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Interferon: History, Correlation, Mechanism, and limitation

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Abstract. Nowadays, more and more patients suffer from cancer in clinical practice, which has become a hot topic in medical care. The researchers are struggling to find new cancer therapy. Cytokines are a group of protein molecules, and Interferon is the class of them. It has regulation and adjusting ability in the immune system. Moreover, in cancer research, it occupies a momentous role in its ability to combine with other drugs and special effects. Interferon was first found in the 20th century and is widely used in Melanoma, chronic myelogenous leukemia, and hepatocellular carcinoma therapy. In simple terms, Interferon possesses anti-tumor effects by regulating NK cells and T cells. It enhances antigen presentation and supervises the immune system. Additionally, it inhibits tumor angiogenesis, triggers apoptosis and necrosis, and alters the tumor micro-environment. However, Interferon isn't denying that having some limitations like side effects, potential risk, bottlenecks and high costs. These may cause patients to get injured. To discuss these aspects, the essay will be based on the research made before and summarize them to get conclusions. Besides, it also uses comparison to argue the issues. The research has shown that although Interferon has different functions and a long period of research, it is still in active research to find new contributions now, and patients may use the new drug or therapy one day to Interferon's ramifications.

Keywords: Interferon; cancer; cytokines.

1. Introduction

In the last decades, cancer therapy gradually become a hot topic. Along with more cancer patients, they already noticed that traditional therapy like chemotherapy and radiotherapy bring strict damage to their physical and mental health. During the treatment, researchers were struggling to explore new cancer therapies to change this situation. In the middle of the 20th century, scientists found and defined Interferon (IFN) as a group of proteins that can regulate the immune system. In cancer therapy research, Interferon is one of the important cytokines because of its unique properties in the regulation, vessel formation suppression, and anti-tumor effect aspects. As a result, it is regarded as a necessary tool with high potential prospects in cancer therapy.

However, this therapy still has some disadvantages. Specially, it may cause some diseases such as lung cough, inflammatory facilitation, toxins, tolerance, and mental disease. In addition, it also may bring bed influences like ethical problems, and high cost. Altogether, the benefit of Interferon therapy overshadows the drawback. So, the research direction is to promote Interferon to become more positive by finding its ramifications rather than replace it. The improved function and decreased side effects of the new product can benefit patients in many ways. The major theme of this research focuses on the mechanism and function of Interferon in cancer therapy of present research, using comparison to discuss the status of Interferon, and assessing the current limitation of Interferon cancer therapy. The research will use a systematic literature review approach to analyze relevant Interferon research from different platforms like medical databases and journals. Besides, it will compare different types of Interferon to support evidence for other researchers.

2. History

In the 1957s, Interferon was first found in vitro experiment, in the test, Issacs and Lindenmann created a vitro environment and put pieces of choro-allantoic membrane in the buffered salt solution. This reflects some property of the interference. The virus was heated in the test and was named MEL. The

research has shown that the normal membrane was cultivated in the buffer and then tested its ability to interfere. Besides, added other groups to compare with the normal one to get the result. The chart indicates that the extractive which from extracted from the membrane apparently suppresses the interference activity of heated MEL in the same conditions. In a word, when heated MEL interacts with the chorioallantoic membrane, it releases Interferon, which can protect other same types of infected cells [1].

Interferon includes three major types from first found until the present. In particular, type one includes IFN-α and IFN-β, they belong to the same subclass. Besides, Type II only has IFN-γ. To identify these types of Interferon, scientists notice that they have different characteristics in the position of chromosomes. IFN-α is originally known as "leukocyte interferon" because it is generated by leukocytes. It docked with human chromosome nine and murine chromosome four at least fifteen genes and nine pseudo-genes. They don't have any introns. The protein formation contains 166 amino acids without glycosylation sites and has stability in the acid. The IFN-β was regarded as "fibroblast interferondue" to its generation from the interaction of epithelial cells and fibroblasts at viruses or other types of nucleic acids. As the research mentioned IFN-α and IFN-β belong to the same type. Therefore, IFN-β docked with human chromosome nine and without any introns. As a result, the protein that is generated here will acquire the same property as in IFN-α (166 amino acids and only one glycosylation). In the acidic environment, it shows stable ability as well even reflecting higher homology. IFN-γ is an unusual type compared to the other two, it was named "immune interferon". Specifically, the formation is from the lymphocytes sensitized by macrophage facilitation. This procedure is only in the external mitogens [2].

