Molecular Biology, Vol. 39, No. 5, 2005, pp. 675–683. Translated from Molekulyarnaya Biologiya, Vol. 39, No. 5, 2005, pp. 776–785.

PRIORITY PUBLICATIONS

UDC 575.1:575.8:612.112

Expression Patterns of the Human and Mouse *IFGP* Family Genes

S. A. Ershova[1], A. M. Najakshin[1], L. V. Mechetina[1], M. M. Peklo[2], A. Ya. Shevelev[2], T. N. Vlasik[2], N. A. Chikaev[1], and A. V. Taranin[1]

[1] *Institute of Cytology and Genetics, Siberian Division, Russian Academy of Sciences, Novosibirsk, 630090 Russia*
e-mail: taranin@bionet.nsc.ru
[2] *Institute of Experimental Cardiology, Cardiology Research Center, Ministry of Health and Social Development of the Russian Federation, Moscow, 121552 Russia*

Received May 11, 2005
Presented for publication by G.A. Nevinskii

Abstract—The *IFGP* gene family has recently been found in human and mouse cells and is structurally related to the leukocytic Fc receptor genes. Expression of six human and four mouse *IFGP* genes was studied. Apart from mouse *IFGP2*, the genes of the family are expressed predominantly in hematopoietic cells. Expression of human *IFGP1–IFGP5* and mouse *IFGP3* is restricted to B cells. Mouse *IFGP1* is expressed in B cells and, possibly, in nonlymphoid cells. *IFGP6* is specifically expressed in CD8+ T cells and natural killers. Alternative splicing was demonstrated for the first time for the human *IFGP1* and *IFGP6* mRNAs. The alternative transcripts code for an IGFP1 isoform devoid of the transmembrane domain and an IFGP6 isoform with a changed cytoplasmic tail. It was assumed that the receptors of the family play a role in controlling differentiation and/or function of effector lymphocytes of the three main types: B cells, CD8+ T cells, and natural killers.

Key words: human and mouse *IFGP* genes, RT–PCR, gene expression pattern, B cells, CD8+ T cells, natural killers

INTRODUCTION

Classical Fc receptors (FcR) of leukocytes are a group of structurally related proteins belonging to the immunoglobulin superfamily and are divided into four main classes: FcγRI, FcγRII, FcγRIII, and FcεRI. Owing to the capability of binding the constant region of IgG and IgE antibodies, FcR provide a link between humoral and cell-mediated immunity [1, 2]. These proteins are involved in phagocytosis, antibody-dependent cell cytotoxicity, immediate hypersensitivity, and regulation of immunoglobulin synthesis. Extracellular regions of FcR consist of two (FcγRII, FcγRIII, and FcεRI) or three (FcγRI) Ig-like domains, which can be classified into three structural subtypes: D1, D2, and D3. By signal properties, FcR are classified as inhibiting and activating. The former include FcγRIIb, whose cytoplasmic region contains an immunoreceptor tyrosine inhibiting motif (ITIM). Other FcR activate the effector functions of leukocytes either by utilizing their immunoreceptor tyrosine activating motif (ITAM) located in the cytoplasmic region or by forming receptor complexes with ITAM-containing signal subunits of FcRγ or TCRζ.

A new group of genes coding for proteins homologous to FcR has recently been discovered in the human genome independently in several laboratories. Two of these genes, *FCRL* and *FCRL2*, code for intracellular proteins [3, 4]. *FCRL* has been alternatively termed *FREB* or *FcRX* [5, 6]. The other genes form a separate family, *IFGP*, also known as *IRTA* or *FcRH* [7–11]. Some members of the family have been designated as *SPAP1, SPAP2*, and *BXMAS1* in other studies [12–14]. The human *IFGP* family includes six functional genes, *hIFGP1–hIFGP6.* These genes all code for transmembrane receptors whose extracellular regions harbor three to nine Ig-like domains (Fig. 1). In addition to D1–D3, domains of two other subtypes, D4 and D5, have been found in receptors of the family. Each receptor has a unique combination of domains. The cytoplasmic regions contain various combinations of ITIM- and/or ITAM-like motifs. The diversity of domain architecture in the intracellular regions and patterns of signal motifs in the intracellular regions is further increased as a result of alternative splicing [8, 9, 12, 13].

The mouse *IFGP* family includes only four genes (Fig. 1). We were the first to describe two of these genes, *mIFGP1* and *mIFGP2* [7]. Analysis of the mouse genome sequence suggested the existence of two other genes, which were termed *mIFGP3* and *mIFGP6.* The structure and expression of *mIFGP3*, termed *mFcRH3*, have been characterized recently [15].

