by certain virus such as Japanese Encephalitis Virus. In the case of SARS-CoV-2, a small percentage of the potentially infected human population produce autoantibody against the virus [12]. This is somewhat more rare. Also, STAT proteins may be degraded. IF activity may also be modulated by environmental factors such as elevated NO_2 levels [13].

IF as a disease modulator

Interferon has been approved for use in humans for several decades. The use of interferon in the treatment of human disease has been met with mixed results. This indicates that in the natural setting interferon alone was not intended by the standards of evolution to act a sole disease modulator. However, in concert with other drugs, IF has been found to add to or enhance the therapy of other drugs. In other words, its effectiveness is enhanced as part of a combination therapy.

One of the larger issues involving stability of the IF molecule was solved in during 2001-2 with the addition of polyethylene glycol to the surface of the IF molecule which resulted in enhanced stability of IF and thus a longer half-life. When used in conjunction with ribavirin, Hepatitis C infections were shown to be modulated [14]. IF therapy is also used in concert with chemotherapy and radiation for the treatment of some types of cancers.

There are a few diseases such as hairy cell leukemia where treatment with IF alone has been shown to modulate the disease [15]. It has been used in the past to combat Kaposi's sarcoma in AIDS patients, if directly injected into the lesion. IF has also been approved for the treatment of multiple sclerosis, but data show that the response varies and is often ineffective.

Conclusion

Although interferon use has been shown to be limited as a therapy, it is an important part of the normal immune response in humans and other animals. IF is relatively easy to manufacture and has been used as a first line therapy in diseases such as SARS where there was no initial alternative. But the original idea of interferon use as a "magic bullet" especially in the treatment of cancer has waned. Scientists and their graduate students study IF still, but mainly now as part of the mechanism of understanding the beauty and simple complexity of the immune response as a whole rather than an overarching therapy.

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