Moreover, the history of IFN-γ is a clear instance to understand the development process. Table 1 shows the development and special issues with time. It is not hard to see that from the first time IFN-γ was found until cloning only used for around 30 years. In the previous research, Wheelock found that human leukocytes had the same antiviral activity compared to IFN-γ in 1965, which is the addition of helping researchers understand the induced virus IFN-γ. Their research has shown that the human white blood cell culture solution that used PHAT to appear the antiviral activity of interferon like. In 1966, researchers launched the immunity induction Interferon. In addition, there was another substance that were found as well, which was plant lectin phytohemagglutinin (PHA), which could also induce Interferon. In the middle of research progress, especially between 1972s and 1973s, two necessary research were launched. They ensured the induced immune IFN-γ had distinction with induced virus IFN-γ, in order to distinguish traditional IFN-α and FN-β. In the late research period, scientists focused on solving issues between becoming more pure and cloning. Specifically, in 20th century 80s, the molecules formula and genetic structure was determined [3]. These three periods show Interferon is in the process of continuous progress. Although the object is the one type of Interferon, it still proves the Interferon family is in the active research from previous to present. Nowadays, Interferon still has a clear prospect and it may bring more contributions in the future.

Table 1. Major issues of IFN-γ history

Year	Event
1965	Induction of an IFN activity in human PBMC by phytohemagglutinin
1966	Antigen-specific induction of IFN activity during virus infections
1972	IFN induced by anti-lymphocyte serum differs physicochemically from classical IFN, IFN-γ was named as 'immune IFN'
1973	IFN produced during DTH reactions differs physicochemically from classical IFN, IFN-γ was named as 'Type II IFN'
1979	Progress in purification
1980	Nomenclature Committee: definitive name 'IFN-γ'
1982	Dimeric structure of IFN-γ suggested

3. Correlation and Mechanism of Cancer Therapy

3.1. IFN-α

IFN-α is an immunotherapeutic protein, which means it is a protein used in immunotherapy. Compared with solid tumors, IFN-α has more influence on hematological malignancies. It has antitumor activity in human malignancies. Moreover, it also shows its ability to prevent tumor growth and development in the mouse model, the CD8+ Cytotoxic T Lymphocytes (CTL) activity is the major reason for this, IFN-α uses unusual ways to modulate CD8+ Tcell growth, it also has an important role in controlling tumor development. In the therapy section, IFN-α has its unique mechanism, it will induce polymorphic effects and target specific gene subsets to the transcript, which has distinguished compare with traditional chemotherapy. As a result, IFN-α is more likely to combine with other interferon like IFN-γ to relevantly treat patients. In tumor metastasis, changes in Major Histocompatibility Complex (MHC) antigen expression is a necessary part. Most of the tumor cell's surface partly or proportionally lacks MHC antigen. Dendritic cells (DCs) are unable to get into the tumor due to the lack activity of T cells, this leads to tumor antigen decrease in the APC DCs. The DCs are the generation of IFN-α with APC, it also play a precious role in anti-tumor immune supervision [4].

Specifically, in melanoma, IFN-α is used as a role of subsidiary, it can directly suppress melanoma cells to grow and decrease the density of microvessel. It may also significantly promote tumor antigenicity and improve the anti-tumor immunity. The research show that IFN-α can stimulate MHC-1 expression, which comes from melanoma and immune cells. Furthermore, IFN-α activates the expression of antigen processing-1 (TAP1) from the MHC-I peptide loading complex. Additionally, IFN-α stimulates natural killer cells and cytotoxic T lymphocytes to secrete factors that enhance anti-melanomolytic activity. Lastly, IFN-α facilitates Th2 to convert to Th1 immunoreaction and enhances transportation from lymphocyte cells to tumor cells. To compare with whether patients who have acquired Interferon therapy or not, after treatment group reflects that CD4 lymphocyte cells gather together in the tumor [5]. IFN-α plays a necessary role in melanoma therapy, its mechanisms include inhibiting melanoma cell growth, improving immunogenicity, and increasing anti-tumor immunity, by boosting MHC-1 and TAP1 expression, and converting TH2 to Th1 to prompt the attack ability of the immune system to against melanoma. The combination of IFN-α with other drugs shows a good reflection in the therapy, which means IFN-α has significant potential ability to treat melanoma.