0026-8933/05/3905-0675

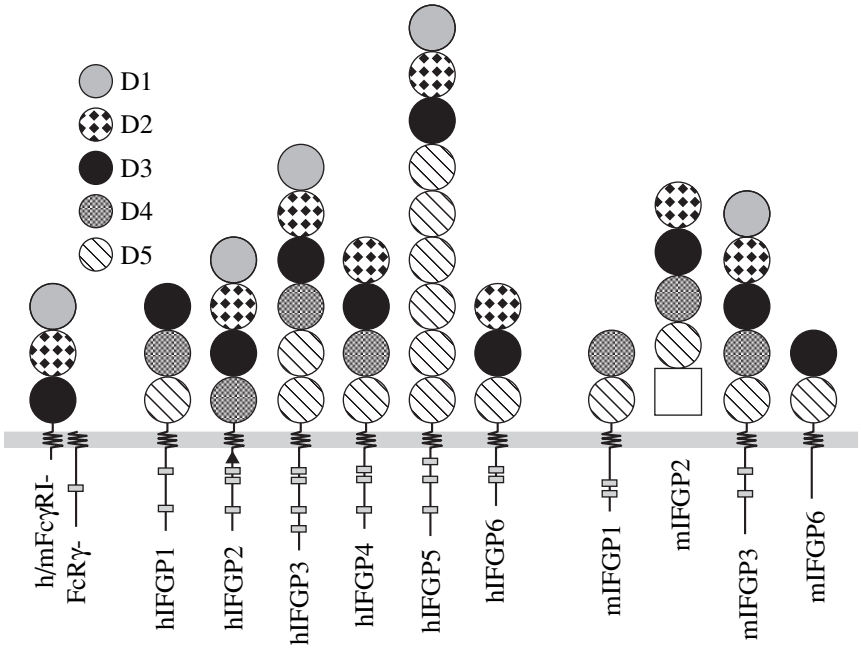

Fig. 1. Domain structure of the human (h) and mouse (m) IGFP-family proteins and FcγRI. Here and in Fig. 4a, circles show Ig-like domains, and squares, scavenger-like domains. Filling variants reflect the structural similarity of domains. The transmembrane region is shown in broken lines. The thick gray line depicts the cell membrane. Gray bars, Tyr residues of classical ITAMs/ITIMs in the cytoplasmic regions of the receptors. A black triangle, Pro-rich motif.

It is noteworthy that each of the ten human and mouse genes of the *IFGP* family codes for a protein with a unique domain architecture (Fig. 1). Phylogenetic analysis of the relationships among the human, mouse, dog, rat, and opossum genes, along with their chromosomal locations, has shown that *mIFGP1, mIFGP4*, and *mIFGP6* are orthologous to *hIFGP1, mIFGP5,* and *hIFGP6*, respectively (our unpublished data). The mouse genome does not contain orthologs of *hIFGP2, hIFGP3,* and *hIFGP4*. In contrast, orthologs of *mIFGP2* have been found only in rodents and carnivores. This gene codes for a mosaic secreted protein that includes four Ig-like domains of the D2, D3, D4, and D5 subtypes and has a C-terminal domain belonging to the scavenger receptor superfamily. It should be noted that the chromosomal location and similarity of the encoded amino acid sequences indicate that *hIFGP6* and *mIGFP6* are orthologs of rat *gp42*. The rat gene was described as early as in 1989 and codes for a GPI-anchored protein that has an unknown function and occurs on the surface of activated natural killer (NK) cells [16, 17]. In contrast to *gp42*, *hIFGP6* and *mIGFP6* code for typical type I transmembrane receptors with cytoplasmic regions (our unpublished data).

The ligands of the IFGP receptors are still unknown. Unlike classical FcR, the IGFP proteins are probably incapable of binding immunoglobulins. Analysis of the expression of *hIFGP1–hIFGP5* has yielded somewhat different results in different labs. In particular, Davis *et al.* [10] and Miller *et al.* [9] have shown that *hIFGP3*/*FcRH3*/*IRTA3* is expressed in lymphoid tissues predominantly by lymphocytes. Xu *et al.* [13], who described this gene as *SPAP2*, have not detected its expression in the spleen and several other lymphoid tissues. According to these authors, *hIFGP3* is expressed in the kidneys, the adrenals, and the uterus and, among all cell lines examined, in the HeLa fibroblastoid cell line [13]. Some differences in mRNA distribution among various cells have been reported for *hIFGP1* and *mIFGP1*. It is still unclear which tissues and cells express *hIFGP6* and *mIFGP6*.

In this study, we compared the expression of the six human *IFGP*-family genes in various tissues, subpopulations of peripheral blood leukocytes, and transformed cell lines. Expression of the four mouse genes of the *IFGP* family was studied in various tissues and cell lines. Our results support the previous data about differential expression of *hIFGP1–hIFGP5* in B cells. We demonstrated for the first time that expression of *hIFGP6* is restricted to cytotoxic CD8+ T and NK cells. Moreover, we found that the *hIFGP1* and *hIFGP6* transcripts are alternatively spliced, which changes various regions of the encoded proteins.

EXPERIMENTAL

Isolation of blood cell subpopulations. We used peripheral and umbilical cord blood of healthy donors. Peripheral blood mononuclear leukocytes

Primers used for RT–PCR and the temperature of their annealing

Target cDNA	Nucleotide sequence	Annealing temperature, °C
hIFGP1	5'-gaggcatctctaggtaccat-3' and 5'-agcctggaatagatgtctaag-3'	58
hIFGP2	5'-gatgcattggatatggagacga-3' and 5'-gtagtctggatctcagagtata-3'	60
hIFGP3	5'-gagctgtttctacatcctgtgct-3' and 5'-aatggtgcaggctgtttcctgtg-3'	68
hIFGP4	5'-cattctggaaactactcctgtga-3' and 5'-gcaggtgataagcctcaagcat-3'	68
hIFGP5	5'-ttccaaggagagagagtg-3' and 5'-cacctgtatccaggatct-3'	54
hIFGP6	5'-cagcatatgctgtacctccaagcctg-3' and 5'-catctcgagcttcttgggctcactc-3'	54
hIFGP6b	5'-aggagtgaaggacagttctatc-3' and 5'-gcgctgtagcttgtttgtacc-3'	64
hIFGP6a	5'-gtgaagccaggtctgctgag-3' and 5'-gcgctgtagcttgtttgtacc-3'	64
mIFGP1	5'-gtgtgtggggaaattgggctg-3' and 5'-cagcaccctctggaggaggag-3'	66
mIFGP2	5'-gaggatccctgtatctcaag-3' and 5'-cagaaagtgctgggtaagac-3'	60
mIFGP3	5'-tgccaagccgacagcttact-3' and 5'-ggaaatgccctgctgacaaa-3'	60
mIFGP6	5'-ggtggaccccaagaatccaac-3' and 5'-gcaatgaccatccctccaagc-3'	60

