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Minireview

The allograft inflammatory factor-1 family of proteins

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Abstract The allograft inflammatory factor-1 (AIF-1) is a 17 kDa interferon-γ-inducible Ca^{2+}-binding EF-hand protein that is encoded within the HLA class III genomic region. Three proteins are probably identical with AIF-1 termed Iba1 (ionized Ca^{2+}-binding adapter), MRF-1 (microglia response factor) and daintain. Considerable but not complete sequence identity with AIF-1 has been described for IRT-1 (interferon-responsive transcript), BART-1 (balloon angioplasty-responsive transcript), and other, yet unassigned alternatively spliced variants. In this review, genomic and functional characteristics of AIF-1-related proteins are summarized and a common nomenclature is proposed.

Key words: Allograft inflammatory factor-1; Ionized Ca^{2+}-binding adapter molecule; Interferon-responsive transcript-1

1. Introduction

The allograft inflammatory factor-1 (AIF-1) is a 17 kDa interferon (IFN)-γ-inducible Ca^{2+}-binding EF-hand protein that is encoded within the HLA class III genomic region [1] and was originally cloned from activated macrophages in human (GenBank accession number U49392) and rat (GenBank accession number U17919) atherosclerotic allogenic heart grafts undergoing chronic transplant rejection (Fig. 1A) [2]. It was initially demonstrated that AIF-1 is a modulator of the immune response during macrophage activation [1,2]. Three proteins are probably identical with AIF-1 but complete functional identity still remains to be established, Iba1 (ionized Ca^{2+}-binding adapter) [3,4], MRF-1 (microglia response factor) [5] and daintain [41]. A range of proteins that share considerable but not complete sequence identity with AIF-1 have been described. Overexpression of IRT-1 (interferon-responsive transcript) protein in vascular smooth muscle cells (VSMCs) alters their morphology and dramatically reduces their proliferative capacity [6]. Following balloon angioplasty of rat carotid arteries, the BART-1 transcript was detected [7]. G1 (EMBL accession number HSY14768) has been cloned from an Epstein–Barr virus-transformed lymphoblastoid cell line, but has only been submitted as a protein sequence without further characterization. A recent report has described the cloning of two novel alternatively spliced variants of AIF-1 by reverse-transcription polymerase chain reaction in peripheral blood leukocytes and in macrophages [8]. In addition, database analyses reveal a number of cloned and in part patented sequences with modular homology to AIF-1 suggesting differential splicing from the AIF-1-encoding gene.

To identify AIF-1-related sequences, the AIF-1 sequence was mapped to its genomic region located on chromosome 6. The encompassing sequences were identified and fragments were compared with nucleotide and expressed sequence tag sequences using the BLAST database retrieval algorithm [9]. Obtained fragments were then assigned to the respective genomic region and splice sites were identified using the HSPL program [10]. Frameshifts were detected by sequence alignment. Signal peptide and pattern localization site analyses were conducted using the SignalP, PSort, HMMTOP and PIR algorithms and databases [11–14].

2. AIF-1 and its homologues Iba1, MRF-1 and daintain

AIF-1 was initially identified early and persistently in chronically rejecting cardiac allografts but not in cardiac syngrafts and host hearts in the Lewis F344 rat model of chronic cardiac rejection. In cardiac allografts AIF-1 transcripts and protein localized to infiltrating mononuclear cells and AIF-1 transcripts could be upregulated by IFN-γ. Treatment with an arteriosclerosis-attenuating diet deficient in essential fatty acids or CTLA-4 Ig (which blocks lymphocyte activation) significantly decreased AIF-1 transcript levels [1]. In addition, AIF-1 mRNA was detected in endomyocardial biopsy specimens from human heart transplants and immunostaining in human heart allografts localized the AIF-1 gene product to a subset of $CD68^+$ macrophages in the interstitial and perivascular spaces suggesting that AIF-1 is involved in the inflammatory response associated with human cardiac transplant rejection [2]. Another report showed that AIF-1 is expressed at low levels in undamaged, at increased levels 1 day and 3 days, and again at low levels 7 days post balloon angioplasty. AIF-1 is inducible in serum- and cytokine-stimulated human smooth muscle cells and was found to be constitutively expressed in lymphoid tissue and augmented by mitogens [15]. Accordingly, AIF-1 has since then been used as a differentiation marker for activated monocytes during graft rejection [16,17]. However, AIF-1 mRNA and protein were also observed in medial vascular smooth muscle cells in immunologic and mechanical models of arterial injury [18]. Comparison of AIF-1 transcripts from different species reveals a high grade of similarity suggesting high evolutionary conservation (Fig. 1B).

