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Review

The Genes of Interferons and Interferon-Related Factors: Localization and Relationships with Chromosome Aberrations in Cancer

OLGA HAUS*

Department of Clinical Genetics, University Medical School, Bydgoszcz, Poland and Genetic Laboratory, Department of Hematology, University Medical School, Pasteura 4, 50-367 Wrocław, Poland

Abstract. The paper presents a review of data on the localization of interferons (IFNs) and IFN system genes and their relationship with human diseases, mainly cancer. Genes of interferon system proteins are located at the sites of breakpoints of the structural chromosome aberrations in cancer. Thus, any of them are rearranged or translocated in various tumor types. As the activity of these genes plays a role in cancer development, their rearrangements may be one of the crucial points in the pathogenesis of some cancer types. Besides, they also take part in organism immunity against viral infections. Transfection experiments with IFN system genes have proved the influence of these genes on cancer behavior and may serve as a basis for clinical gene therapy. IFN-α and IFN-β genes are located at 9p21-22, the site of frequent homozygotic deletions in cancer. Their loss sensitizes cells to the growth inhibitory actions of exogenous IFNs. The IFN-γ gene, a representative of class II genes, is located at 12q24.1. Transfection of class II IFNs genes to cancer cell lines causes cell proliferation arrest and augments the expression of HLA antigens, which may be clinically useful in stimulating the immune destruction of tumor cells. The interferon regulatory factor 1 (IRF-1) gene is located at 5q31, the site of common deletions in myelodysplastic syndromes (MDS) and secondary leukemias. The loss of heterozygosity of this gene was found in MDS, which proves that IRF-1 may be a tumor suppressor. A transfection of its gene causes neoplastic transformation arrest. The double-stranded RNA-activated protein kinase (PKR) gene is located at 2p21-22, a region which is frequently rearranged in leukemia. Transfection of a wild type PKR gene reverses neoplastic transformation caused by transfection of a mutated PKR gene, proving that PKR acts as a dominant negative cancer suppressor.

Key words: interferon system; gene localization; gene transfer; cancer; chromosome aberrations.

The interferon (IFN) system is one of the major mechanisms involved in human immunity. Its disregulation may result in a grater tendency to infectious diseases and to the development of cancer. This paper presents data on the localization of genes of IFNs and IFN-related factors and their relationships with chromosome changes in cancer as well as the data from transfection experiments that show the regulatory role of these genes in normal and neoplastic growth and development. Transfection experiments may serve as a basis for clinical trials of interferon gene therapy.

* Correspondence to: Dr. Olga Haus, Department of Clinical Genetics, University Medical School, M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland, tel.: 48 52 341 5171, fax: 48 52 340 0969, e-mail: haus@aci.amb.bydgoszcz.pl

IFN-α and IFN-β (Class I Interferons)

IFN-α and IFN-β are pH stable interferons produced by leukocytes (IFN-α) and fibroblasts (IFN-β) in response to viral infections. Both belong to class I interferons. The IFN-α gene family (about 26 genes, including pseudogenes) and the IFN-β gene are located at band 21 of the chromosome 9 short arms (9p21) (Table 1), the latter more distally than the former[29]. IFN-α and IFN-β are intronless genes originating from a common ancestor gene[21, 29]. Translocations involving 9p21-22 bands are frequently found in hematologic malignancies, e.g. t(8;9) (q12;p21-22) in acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma, t(9;11) (p21-22;q23), which transfers the IFN-β gene to the 11q23 band near the MLL gene, in acute myeloid leukemia (AML) M5a type[3].

Human chromosome 9 was preferentially lost from tumorigenic lines of somatic hybrid cells mouse : man. The addition of the lacking chromosome 9 blocked tumorigenicity of those lines[23]. Moreover, 9p21 deletion and/or a loss of heterozygosity (LOH) of the genes located there, are frequently found in many cancers *in vivo* and in neoplastic cell lines, e.g. renal and bladder cancer, glioblastoma, 36% of neuroblastoma cases (LOH at IFN-β *locus*), melanoma, 30% of ALL cases[9, 24, 38]. Frequent LOH of a homologous chromosome band in various neoplasms proves the presence of a tumor suppressor gene on it. Its double-allelic loss unblocks the development of cancer, according to the two-hits theory of KNUDSON[24]. It might be a gene coding for a cell cycle protein p16 (CDKN2, MTS 1), located proximally to the IFN-α genes[22]. Its homozygous deletions are very frequent in cancer and this gene is now recognized as a tumor suppressor gene. This fact does not exclude, however, a nearby location of another tumor suppressor gene, i.e. an IFN-α/β gene.