(PML) umbilical cord blood mononuclear leucocytes (CML) were isolated using a lymphocyte separation medium (ICN, United States) as recommended by the manufacturer. A portion of PML were subjected to mitogenic stimulation in the presence of 5 μg/ml concanavalin A (ICN), phytohemagglutinin (Pan Eco, Russia), and/or the *Phytolacca* mitogen (Gibco, United States) at 37°C in a CO_2 incubator for three days [18, 19]. The PML activation was estimated by morphological criteria (the appearance of blasts and mitoses) and by the presence of CD25 and CD71. NK cells were isolated from PML with the use of NK isolation kit II (Miltenyi Biotec, Germany) as recommended by the manufacturer. Other cell subpopulations were isolated by magnetic sorting with Dynabeads M-450 (Dynal Biotech, United States) or streptavidin magnetic microbeads (Miltenyi Biotec) as recommended by the manufacturers.

Hematopoietic cell lines. Cells of human and mouse hematopoietic lines were incubated in RPMI-1640 supplemented with 2 mM *L*-glutamine, 10% fetal bovine serum, and 50 μg/ml gentamicin sulfate in a CO_2 incubator at 37°C for two days.

RNA isolation. Total RNA was isolated from human PML subpopulations, human and mouse hematopoietic cell lines, and human and mouse tissues according to a published protocol [20].

RT–PCR. Total cell RNA was used to synthesize cDNA as recommended by Clontech (United States). The resulting cDNA was denatured at 94°C for 5 min and amplified for 30 (in the case of PML and cell line cDNAs) or 45 (in the case of tissue cDNAs) cycles of 94°C for 30 s, 54–68°C for 30 s, and 72°C for 45 s to 2 min. The primers and their annealing temperatures are given in the table. The cDNA quality was checked by amplification of the β-actin cDNA with the primers 5'-cgcgagaagatgacccagatc-3' and 5'-ttgctgatccacatctgctgg-3'.

Synthesis and cloning of the *hIFGP1b* and *hIFGP6b* cDNAs. Tonsillar cDNA was denatured at 94°C for 5 min and amplified with specific primers in 45 cycles of 94°C for 30 s, 62–64°C for 30 s, and 72°C for 2 min. The primers were 5'-taggtaccatccctgacctg-3' and 5'-aggagccggcaggaatctggttc-3' (annealing temperature 62°C) in the case of *hIGFP1b* and 5'-ttccctccgctgtgccagaa-3' and 5'-gaacccagggttcaggtgct-3' (annealing temperature 64°C) in the case of *hIGFP6b*. The RT–PCR products were cloned in pBluescript KS (Stratagene, United States) and sequenced in an ABI PRISM 310 automated fluorescence sequencer (Applied Biosystems, United States).

RESULTS AND DISCUSSION

Expression of the Human *IFGP* Genes in Tissues and Organs

The cDNAs of the six human *IFGP* genes were cloned previously with the use of 5'- and 3'-RACE with tonsillar mRNA [7]. To study the tissue distribution of the *IFGP* transcripts, several pairs of primers were synthesized for each cDNA by RT–PCR. Preliminary analysis of control plasmids and mRNAs of several human tissues allowed us to select the primer pairs that ensured specific cDNA amplification for the six genes (table).

RT–PCR analysis showed that the *hIFGP* genes are expressed in the tonsils and the spleen but not in

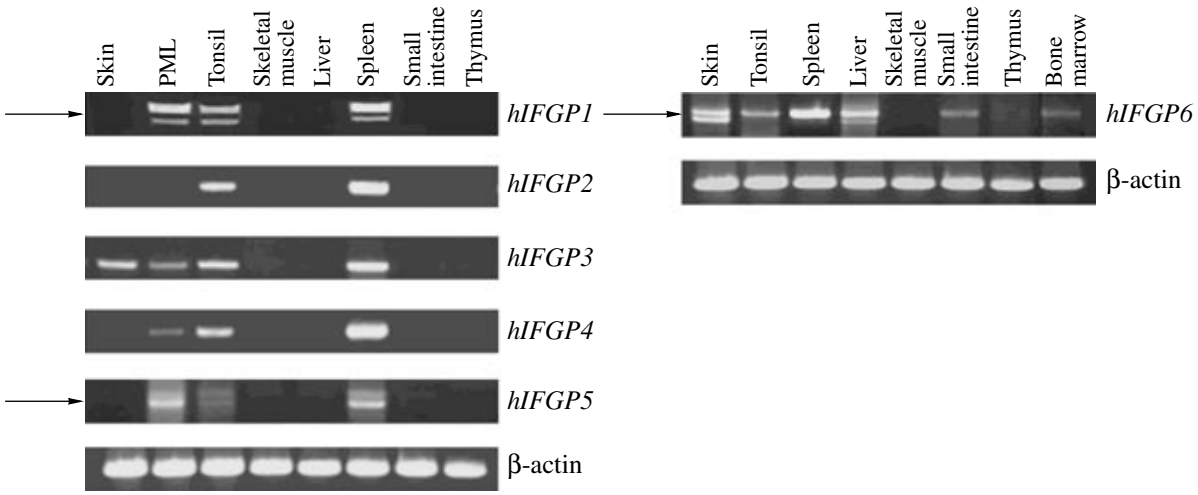

Fig. 2. Profiles of *hIFGP1–hIFGP6* expression in tissues and organs. RT–PCR products were synthesized with gene-specific primers from total RNAs of human tissues and organs and separated electrophoretically. Here and in Figs. 3 and 5, fragments corresponding in size to the control ones are indicated with arrows.

the thymus (Fig. 2). The transcripts of all but one (*hIFGP2*) gene were detected in PML. Expression of two genes, *hIFGP3* and *hIFGP6*, was observed in nonlymphoid tissues. The *hIFGP3* transcripts were found in the skin, and the *hIFGP6* transcripts were found in the skin, the liver, and the small intestine. The results of RT–PCR were verified by Northern blotting and/or dot hybridization with commercial poly(A^+)-RNA (Clontech). We did not detect expression of the human *IFGP* genes in the brain, the kidneys, and the heart (data not shown).

