**INTERFERON-INDUCIBLE GENES - TRANSCRIPTION REGULATORY REGIONS DATABASE (IIG-TRRD).**

ANANKO E.A., BAZHAN S.I., BELOVA O.E.

Institute of Cytology and Genetics, (Siberian Branch of the Russian Academy of Sciences), 10 Lavrentieva ave., Novosibirsk, 630090 Russia

State Research Center of Virology and Biotechnology Vector, Koltsovo, Novosibirsk region, 133159 Russia

Keywords: interferon-inducible genes, transcription, regilatory regions, database, eukariotes, mechanism, transcription factor, gene networks, regulatory feedbacks

The volume of experimental data on regulation of functioning of both the interferon genes proper and IFN-inducible genes is growing fast. To generalize and systematize these data, we have designed an informational system for description of interferon-inducible gene transcription regulation IIG-TRRD (Interferon-Inducible Genes - Transcription Regulatory Regions Database). It is a constituent of the TRRD database [A.E. Kel’ et al., 1997] on transcription regulatory regions of eukaryotes and consists of two major parts: (1) a formalized description of the structure of gene regulatory regions and peculiarities of their regulation and (2) a hypertext-based description of interferon system functioning containing tables, figures, and schemes. The IIG-TRRD helps to visualize the functional interactions of genes and their products.

The current release of IIG-TRRD compiles the data on over 60 IFN-inducible genes and is available at <http://www.bionet.nsc.ru/trrd/>.

The information system for description of interferon-inducible gene transcription regulation IIG-TRRD (Interferon-Inducible Genes - Transcription Regulatory Regions Database) is a section of the TRRD database [A.E. Kel' et al, 1997] on transcription regulatory regions, compiling the available information on regulation of gene systems controlling different functions of eukaryotic organisms [Podkolodnaya and Stepanenko, 1997; Anan’ko et al., 1997; O.V. Kel' and A.E. Kel’, 1997; Merkulova et al., 1997; Ignat’eva et al., 1997]. IIG-TRRD consists of two major parts: (1) a formalized description of the structure of gene regulatory regions and peculiarities of their regulation in the TRRD format [A.E. Kel et al., 1995] and (2) a hypertext-based description of interferon system functioning containing tables, figures, and schemes, both cross-linked and linked to the formalized description. IIG-TRRD helps to follow the functional interactions of genes and their products. The interface of the IIG-TRRD front page listing its main sections is shown in Fig. 1. All section have a hierarchical structure and contain a number of cross-linked subsections.

Interferons are cytokines with a wide range of biological action. Interferons are involved in regulation of antiviral response, cell proliferation and differentiation, modulation of immune

and inflammatory responses through transcription regulation of IFN-inducible genes coding for various proteins. Investigation of the mechanisms of interferon expression regulation and their effects on the target genes is of great theoretical and applied importance, since it contributes to the understanding of the causes of organism function disorders. Analysis of the information from the IIG-TRRD database has demonstrated that the gene sets induced by type I and II interferons are partially overlapping (Table 1). IFN-inducible genes code for a variety of products: enzymes, nucleotide-binding proteins, transcription factors, major histocompatibility complex (MHC) class I and II antigens, regulatory proteins, lymphocyte antigens, certain cytokines and their receptors, Fc receptors with high affinity for IgG, and a number of proteins with yet unknown functions (Table 1). As a result, a complex gene network [Kolpakov et al.,

Table 1. Interferon-inducible genes contained in the IIG-TRRD database

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Gene | Number of TRRD\* | IFN inducibility | | Function |
|  | entries | a/b | g |  |
| REGULATORY PROTEINS | | | | |
| Transcription factor IRF-1 | 2 | + | + | Transcription regulation of |
| Transcription factor ICSBP | 1 | - | + | interferons and interferon-inducible |
| Transcription factor IRF-2 | 1 | + | - | genes |
| Transcription factor HNF-3b | 1 | . | + | Regulation of hepatocyte-specific gene expression |
| IP-10 | 1 | + | + | Inflammatory response |
| Interleukin-6 | 1 | - | + | Immunomodulatory effect |
| Interleukin-2 | 1 | + | - | Immunomodulatory effect |
| Serine protease inhibitor Spi2.1 | 1 |  |  | Antiproliferative effect |
| Cyclin-dependent kinase inhibitor CDKIp21 | 1 |  | + | Antiproliferative effect |
| Inhibitor C1INH | 1 | + | + | Immunomodulatory effect |
| Genes 202, 204 | 2 |  |  | Antiproliferative effect |
| Mx protein | 1 | + | - | Antiviral activity |
| Complement Bf protein | 1 | - | + | Immunomodulatory effect |
| ENZYMES | | | | |
| 2'-5' oligoadenylate synthetase OAS | 2 | + | - | Antiviral effect |
| Tryptophanyl-tRNA synthetase IFP-53 | 1 | +/- | + | Tryptophan metabolism |
| Macrophage inducible nitric oxide synthase iNOS | 1 | - | + | Macrophage cytotoxicity |
| Indoleamine 2,3-dioxygenase IDO | 1 | +/- | + | Antiproliferative effect |
| Protein kinase PKR | 1 | + | + | Antiviral and antiproliferative effects, activation of NFk B |
| LYMPHOCYTE ANTIGENS | | | | |
| Lymphocyte antigens | 2 | + | + | Lymphocyte activation |
| RECEPTORS | | | | |
| IgG receptors Fcg RI | 2 | - | + | Antibody exposure |
| IL receptors | 2 | - | + | Increase in response to IL-2 |
| CELL ADHESION PROTEINS | | | | |
| ICAM-1, VCAM-1 | 2 | - | + | Antiinflammatory effect |
| NUCLEOTIDE-BINDING PROTEINS | | | | |
| Guanylate-binding proteins | 3 | + | + | Antiviral and antibacterial effects |
| RNA-binding protein | 1 | + | +/- | Antiviral effect |
| MAJOR HISTOCOMPATIBILITY COMPLEX COMPONENTS | | | | |
| MHC class II: | 16 | - | + | Antigen presentation, stimulation of T- and B-cell-mediated |
| MHC class I | 8 | + | + | immunity |
| OTHER GENES | | | | |
| p44, IFI-56K, ISG-15, ISG-54, and 6-16 | 5 | + | - | Functions unknown |
| Acid cytokeratin K17, gene mig | 2 | - | + |  |