3.2. IFN-γ

Generally, IFN-γ was regarded as a core role of antitumor immunity. It can directly against tumor cells and has a specific antitumor effect. IFN-γ is generated by NK and natural killer T(NKT) cells and T cells (Th1 with CTLs) in the adaptive arm which is located in the immune system. When the IFN-γ signal is activated, which is results in its exclusive receptor-α subunit binding with it. This subunit is made by IFNGR1 and IFNGR2, The IFNGR2 subunit activates Janus-activated kinases (JAK1 and JAK2), and this part takes responsibility for the intracellular relay of signals. STAT1 is the prime activator and effector molecule and is responsible for helping IFN-γ to signal the downstream. In addition, phosphate STAT1 also can translocation to the nucleus and bind with IFN-γ to active γ-activated sequence (GAS) sites, GAS is located on the different kinds of genes' promoters and activates them to express.

However, the evidence has shown that whether STAT1 exists or not in some cases, IFN-γ also can activate represented non-conventional signaling pathways because IFN-γ can activate the GAS-regulated gene via activating STAT3 [6]. For instance, p21 and p27 are cell cycle regulatory proteins, they can stop the cell cycle to inhibit the proliferation of tumor cells. Besides, it can induce various types of tumor cells to die to fulfill its function in antitumor effect. Moreover, IFN-γ can suppress tumor angiogenesis and activate serine-threonine kinase to induce necro-like regulated cell death, which is called necroptosis. In addition, IFN-γ-mediated secretion by mesenchymal stromal cells in the tumor micro-environment can repolarize relevant tumor macrophages to the phenotype of M1

inflammatory, this will reduce the tumor load from the mouse neuroblastoma model. From another aspect, IFN-γ can support immunosuppressive T cells to develop and drive T cell fragility to enhance anti-tumor immunity and facilitate tumor cell cleaning [6].

3.3. IFN-β

The last major type of entire Interferon is IFN-β, which is widely used in immune response but not in cancer therapy. Simply put, its functions include immune system regulation, cell repair, and proliferation. There are several reasons that IFN-β is not more crucial than IFN-α and IFN-γ. First of all, IFN-β primarily works to protect the virus and treat Multiple Sclerosis (MS). Secondly, it still lacks the amount of clinical research to indicate it involves more effects than IFN-α and IFN-γ.

4. Limatation

Although in the former essay describes some benefit of Interferon in the cancer therapy, it still contains many issues such as bottlenecks, ethical, cost, and side effects. From past few decades, the side effects of Interferon were the hot debate. More dangerous risk issues are pointed by the research in the Interferon therapy. This part will majorly focus on limitation of IFN-α and IFN-γ and provide some potential solutions in future prospects.

4.1. IFN-α

To begin with, researchers notice that the patients who use cancer therapy of IFN-α will cause the cough incidence in lung function inception. Specifically, when only use IFN-α to treat patients may cause a lower percentage of cough than a combination of two different drugs (around 5.6 vs. 9.6%) [7].

Moreover, the therapy may has particular toxicity, which can be classified into different aspects like neuropsychiatric, constitution, and blood influence. The side effects can be divided into occurring urgently and then reducing the side effects following the time-increasing and chronic side effects. The side effects severity directly depends on the maintenance time and the dose of the interferon therapy drug. At acute toxicity, patients form fevers, chills, and rigors in 3 to 6 hours after using IFN. If using INF for a long period, this may cause patients to develop tolerance. At the beginning of treatment, research finds that patients can amend the IFN does to regulate elevated aminotransferase and neutropenia. If the patients do not control these two indexes, it may cause more damage to the liver like fatal hepatotoxicity. For chronic toxicity, 70% to 100% of cancer patients who use IFN are more likely to experience fatigue, 40% to 70% may experience anorexia, and over 30% may experience neuropsychiatric symptoms. Generally, cancer patients have a high risk of developing clinical depression. Research finds that patients who use high doses of INF for a long period have a higher possibility of having clinical depression. In some situations, patients even commit suicide. The strangest result is that the patients who did not have any history of previous psychiatric problems will develop clinical depression as well. The researchers found that the reason is endocrine dysfunction, this can mislead the patient's hormone and stimulate the hypothalamus, significantly impacting the pituitary axis [8].