Expression of the Human *IFGP* Genes in PML Subpopulations

To study the distribution of the *hIGFP1–hIFGP6* mRNAs among cell subpopulations, CD14+, CD19+, CD3+, CD8+, and CD56+ cells were isolated from PML of healthy donors by magnetic sorting. RT–PCR with mRNAs of individual subpopulations showed that *hIFGP1* and *hIFGP3–hIFGP5* are expressed only in CD19+ cells, i.e., in B cells. Expression of *hIFGP2* was not observed in total PML nor in isolated cell subpopulations (Fig. 3a).

The *hIFGP6* gene proved to be expressed in CD3+, CD3–, CD8+, CD8–, CD56+, and CD56–, but not in CD14+, CD4+, and CD19+ cells (Fig. 3a). Thus, *hIFGP6* is active in CD8+ T cells and in PML other than T cells, B cells, or monocytes. We assumed that CD3– cells expressing *hIFGP6* are NK. To verify, NK cells were isolated from PML by removing CD3+, CD4+, CD14+, CD15+, CD19+, CD36+, CD123+, and glycophorin A-positive cells. The resulting cell subpopulation displayed the NK-specific set of markers (49% CD8+, 38% CD56+, 25%CD57+, and 82% CD16+) and expressed *hIFGP6*. After further sorting, both CD8+ and CD8– fractions of the NK subpopulation proved to express *hIFGP6*. Our findings suggest that *hIFGP6* is expressed only in cytotoxic lymphocytes, that is, in CD8+ T and NK cells. It is well known that peripheral blood CD8+ T cells are phenotypically and functionally heterogeneous and include naive, memory, and effector cells [21, 22]. The lack of *hIFGP6* expression in the thymus suggests that *hIFGP6* is inactive in native, antigen-nonstimulated CD8+ T cells. This assumption was confirmed by the analysis of *hIFGP6* expression in mononuclear leukocytes of the cord blood, which contains exclusively, or at least mostly, naive T cells [23]. Expression of *hIFGP6* was observed in CD3– but not in CD3+ cells in three samples of cord mononuclear leukocytes (CML) (Fig. 3a).

Expression of the Human *IFGP* Genes in Hematopoietic Cell Lines

Along with PML subpopulations, several human hematopoietic cell lines were tested for expression of the *IFGP* genes (Fig. 3b). We examined two CD4+ CD8– T-cell lines (MOLT-4 and Jurkat E06); the HL-60 promyelocyte line; the Raji, BJAB, IM-9, CBMI, and BL-2 B-cell lymphoma cell lines; and the K562 erythroid cell line. Expression of *hIFGP1* and *hIFGP4* was observed in three (BJAB, BL-2, and Raji) out of the five B-cell lines and in the HL-60 promyelocyte line. The *hIFGP2* transcripts were found in the IM-9, CBMI, BJAB, and Raji cell lines; a weak signal was detected for the K562 line. Expression of *hIFGP3* was observed in the IM-9, Raji, and HL-60 lines. The *hIFGP5* mRNA was found only in the