Pancreas carcinoma cell lines having a high incidence of homozygous deletions of the p16 gene were examined for the frequency of codeletion of IFN genes. Their loss, especially of the IFN-α gene, besides the p16 gene loss, sensitized cells to the growth-inhibitory actions of exogenous IFN-s, which suggests a good therapeutic response of IFN gene-lacking cancers to IFN-α/β. However, the tumorigenic potential of cell lines with IFN genes did not differ much from those without, which allows doubt as to the tumor suppressor features of these IFNs[5].

IFN-γ and Other Class II Interferons

The IFN-γ belongs, together with IFN-τ and others, to class II interferons, pH labile, produced by T and NK

Table 1. Localization of some genes of interferons and interferons-associated factors

Localization	Genes	Chromosome aberrations	References
2p21-p22	PKR	2p21-p22 – AML and many other hematologic malignancies	12, 29
5q31	IRF-1	-5/5q – secondary leukemias, MDS	2, 29, 41, 42
6q23	IFN-γ R1	6q15-q23 – ovary cancer 6q11-q27 – melanoma 6q14-q27 – ALL, CLL, nHL 6q23 – CML-blastic crisis	14, 16, 30
9p21-p22	IFN-α IFN-β1 p16 (MTS 1)	del 6p22 – ALL, L-L, neuroblastoma t(8;9) – ALL, nHL t(9;11) – AML M5a LOH in many tumor types	5, 9, 22, 24, 38
12q24.1	IFN-γ	chromosome breakpoint after radiotherapy	1, 7, 29
13q32	PKR RI (p58)	chromosome breakpoint in AL. Trisomy 13 in MDS	18, 25, 27
21q22	IFN-γ R2 IFN-α/β R ISGs	21q – AML, CML t(8;21) – AML M2 trisomy 21 – Down syndrome	14, 15, 29, 36

Legend: IFN – interferon, IFN R – receptor of interferon, IRF – interferon regulatory factor, p16 – cell cycle protein, tumor suppressor (= MTS 1), ISGs – interferon-stimulated genes, PKR – double-stranded RNA-activated protein kinase, PKR RI – inhibitor of PKR receptor.

AL – acute leukemia, ALL – acute lymphoblastic leukemia, L-L – leukemia-lymphoma, AML – acute myeloblastic leukemia, CML – chronic myeloid leukemia, MDS – myelodysplastic syndrome, nHL – non-Hodgkin lymphoma, LOH – loss of heterozygosity, CLL – chronic lymphocytic leukemia.

cells in response to antigens and mitogens. They are unrelated to class I interferons[10, 29]. The IFN-γ gene, which shares very little homology with class I interferon genes, is located at 12q24.1, where a fragile site FRA 12D is also located (Table 1). This band is a frequent chromosome breakpoint after radiotherapy[1]. Moreover, trisomy 12 is one of the major karyotypic changes in chronic lymphocytic leukemia (CLL) [7]. It may be that the triple dose of the IFN-γ gene is responsible for some symptoms of more aggresive forms of CLL, characterized by the presence of trisomy 12.

IFN-γ acts by activating interferon regulatory factor 1 (IRF-1) and by stimulating its translocation to the cell nucleus[34].

The antineoplastic activity of IFN-γ is partially due to the induction of apoptosis independent from p53. IFN-γ increases the sensitivity of cancer cells to cell death mediated or stimulated by TNF-α, anti-Fas antibody, γ-irradiation and cytostatic drugs. Through activation of IRF-1, IFN-γ induces many apoptosis-related genes, such, as Ice (IL-1β converting enzyme gene) or the apopain gene[34, 39]. Of the BCL-2 apoptotic gene family it directly induces BAK, whereas another member of this family, the BAX gene, is induced on the p53 apoptotic pathway[34].