In the cost aspect, IFN-a melanoma therapy cost is a huge cost for patients and their family. In detail, the costs mainly contain relevant medical expenses, chemotherapy expenses, hospitalization expenses, and medication expenses. The patients who in stage III and IV are required to pay more for treatment. However, the research has shown that the therapy may not bring significant promotion and effects to patients in some cases [9].

4.2. IFN-γ

Besides, IFN-γ also has some limitations. Initially, IFN-γ has some bottlenecks of development. In the last few years, because of the clinical result were different, researchers were constantly discussing that it is a role of tumor promotion or tumor suppression and how to predict the effects. According to

the research, during the process of IFN-γ therapy, the low doses of IFN-γ which is generated in the proportion of tumor can improve the transfer and survival of circulating tumor cell and the concentration of IFN-γ in the TME determines the IFN-γ facilitate or anti-tumor. IFN-γ converts cancer cells to metastatic cancer stem cells via inducing the chemokine receptor CXCR4, this improves the ability of tumor cells and help tumor cells to form the growth environment in the certain area [10]. In addition, it will influences cancer immunoevasion and promote it in some situations. The research has shown that in the mouse model which is SOCS1 gene heterozygosity, the hepatocellular carcinoma induced by carcinogens will build up [11]. Moreover, during the phase of elimination and balancing immunoediting, the immune system exerts selective pressure will lead to elimination of highly immunogenic tumor cells and facilitate the modified cells which are genetically reduced immunogenicity. This will cause them to hide the detection of body and ensure tumor can grow up. IFN-γ signal transfer is regulated by several ways, in this mechanical ways, SOCS1 is also the regulation factor and it shows ability to enhance the carcinogenicity. In the next experiment, researchers recover the expression of SOCS1 in the T cells and B cells. The consequence indicate that the formation of induced cancer is caused by IFN-γ signaling transfer. More evidence indicates that IFN-γ avoid the detecting via activating immune checking cite. In this cite, PD-L1 and PD-L2 expression are regarded as the most necessary mechanism. IFN-γ induced PD-L1 and PDL-2 ligands bind with PD-1, which is immunosuppressive receptor. This interaction will depress the activity of T cells and NK cells. Furthermore, the tumor cells are exposed to the IFN-γ signal transfer where in the tumor micro-environment will be activated the expression of many kind ligands expression, it also prompt the resistance of immune therapy in the checking-cite [6].

In the future expectation, Interferon has a positive prospect. So, researchers are struggling to find new products or new therapies to resolve the limitation. Specifically, the combination therapy of anti-CD20-interferon-α fusion protein can contribute to inducing apoptosis and promote the elimination of B cells lymphoma expression in human CD20. Currently, the experiment shows that anti-CD20-gIFNα shows a high therapy effect during the treatment and effectively retains the activity of ADCC [12]. The new combination drug is still in active research, and the next step will be a clinical trial in the creature body.

5. Conclusion

In a word, from the 20th century to the present, Interferon experienced a long period of changes and development, it developed from basic theory to already gotten some achievements in cancer and other fields of therapy, and it can be seen as advanced. Besides, because of its unique mechanisms as research, it contributes to the changing tumor micro-environment, activating the immune system, and inhibiting tumor growth. However, the therapy still confronts some limitations, which include cost issues, side effects, bottlenecks, and potential risks. Although it has some limitations, it still plays a crucial role in cancer therapy. Its contribution still benefits many patients and brings hope to them. In future research, researchers will look forward to inventing new derivatives or less harmful combined therapy to plan the personal therapy policy for each patient. Following this goal, researchers believe that more and more patients can acquire benefits from future Interferon development by constantly innovating and discover.

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