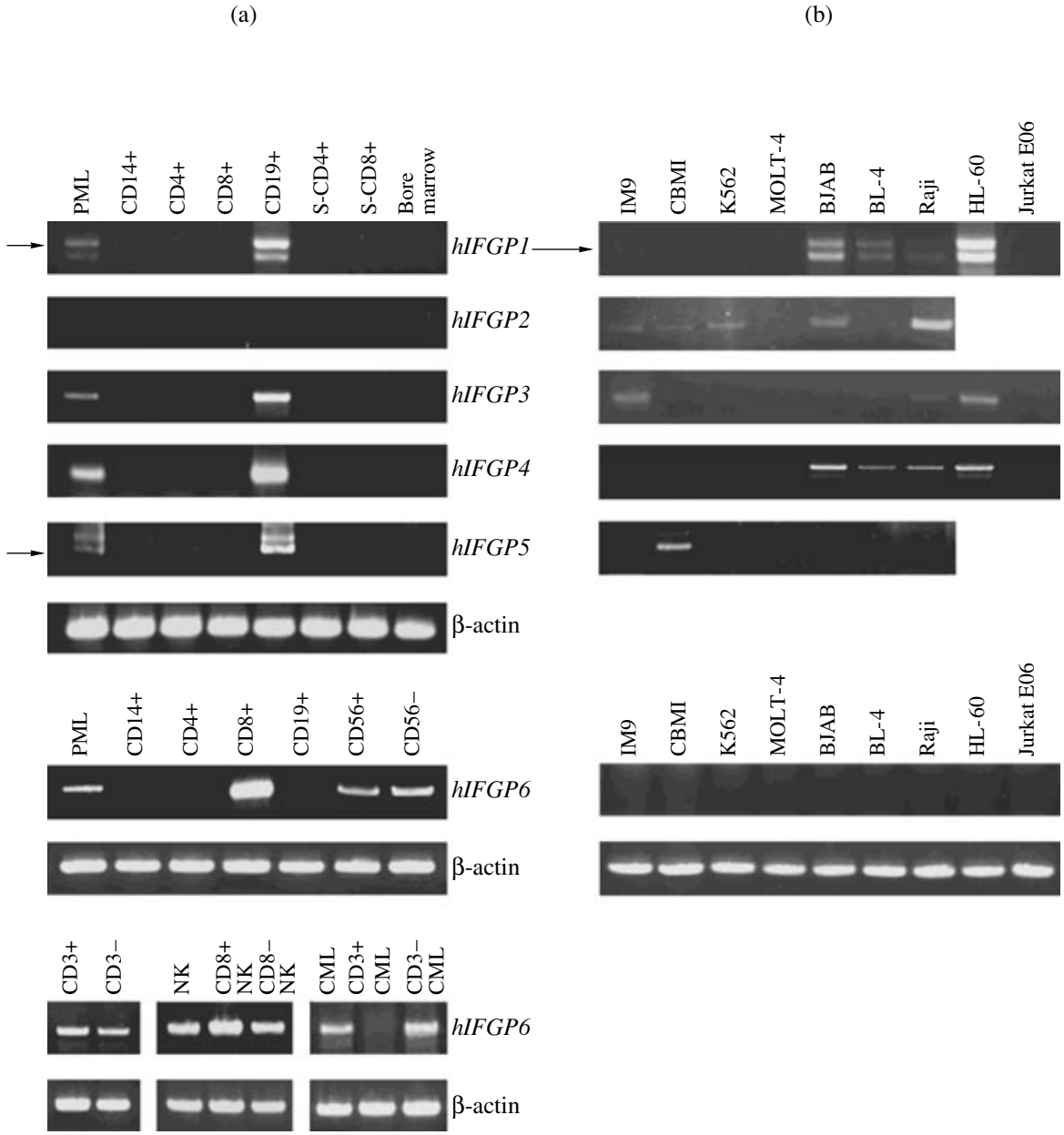

Fig. 3. Profiles of the human *IFGP* expression in (a) subpopulations of peripheral and umbilical cord blood and (b) human hematopoietic cell lines. RT–PCR products were synthesized with primers specific to *hIFGP1–hIFGP6* from total RNAs of cell subpopulations and cell lines and separated electrophoretically. S-CD4+ and S-CD8+ are CD4+ and CD8+ cells assayed after mitogenic stimulation.

CBMI line. None of the lines expressed *hIFGP6*. These findings agree with the published data that *hIFGP1–hIFGP5* are expressed predominantly in B cells [8–10, 12, 13] and demonstrate for the first time that *hIFGP6* is selectively expressed in cytotoxic cells. The fact that Xu *et al.* [13] have not observed *hIFGP3*/*SPAP2* expression in lymphoid tissues may be explained by a poor choice of primers. It is important to note the differential character of *hIFGP1–hIFGP6* expression in lymphocytes. Similar expression patterns were observed only for *hIFGP1* and *hIFGP4*.

Alternative Transcripts of *hIFGP1* and *hIFGP6*

In addition to the major products, corresponding in size to the control ones, other fragments were detected in the RT–PCR patterns of *hIFGP1, hIFGP5*, and *hIFGP6*. In the case of *hIFGP1*, the additional fragment was about 140 bp shorter than the major one and was detected in all tissues and cell lines expressing this gene (Figs. 2, 3). Since alternative mRNAs have been reported for *hIFGP3, hIFGP4*, and *hIFGP5* [8, 9, 12, 13], we assumed that alternative splicing is also characteristic of *hIFGP1* and *hIFGP6* expres-