Additionally, IFN-γ acts as an antineoplastic factor by upregulating a lipopolysaccharide-induced production of TNF-α. It also increases the transcription of the TNF-α gene, the stability of the TNF-α mRNA, as well as the expression of both types of TNF-α receptors on a variety of different cell types[10]. IFN-γ exerts its antineoplastic activity synergistically not only with TNF-α, but also with IL-1, which enhances the synthesis of its receptor at the mRNA level, and IL-2, with which it increases the cytostatic activity of NK cells. IFN-γ stimulates the expression of IL-2 receptors[10, 40].

Transfection of class II IFN cDNA to a myeloma cell line caused cell growth inhibition and upregulation of the expression of CEA and HLA class I and class II antigens. This approach may be useful in stimulating the immune destruction of tumor cells[43].

IFN-γ gene transfection to a renal cancer cell line was an experimental approach to clinical gene therapy. Exogenous IFN-y caused morphologic changes of cells, cell growth and proliferation arrest, augmented secretion of intrinsic IFN-γ and augmented expression of HLA, mainly class II, antigens. The two latter features were also present after irradiation and cryopreservation of transfected cells, thus giving a basis for an application of this method to autologous renal cancer vaccines[32].

Moreover, the knock-out of the IFN-γ gene from mice bearing B16F10 melanoma caused multiple defects of immunological functions, e.g. a loss of anticancer activity of IL-12 and an inhibition of lymphokine activated killer (LAK) induction[4, 8].

Transfection experiments with IFN genes are performed not only in the field of oncology. Recently, *in vitro* transfection of the IFN-γ gene to endothelium cells resulted in not naturally seen IFN-γ expression and secretion by these cells, and also in a reduced proliferation of cocultured vascular smooth muscle cells, such proliferation and migration being known as a step in the multistep atherosclerosis pathogenesis. The therapeutic implications of this experiment may concern all vascular proliferative diseases[37].

Interferon Regulatory Factor 1

IRF-1, activated by IFN-γ, is a positive transcriptional regulator of class I IFNs. Transfection experiments confirmed that it also induces the expression of its opponent, IRF-2, and of interferon-stimulated genes (ISGs) [18]. The IRF-1 gene is located at 5q31 (Table 1). Chromosome 5 monosomies and deletions of its long arms are common aberrations in myelodysplastic syndromes (MDS) and secondary acute myeloid leukemias (sAML) [41]. This observation allows the suggestion that a tumor suppressor gene may be located on 5q. LOH of the IRF-1 gene and lack of its expression and the expression of IRF-1 – induced double-stranded RNA--activated protein kinase (PKR) was also shown in MDS[2]. This may prove that IRF-1 may be a sought tumor suppressor[42].

A cotransfection of IRF-1 gene reversed neoplastic transformation induced by transfection of the IRF-2 gene in a NIH 3T3 mouse fibroblast cell line[13].

RT-PCR measurement of the ratio of IRF-1 to IRF-2 expression in chronic myeloid leukemia (CML) may have a clinical significance. It was shown that IRF-1/IRF-2 > 2.0 in about 50% of patients with cytogenetic and molecular response to IFN-α and in only 10% of non-responders. Complete remission (CR) after IFN-α was easily obtained in patients with IRF-1/IRF-2 expression > 5, while no remission was observed in those with IRF-1/IRF-2 < 2.5[19].

IFN-γ receptor 1

The IFN-γ R1 gene is located at 6q23.1, near the c-myb oncogene (Table 1)[29, 30]. Breaks and deletions of a part of the chromosome 6 long arms (q11-q27) are

frequent in various neoplasms, e.g.: ovary cancer (6q15-q23) and lymphoid malignancies (6q14-q27)[16]. Breaks at 6q23, which besides the c-myb oncogene may rearrange the IFN-γ R1 gene, occur in AML and the blastic phase of CML[14].