1998] that regulates the functioning of interferon system is formed, that is, the system regulating interferon induction and action. A fragment of this gene network involving major relevant transcription factors (STAT1a , ISGF3, IRF-1, and IRF-2) is shown in Fig. 2.

Regulation of interferon system functioning illustrates the peculiarities of gene network organization:

1. Specificity of action, providing a directional response of the organism to different external stimuli (viral infection, etc.).

2. Functional crossing of gene activation pathways in various gene network nodes, providing the reliability of physiological response.

3. Occurrence of positive and negative regulatory feedbacks, that is, chains of events that lead to increase or decrease in gene expression. The different directionalities in regulatory feedbacks along with their nonsimultaneity allows the system to perform self-control and optimize the response depending on the strength of external stimuli through either increasing its efficiency or switching off the system.

4. Synergistic action of several factors providing nonadditive increase in response to simultaneous action of several inducers [Anan'ko et al., 1997].

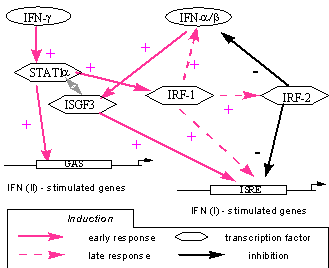


Figure 1. The main components of the IFN gene network

The IIG-TRRD is linked with the GeneNet system for automated gene network visualization [Kolpakov et al., 1998], generating a more complete scheme of the gene network for IFN-dependent antiviral response.

**Acknowledgments**

The work was partially funded by the Russian Human Genome Program (12312 GCh-5), the State Committee of Science and Technology of the Russian Federation ("Database of regulatory genomic sequences"), Russian Foundation for Basic Research (96-04-50006), the US Department of Energy (No. OR00033-93CIS002), and Siberian Division of the Russian Academy of Sciences.

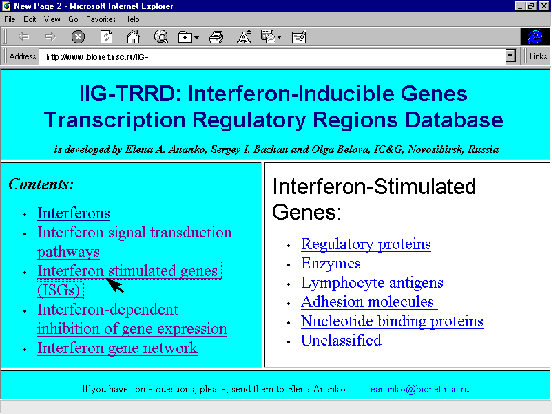


Figure 2. Interface of IIG-TRRD front page

**References:**

1. E.A. Ananko, S.I. Bazhan, O.E. Belova, and A.E. Kel, “Mechanisms of transcription of the interferon-inducible genes: a description in the IIG-TRRD information system” Mol. Biol. (Mosk,), 31, 592-605 (1997).
2. E.V. Ignateva, T.I. Merkulova, O.V. Vishnevskii, and A.E. Kel, "Transcription regulation of lipid metabolism genes as described in the TRRD database" Mol. Biol. (Mosk.) 31, 575-591 (1997)
3. A.E. Kel, N.A. Kolchanov, O.V. Kel, A.G. Romashchenko, E.A. Anan’ko, E.V. Ignateva, T.I. Merkulova, O.A. Podkolodnaya, I.L. Stepanenko, A.V. Kochetov, F.A. Kolpakov, N.L. Podkolodny, and A.N. Naumochkin, “TRRD: database on transcription regulatory regions of eukaryotic genes” Mol. Biol. (Mosk.), 31, 521-530 (1997).
4. O.V. Kel, A.G. Romaschenko, A.E. Kel, E. Wingender, and N.A. Kolchanov, “A compilation of composite regulatory elements affecting gene transcription in vertebrates” Nucleic Acids Res., 23, 4097-4103 (1995).
5. O.V. Kel and A.E. Kel, “Complex gene network in cell cycle regulation: central role of the E2F family” Mol. Biol. (Mosk.), 31, 548-561 (1997).
6. Kolpakov F.A., Ananko E.A., Kolesov G.B., Kolchanov N.A. “GeneNet: a database for gene networks and its automated visualization through the Internet” Bioinformatics, in press., (1998).
7. T.I. Merkulova, V.M. Merkulov, and R.L. Mitina, “Glucocorticoid regulation mechanisms and glucocorticoid-controlled gene regulatory regions: description in the TRRD database”Mol. Biol. (Mosk.), **31,** 605-615 (1997).
8. O.A. Podkolodnaya and I.L. Stepanenko, “Mechanisms of transcription regulation of the erythroid-specific genes.” Mol. Biol. (Mosk.), **31,** 562-574 (1997).