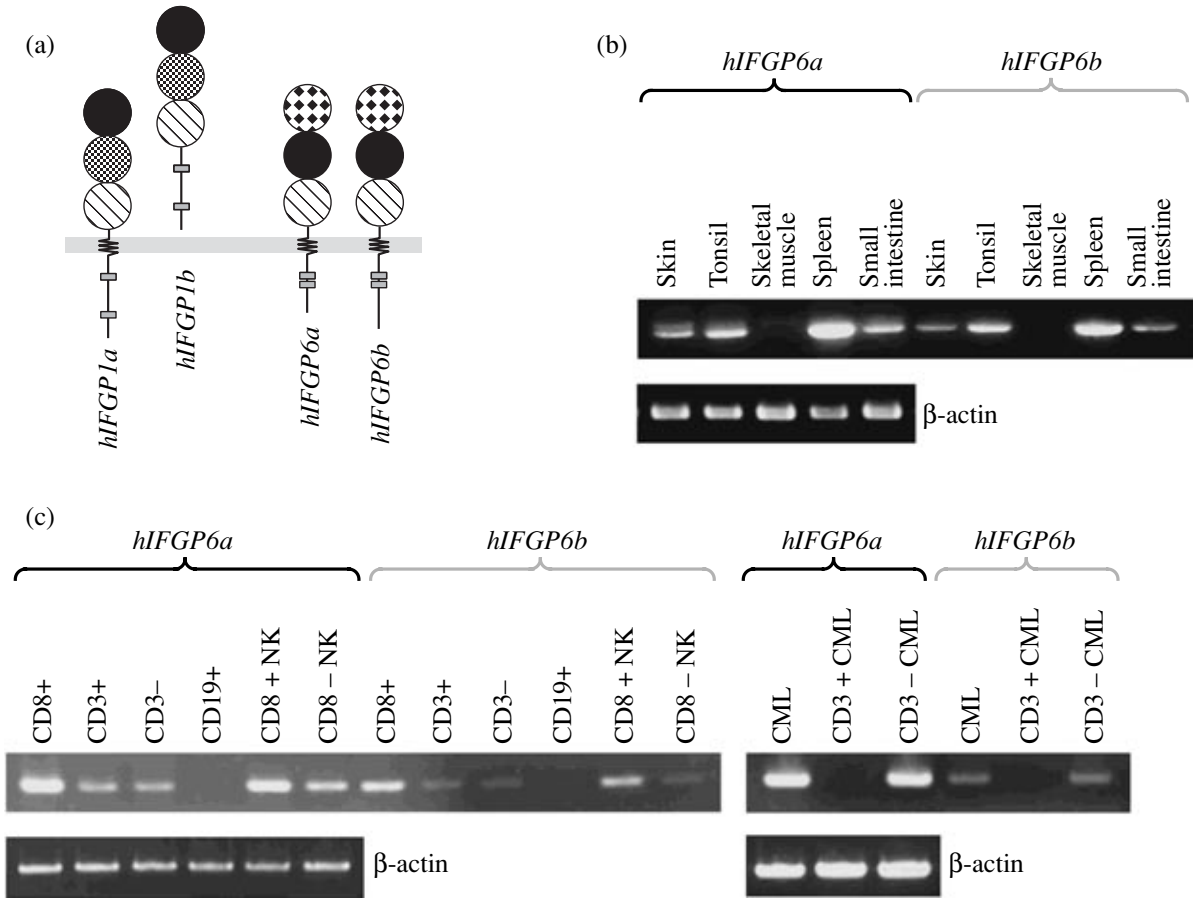

Fig. 4. (a) Domain structure of the alternative isoforms of hIFGP1 and hIFGP6. (b, c) RT–PCR analysis of the *hIFGP6a* and *hIFGP6b* transcripts in (b) human organs and tissues and (c) cell subpopulations of peripheral and umbilical cord blood with variant-specific primers. As templates, we used total RNAs isolated from the corresponding tissues or cell subpopulations.

sion. In either gene, the first two exons code for a leader peptide; the third, fourth, and fifth exons, for the extracellular Ig-like domains; and the sixth exon, for the transmembrane domain. The cytoplasmic regions of hIFGP1 and hIFGP6 are encoded by five and four exons, respectively. Sequencing showed that the shorter PCR product of *hIFGP1* is indeed an alternative cDNA (designated as *hIFGP1b*) that lacks the sixth exon, which codes for the transmembrane domain (Fig. 4a). The protein product of the corresponding mRNA is probably secreted.

In the case of *hIFGP6*, an additional band in the cDNA amplification pattern was observed only for nonlymphoid tissues, such as the liver and the skin (Fig. 2). The corresponding fragment was cloned and sequenced. The clone proved to be aberrant: splicing within an exon eliminated half of the third exon, shifted the frame, and generated a premature stop codon in the 5'-terminal region of the fourth exon (data not shown). Still, a search for alternative *hIFGP6* mRNAs revealed an additional, potentially functional transcript which lacked the tenth exon and has a different frame of the last, tenth exon. The encoded protein (hIFGP6b) differs from the full-size hIFGP6 in the C-terminal region of the cytoplasmic domain. The C-terminal region of hIFGP6b contains an additional Tyr residue, which may change its signal properties (Fig. 4a). The expression of *hIFGP6a* and *hIFGP6b* was analyzed with variant-specific primers. Both transcripts were found in all tissues and cell subpopulations that express *hIFGP6* (Figs. 4b, 4c).

Expression of the Mouse *IFGP* Genes

Three of the four mouse genes of the *IFGP* family have been characterized so far. We earlier analyzed the expression of *mIFGP1* and *mIFGP2* in various tissues by RNA blot hybridization [7]. Davis *et al.* [15] have obtained similar data and studied the expression of *mIFGP3* (*mFcRH3*). In this study, we analyzed the expression of all four mouse *IFGP* genes not only in various tissues, but also in several cell lines by RT–PCR, which is more sensitive than RNA blotting (Fig. 5). To construct *mIFGP6*-specific primers, we used the

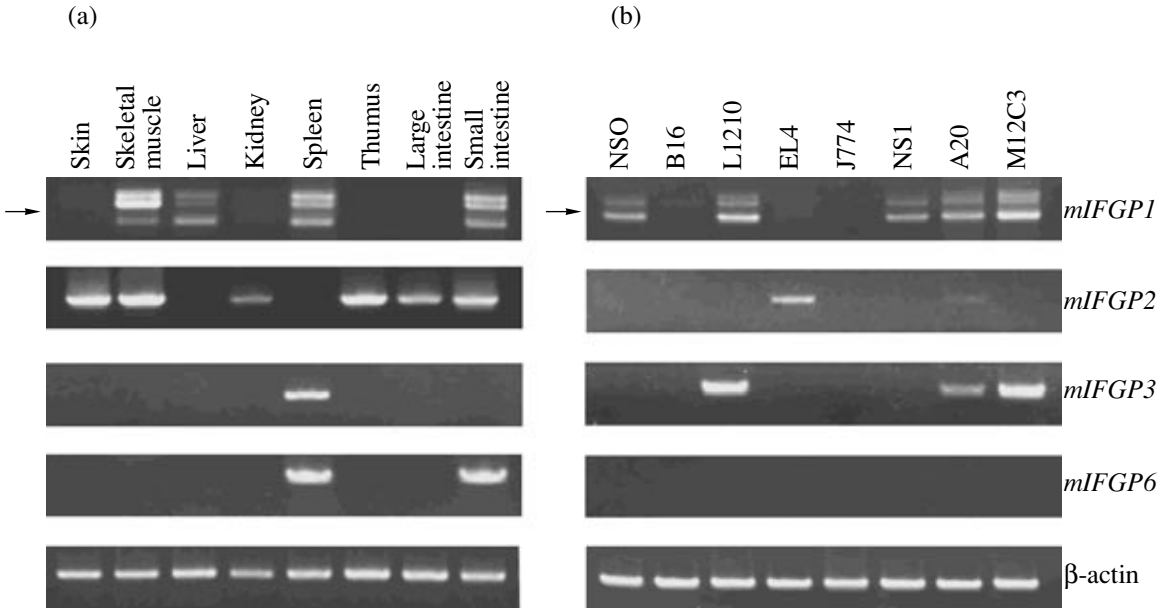

Fig. 5. Profiles of *mIFGP* expression in (a) mouse tissues and (b) mouse hematopoietic cell lines. RT–PCR products were synthesized with primers specific for *mIGFP1, mIFGP2, mIFGP3*, and *mIFGP6* and total RNAs isolated from the corresponding tissues or cell lines. The products were separated electrophoretically.