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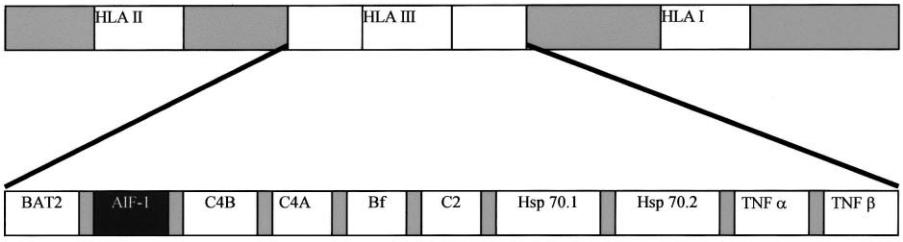
A) The AIF family of proteins is located in the HLA class III region of chromosome 6



B) AIF-1 is highly conserved among different species

Designation	AA-sequence					Accession #
AIF-1-hum-Rowen-10/96	MSQTRDLQGG	KAFRLLKAQQ	EERLDEINKQ	FLDDPKYSSD	EDLPSKLEGF	AAD18087
AIF-1-hum-Utans-3/96	MSQTRDLQGG	KAFGLLKAQQ	EERLDEINKQ	FLHDPKYSSD	EDLPSKLEGF	AAA92457
AIF-1-mouse-Hu-6/98	MSQSRDLQGG	KAFGLLKAQQ	EERLEGINKQ	FLDDPKYSND	EDLPSKLEAF	AAC24189
AIF-1-mouse-Hu-7/98	MSQSRDLQGG	KAFGLLKAQQ	EERLEGINKQ	FLDDPKYSND	EDLPSKLEAF	AAC25604
AIF-1-mouse-Watano-7/98	MSQSRDLQGG	KAFGLLKAQQ	EERLEGINKQ	FLDDPKYSND	EDLPSKLEAF	BAA28216
AIF-1-rat-Utans-10/95	MSQSKDLQGG	KAFGLLKAQQ	EERLDGINKH	FLDDPKYSSD	EDLQSKLEAF	AAA80105
AIF-1-bos-Glover-4/01	MSETRDLQGG	KAFGLRKAQQ	EERINEINQQ	FLDDPKYSSD	EDLPSKLEAF	AAK30155
AIF-1-pagrus-Miyata-1/99	MDSTA--QGG	KAFGLLKSHQ	EEKLNSINEA	FLSDPQYAEE	EDLSSKLEAF	BAA36938
AIF-1-hum-Rowen-10/96	KEKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	GEVSSGSG-E	AAD18087
AIF-1-hum-Utans-3/96	KEKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	GEVSSGSG-E	AAA92457
AIF-1-mouse-Hu-6/98	KVKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKRLI	REVSSGSE-E	AAC24189
AIF-1-mous-Hu-7/98	KVKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKRLI	REVSSGSE-E	AAC25604
AIF-1-mouse-Watano-7/98	KVKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKRLI	REVSSGSE-E	BAA28216
AIF-1-rat-Utans-10/95	KTKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	REVSSGSE-E	AAA80105
AIF-1-bos-Glover-4/01	KKKYMEFDLN	EDGGIDIMSL	KRMMEKLGVP	KTHLELKKLI	MEVSSGPG-E	AAK30155
AIF-1-pagrus-Miyata-1/99	KKKYMEFDLN	DKGEIDIMGL	KRMLEKLGLA	KTHLELKKMM	SEVCGGTSKE	BAA36938
AIF-1-hum-Rowen-10/96	TFSYPDFLRM	MLGKRSAILK	MILMYEEKAR	EKE-KPTGPP	AKKAISELP.	AAD18087
AIF-1-hum-Utans-3/96	TFSYPDFLRM	MLGKRSAILK	MILMYEEKAR	ERK-TNTPPS	QESPI----.	AAA92457
AIF-1-mouse-Hu-6/98	TFSYSDFLRM	MLGKRSAILR	MILMYEEKNK	EHK-RPTGPP	AKKAISELP.	AAC24189
AIF-1-mous-Hu-7/98	TFSYSDFLRM	MLGKRSAILR	MILMYEEKNK	EHK-RPTGPP	AKKAISELP.	AAC25604
AIF-1-mouse-Watano-7/98	TFSYSDFLRM	MLGKRSAILR	MILMYEEKNK	EHK-RPTGPP	AKKAISELP.	BAA28216
AIF-1-rat-Utans-10/95	TFSYSDFLRM	MLGKRSAILR	MILMYEEKNK	EHQ-KPTGPP	AKKAISELP.	AAA80105
AIF-1-bos-Glover-4/01	TFSYSDFLKM	MLGKRSAILK	MILMYEEKAR	EQE-KPTGLP	AKKAISELP.	AAK30155
AIF-1-pagrus-Miyata-1/99	TFGYHDFLNM	MLGKRNAILK	LILMFEGMGK	EHESKDAAPP	PRKTFSDLP.	BAA36938

