The Progress of IFN and the Correlation with Hepatitis B virus

Xiao Minghui[12], Fan Lihua[1]

1. Harbin Medical University
2. Harbin Pharmaceutical Group Bioengineering CO.LTD
xiaomh@hayaobio.com.cn

Abstract: IFN affects a number of processes including those regulating cell growth, differentiation, and apoptosis, as well as the modulation of the immune response. This review focuses on the mechanism of IFN in treatment and the correlation with Hepatitis B virus. [Nature and Science. 2007;5(3):78-81]. (ISSN: 1545-0740).

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Interferon

Interferon (IFN) was discovered as an antiviral agent during studies on virus interference [1,2]. Isaacs and Lindenmann first reported in 1957 that influenza virus-infected chick cells produced a secreted factor that mediated the transfer of a virus-resistant state active against both homologous and heterologous viruses [1]. This seminal observation, along with similar findings described by Nagano and Kojima in 1958 [2], set the stage for subsequent studies that led to the elucidation of the IFN system in exquisite detail[3].

The IFN system has three types of interferon. IFNs were approved as therapeutics and moved from the basic research laboratory to the clinic. Advances made while elucidating the IFN system contributed significantly in multiple areas of mammalian cell biology and biochemistry, ranging from pathways of signal transduction to the biochemical mechanisms of transcriptional and translational control to the molecular basis of viral pathogenesis.

The system includes cells that synthesize IFN in response to an external stimulus such as viral infection and cells that respond to IFN by establishing an antiviral state[4,5,6]. Animal viruses are inducers of IFN, and are also sensitive to the antiviral actions of IFNs. Some animal viruses encode products that antagonize the IFN antiviral response. The IFN response represents an early host defense, one that occurs prior to the onset of the immune response. IFNs possess a wide range of biological activities in addition to the characteristic antiviral activity by which they were discovered[7].

Success in the basic research laboratory led to the subsequent utilization of IFNs as therapeutics in the clinic. Three kinds of human IFNs, IFN-α, IFN-β, and IFN-λ, have been approved for clinical use by the Food and Drug Administration. Diseases of known viral origin for which IFN-αspecies are most widely used are hepatitis C and hepatitis B (Table 1)[3].

TABLE 1. IFNs approved by the Food and Drug Administration for the treatment of viral hepatitis

IFN	Trade name	Manufacturer	Disease
IFN-α2a	Roferon A	Hoffman LaRoche	Hepatitis C
IFN-α2b	Intron A	Schering	Hepatitis B, Hepatitis C
IFN-αnl (lympho-blastoid)	Wellferon	Glaxo Wellcome	Hepatitis C
IFN-αcon	Infergen	Amgen	Hepatitis C
Peg-IFN-α2b	PEG-Intron	Schering	Hepatitis C

Tremendous progress has been made in understanding the molecular basis of the antiviral actions of IFN, and the strategies that viruses have evolved to antagonize these actions. The actions of IFN are pleiotropic and affect many biological processes in addition to the multiplication of viruses.

Hepatitis B virus

Hepatitis B virus (HBV) is an enveloped virus associated with significant morbidity and mortality[8,9]. HBV causes both acute and chronic liver disease.

The genome of HBV is a partially double-stranded circular 3.2 kb DNA molecule. The DNA genome of the virus is transcribed in the nucleus of the hepatocyte to produce the 3.5, 2.4, 2.1 and 0.7 kb viral transcripts [9,10]. The level of these transcripts are regulated by the enhancer 2/core promoter, the large surface antigen promoter, the major surface antigen promoter and the enhancer 1/X gene promoter, respectively [11,12,13].The 3.5 kb pregenomic HBV transcript encodes the viral polymerase and the nucleocapsid or core polypeptide[14]. The HBV polymerase binds to the packaging sequence (ε) in the pregenomic RNA and this complex is encapsidated by core polypeptides to form an immature viral capsid[15,16,17]. The reverse transcriptase/DNA polymerase activity of the viral polymerase converts the pregenomic RNA into the partially double-stranded DNA genome present in the mature capsid[18]. The mature capsid interacts with the surface antigen polypeptides and subsequently buds into the lumen of the endoplasmic reticulum as a virus particle[19,20,21]. Virions pass through the endoplasmic reticulum and Golgi apparatus prior to release from hepatocytes[22].