mIFGP6 nucleotide sequence predicted on the basis of analysis of mouse genome sequences. We examined the brain, skeletal muscles, the liver, the kidneys, the spleen, the thymus, and the small and large intestines. Expression of *mIFGP1* was observed in skeletal muscles, the liver, the spleen, and the small intestine (Fig. 5a). Three *mIFGP1*-specific fragments of different sizes were found for all tissues expressing *mIFGP1*. The medium-sized PCR fragment corresponded to the cDNA coding for the full-size protein. As with *hIFGP1*, the shortest fragment corresponded to the alternative *mIFGP1* transcript that is devoid of the exon coding for the transmembrane domain and, presumably, codes for a secreted protein. The structure of the largest PCR product remained unclear. Analysis of database expression sequence tags (ESTs) suggested erroneous splicing, which preserves an intron fragment (65 bp) between the second and third exons and generates premature stop codons in all three reading frames. The largest PCR product corresponds in size to this *mIFGP1* transcript.

The *mIFGP2* mRNA was detected in the brain, skeletal muscles, the kidneys, the thymus, and in the small and large intestines, but not in the spleen (Fig. 5a). The RT–PCR results generally agree with the data obtained by RNA blot hybridization for *mIGFP1* and *mIGFP2* [7]. For instance, the multiplicity of *mIFGP1* transcripts is detectable by both methods. The only significant difference is that RT–PCR did not confirm *mIFGP1* expression in the brain. Likewise, Davis *et al.* [15] have reported the absence of *mIFGP1* mRNA from the brain. It should be noted, however, that *mIFGP1* cDNAs of several types are present among mouse hypothalamic ESTs. Hence, *mIFGP1* may be expressed in particular regions of the brain. If so, the results of mRNA analysis depend on the brain region used to isolate mRNA.

The *mIFGP3* transcripts were found only in the spleen (Fig. 5a). This result fully agrees with the published data [15]. We were the first to demonstrate that *mIFGP6* is expressed in the spleen and the small intestine (Fig. 5a). The reliability of this finding was confirmed by sequencing PCR products (data not shown). Since the small intestine has considerable masses of lymphoid cells, it is possible to assume that *mIFGP6* is active only in hematopoietic cells.

The *IFGP* mRNAs were assayed not only in tissues, but also in several hematopoietic cell lines: NS0, NS1 (myeloma cell lines), L1210 (pre-B cells), A20, M12 (B-cell lymphomas, mature B cells), EL4 (T cells), and J774 (macrophages). In addition, the B16 melanoma cell line was examined (Fig. 5b). RT–PCR detected *mIFGP1* expression in all B-cell lines. The *mIFGP2* gene proved to be expressed in the EL4 T-cell and A20 B-cell lymphoma lines. The *mIFGP3* transcripts were found in the L1210, A20, and M12C3 B-cell lymphoma lines but not in the myeloma cell lines. Expression of *mIGFP6* was not observed in any line.

The above results demonstrate that *mIFGP1* and *mIGFP3* are expressed in B cells in lymphoid tissues. Like *hIFGP1–hIFGP5*, *mIFGP3* is selectively expressed by B cells. Davis *et al.* [10] have made a

similar conclusion for *mIFGP1*. Yet this conclusion disagrees with our findings and the fact that *mIFGP1* ESTs have been detected in many tissues (the aorta, osteoclasts, the hypothalamus, and the mammary gland), suggesting that *mIFGP1* is also active in other, still unidentified cells of nonhematopoietic origin. Further studies are necessary to identify the cells that express *mIFGP6*. In view of the considerable similarity between mouse and rat, it is possible to assume that, like rat gp42, mIFGP6 is a marker of NK cells. The properties of *mIGFP2* are of particular interest. This gene differs from other members of the family not only in structure of the encoded protein, but also in the spectrum of expressing tissues. The presence of the *mIGFP2* transcripts in the EL4 and A20 lymphoma cell lines testifies that *mIFGP2* is active in lymphocytes. It is clear, however, that the function of *mIFGP2* is not restricted to the immune system.

An important feature of the IFGP family is the striking variation of the domain architecture of its members. Each of the ten human and mouse proteins has a unique domain composition and, as receptors, a unique combination of intracellular signal motifs. The expression patterns make it possible to assume that the *IFGP* genes are involved in regulating the development and/or the functional state of the three main effector lymphocyte populations: B, CD8+ T, and NK cells. Studies of the functional roles of the IFGP-family proteins will contribute to the understanding of the mechanisms regulating differentiation and effector properties of these cells. Owing to their differential expression, the *IFGP* genes and their protein products can be used as additional markers for distinguishing individual stages and lineages of B lymphocytes and cytotoxic cells and diagnosing blood cell malignancies. The distinct species-specific features of the structure and expression patterns of the *IFGP* genes are of particular interest. It has become clear recently that the mechanisms that finely regulate immune response vary strikingly among mammals, although general principles of the functioning of the immune system are much the same. The variation is to a great extent due to species-specific evolution of immune molecules [24]. Further studies of the human and mouse receptors of the IFGP family may be of importance for the correct use of mice as an experimental model of human immune reactions.

ACKNOWLEDGMENTS

This study was supported by the Russian Foundation for Basic Research (project no. 03-04-48 531).