Transfection of the human IFN-γ R1 gene to mouse cells caused a strong binding of human and mouse IFN-γ. However, a successive activation of genes involved in the IFN pathway did not appear. Thus, the presence of an unchanged IFN-γ R1 alone is not sufficient for the development of the full immune response to IFN-γ. Its absence, however, may cause a severe immune response failure. A molecular analysis in 4 children with unexplained genetic susceptibility to severe mycobacterial infection showed that all had a point mutation in the IFN-γ R1 gene that led to the absence of this receptor[17, 33].

IFN-γ R2, IFN-α/β and IFN-Stimulated Genes

The 33 kb gene for IFN-γ receptor 2, a gene for the common class I interferon receptor, as well as many interferon stimulated genes (ISGs), e.g. the MxA protein gene, are located at 21q22 (Table 1). This region is a common breakpoint in CML and AML, mainly in AML M2, where it is involved in a translocation t(8;21)(q22;q22), characteristic of this AML type[15, 29, 36]. The breaks at 21q22 cause mainly a rearrangement of the hematopoiesis regulator – AML-1 gene. However, structural aberrations of this region may cause changes of gene position that could influence the activity of IFN-related genes. Moreover, an acquired trisomy 21 is a common change in myeloid disorders and additional copies of IFN-related genes may be responsible for some disease features[14]. The congenital trisomy 21 provides a basis for the Down's syndrome phenotype, with its lack of immunity and leukemia proneness. Horisberger[20] showed that patients with Down's syndrome have an increased expression, i.e., increased antiviral activity, of MxA protein. Besides this, their cells reveal an increased sensitivity to IFNs *in vitro* as a result of the augmented dose of IFN-related genes. This does not, however, protects the patients from influenza and other upper respiratory tract infections.

Double-Stranded, RNA-Activated Protein Kinase (PKR) and an Inhibitor of Its Receptor (PKR RI)

As mentioned above, PKR is an IFN-stimulated gene activated by IRF-1 and double-stranded RNA. It is located at 2p21-p22 (Table 1)[29]. The aberrations of this region occur nonrandomly in many hematologic malignancies, especially AML. It raises the possibility of a certain role for this protein kinase in leukemogenesis. PKR protein displays an antiviral and anticancer activity[12].

Transfection of a mutated PKR gene to NIH 3T3 provoked a neoplastic transformation of the cells. Their *in vivo* inoculation to mice resulted in mutiple tumor development. Cotrafection with wild type PKR gene changed this pattern: after a long latency period only a small number of tumors developed[31]. This indicates that wild type PKR may function as a dominant negative tumor suppressor gene[21]. Moreover, some oncogenic viruses act by invaction of PKR protein, similarly to oncogenic viruses acting by Rb tumor suppressor protein inactivation[6].

PKR RI (p58) is located at 13q32 (Table 1). It regulates the activity of PKR during infection or in its absence. PKR RI has oncogenic properties when overexpressed[25]. Aberrations of chromosome 13 are found in many human neoplasms, particularly acute leukemias. Trisomy 13 has been described in AML and myelodysplastic syndromes[27].

All the transfection experiments mentioned above allow the recognition of the functions and activities of interferons and interferon-related factors, giving information about their usefulness and possible results of their application in immunomodulatory gene therapy. The IFN-γ gene is the only one among all IFN system genes that has been already used in clinical gene therapy to overcome primary and metastatic cancers[11, 35]. However, there were only a few accepted clinical trials of therapy with the IFN-γ gene. The examples are presented in Table 2. The methods used in these trials were autovaccination or tumor infiltrating lymphocytes (TILs) transfection. In the majority of the trials, the IFN-γ gene was cotransfected with a gene of IL-2, which acts synergistically to IFN-γ[10, 28].

Table 2. The examples of clinical protocols of interferon γ gene therapy (after[28], modified)

Tumor	Gene	Method of therapy
Melanoma	IL-2 + IFN-γ	TIL transfection
	INF-γ	auto-vaccination
Renal cancer	IL-2 + IFN-γ	TIL transfection
Neuroblastoma	IFN-γ	auto-vaccination
Prostate cancer	IL-2 + IFN-γ	allo-vaccination

Legend: IL-2 – interleukin 2, IFN-γ – interferon γ, TIL – tumor infiltrating lymphocytes.

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