Infection with hepatitis B virus is a significant public health concern. Worldwide, an estimated 2 billion people are infected with the hepatitis B virus (HBV)[23].1 A total of 350 million people have the chronic form of hepatitis B infection, 75% of whom live in Asia[24].

most acquired the disease by vertical transmission or during preschool childhood. In the absence of vaccination most exposed neonates and young children will be infected and become lifelong carriers (Fiureg 1)[25]. Chronic infection, particularly of males, is often complicated by the eventual development of cirrhosis and then liver failure or hepatoma. In contrast, primary exposure of adults to hepatitis B virus typically causes acute resolving infection with clearance of the virus (Figure 1).

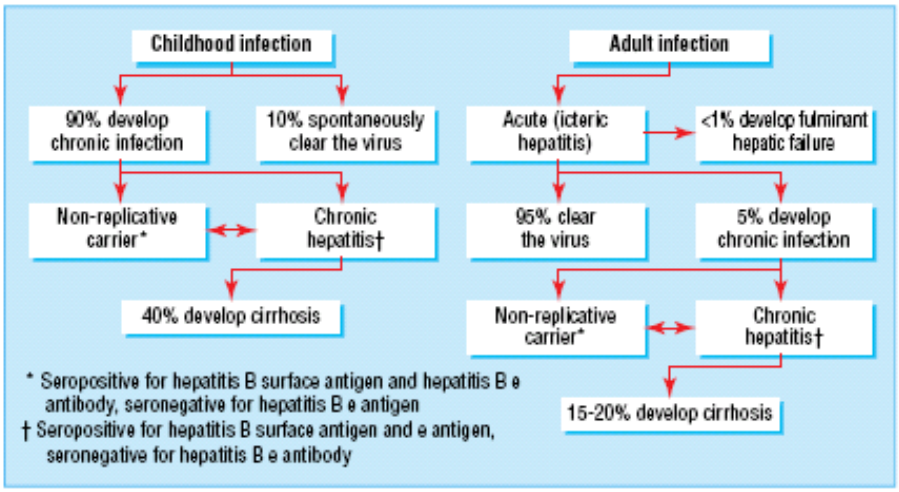

Fig 1 Natural course of primary hepatitis B infection acquired during childhood or adulthood

Chronic infection increases the risk for primary liver cancer. Endemic hepatitis B infection in Asia's large population contributes to primary liver cancer's position as the fourth leading cause of cancer death worldwide [26,27,28].

Interferon treatment

Interferon treatment (5 million units three times weekly for four to six months) increases the conversion rate from high level to low level viral replication in up to 15-20% of patients a year. Response rates are enhanced by higher doses, but the safety and tolerability of high dose interferon are a concern.

Chronic HBV infection is associated with liver cirrhosis and hepatocellular carcinoma[10,11]. A widely used therapeutic intervention is treatment with interferon α (IFN-α). IFN-α therapy can reduce viral replication and liver damage associated with viral infection.

Until recently, interferon alfa (IFN-α)was the only drug licensed for the treatment of chronic hepatitis

B. Interferon treatment is intended to inhibit viral replication and to augment the clearance of virally infected hepatocytes. Among patients with chronic infection, about 5% a year undergo spontaneous conversion from a state of high level viral replication to low level replication.

IFN-α is also generally recognized as the most important therapeutic agent in chronic hepatitis C[29]. In fact, normalization of alanine aminotransferase (ALT) levels and improvement in chronic liver inflammation and necrosis are reported in approximately 50-60% of patients. However, 50% of these responder patients are known to relapse at the end of therapy [30,31].

Conclusion

The use of IFN system reagents in studies of the virus host interaction, both in cell culture and in intact animals, continues to provide seminal contributions not only of mechanisms of viral pathogenesis but also of mechanisms of signal transduction and the transcriptional and translational control of macromolecular synthesis that is so important in many areas of mammalian cell biology and virology. The emergence of new tools and approaches for study of the virus-host interaction, including functional genomics and proteomics, together with advances in the areas of structural biology and combinatorial chemistry for the identification of novel molecules that affect the function of viral and cellular targets, should lead to further insights into the structure-function relationships for the IFN system components.

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