REFERENCES

1. Ravetch J.V., Kinet J.-P. 1991. Fc receptors. *Annu. Rev. Immunol*. **9**, 457–492.
2. Daeron M. 1997. Fc receptor biology. *Annu. Rev. Immunol*. **5**, 203–234.
3. Mechetina L.V., Najakshin A.M., Volkova O.Y., Guselnikov S.V., Faizulin R.Z., Alabyev B.Y., Chikaev N.A., Vinogradova M.S., Taranin A.V. 2002. FCRL, a novel member of the leukocyte Fc receptor family possesses unique structural features. *Eur. J. Immunol*. **32**, 87–96.
4. Chikaev N.A., Bykova E.A., Najakshin A.M., Mechetina L.V., Volkova O.Y., Peklo M.M., Shevelev A.Y., Vlasik T.N., Roesch A., Vogt T., Taranin A.V. 2005. Cloning and characterization of the human FCRL2 gene. *Genomics*. **85**, 264–272.
5. Facchetti F., Cella M., Festa S., Fremont D.H., Colonna M. 2002. An unusual Fc receptor-related protein expressed in human centroblasts. *Proc. Natl. Acad. Sci. USA*. **99**, 3776–3781.
6. Davis R.S., Li H., Chen C.-C., Wang Y.-H., Cooper M.D., Burrows P.D. 2002. Definition of an Fc receptor-related gene (FcRX) expressed in human and mouse B cells. *Int. Immunol*. **14**, 1075–1083.
7. Guselnikov S.V., Ershova S.A., Mechetina L.V., Najakshin A.M., Volkova O.Y., Alabyev B.Y., Taranin, A.V. 2002. A family of highly diverse human and mouse genes structurally links leukocyte FcR, gp42 and PECAM-1. *Immunogenetics*. **54**, 87–95.
8. Hatzivassiliou G., Miller I., Takizawa J., Palanisamy N., Rao P.H., Iida S., Tagawa S., Taniwaki M., Russo J., Neri A., Cattoretti G., Clynes R., Mendelsohn C., Chaganti R.S., Dalla-Favera R. 2001. IRTA1 and IRTA2, novel immunoglobulin superfamily receptors expressed in B cells and involved in chromosome 1q21 abnormalities in B cell malignancy. *Immunity*. **14**, 277–289.
9. Miller I., Hatzivassiliou G., Cattoretti G., Mendelsohn C., Dalla-Favera R. 2002. IRTAs: A new family of immunoglobulin-like receptors differentially expressed in B cells. *Blood*. **99**, 2662–2669.
10. Davis R.S., Wang Y.H., Kubagawa H., Cooper M.D. 2001. Identification of a family of Fc receptor homologs with preferential B cell expression. *Proc. Natl. Acad. Sci. USA*. **98**, 9772–9777.
11. Davis R.S., Ehrhardt G.R., Leu C.M., Hirano M., Cooper M.D. 2005. An extended family of Fc receptor relatives. *Eur. J. Immunol*. **35**, 674–680.
12. Xu M.J., Zhao R., Zhao Z.J. 2001. Molecular cloning and characterization of SPAP1, an inhibitory receptor. *Biochem. Biophys. Res. Commun*. **280**, 768–775.
13. Xu M.J., Zhao R., Cao H., Zhao Z.J. 2002. SPAP2, an Ig family receptor containing both ITIMs and ITAMs. *Biochem. Biophys. Res. Commun*. **293**, 1037–1046.
14. Nakayama Y., Weissman S.M., Bothwell A.L. 2001. BXMAS1 identifies a cluster of homologous genes differentially expressed in B cells. *Biochem. Biophys. Res. Commun*. **285**, 830–837.
15. Davis R.S., Stephan R.P., Chen C.-C., Dennis G.Jr., Cooper M.D. 2004. Differential B cell expression of mouse Fc receptor homologs. *Int. Immunol*. **16**, 1343–1353.
16. Imboden J.B., Eriksson E.C., McCutcheon M., Reynolds C.W., Seaman W.E. 1989. Identification and characterization of a cell-surface molecule that is selectively induced on rat lymphokine-activated killer cells. *J. Immunol*. **143**, 3100–3103.

17. Seaman W.E., Niemi E.C., Stark M.R., Goldfien R.D., Pollock A.S., Imboden, J.B. 1991. Molecular cloning of gp42, a cell-surface molecule that is selectively induced on rat natural killer cells by interleukin 2: Glycolipid membrane anchoring and capacity for transmembrane signaling. *J. Exp. Med*. **173**, 251–260.
18. Klaus G.G.B. 1987. *Lymphocytes. A Practical Approach*. Oxford: IRL Press.
19. Sieber G., Bochert G., Enders B., Ruhl, H. 1980. Characteristics of immunoglobulin secretion in man evaluated by a reverse hemolytic plaque assay. *Blut*. **41**, 81–92.
20. Chomczynski P., Sacchi N. 1987. Single-step method of RNA isolation by acid guanidinium thiocyanate–phenol–chloroform extraction. *Anal. Biochem*. **162**, 156–159.
21. Lanzavecchia A., Sallusto F. 2000. Dynamics of T lymphocyte responses: Intermediates, effectors, and memory cells. *Science*. **290**, 92–97.
22. Kaech S.M., Wherry E.J., Ahmed, R. 2002. Effector and memory T-cell differentiation: Implications for vaccine development. *Nature Rev. Immunol*. **2**, 251–262.
23. Harris D.T., Schumacher M.J., Locascio J., Besencon F.J., Olson G.B., DeLuca D., Shenker L., Bard J., Boyse E.A. 1992. Phenotypic and functional immaturity of human umbilical cord blood T lymphocytes. *Proc. Natl. Acad. Sci. USA*. **89**, 10006–10010.
24. Mestas J., Hughes C.C. 2004. Of mice and not men: Differences between mouse and human Immunology. *J. Immunol*. **172**, 2731–2738.