C) AIF-1 homologues Iba1, MRF-1 and Daintain

Designation	AA-sequence					Accession #
AIF-1-hum-Rowen-10/96	MSQTRDLQGG	KAFRLLKAQQ	EERLDEINKQ	FLDDPKYSSD	EDLPSKLEGF	AAD18087
Iba1-hum-Imai-2/99	MSQTRDLQGG	KAFGLLKAQQ	EERLDEINKQ	FLDDPKYSSD	EDLPSKLEGF	BAA13088
Iba1-rat-Imai-2/99	M-KPEEISRG	KAFGLLKAQQ	EERLDGINKH	FLDDPKYSSD	EDLQSKLEAF	BAA11533
Iba1-mouse-Imai-11/99	MSQSRDLQGG	KAFGLLKAQQ	EERLEGINKQ	FLDDPKYSND	EDLPSKLEAF	BAA86387
MRF-1-rat-Tanaka-5/99	MSQSKDLQGG	KAFGLLKAQQ	EERLDGINKH	FLDDPKYSSD	EDLQSKLEAF	BAA19189
Daintain-pig-Chen-12/98	-SETIDLQGG	KAFGLLKAQQ	EGRLNEINKQ	FLDDPKYSSD	EDLSRKLEAF	P81076
AIF-1-hum-Rowen-10/96	KEKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	GEVSSGSGET	AAD18087
Iba1-hum-Imai-2/99	KEKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	GEVSSGSGET	BAA13088
Iba1-rat-Imai-2/99	KTKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	REVSSGSEET	BAA11533
Iba1-mouse-Imai-11/99	KVKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKRLI	REVSSGSEET	BAA86387
MRF-1-rat-Tanaka-5/99	KTKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	REVSSGSEET	BAA19189
Daintain-pig-Chen-12/98	KQKYMEFDLN	GNGDIDIMSL	KRMLEKLGVP	KTHLELKKLI	KEVSSGSGET	P81076
AIF-1-hum-Rowen-10/96	FSYPDFLRMM	LGKRSAILKM	ILMYEEKARE	KEKPTGPPAK	KAISELP...	AAD18087
Iba1-hum-Imai-2/99	FSYPDFLRMM	LGKRSAILKM	ILMYEEKARE	KEKPTGPPAK	KAISELP...	BAA13088
Iba1-rat-Imai-2/99	FSYSDFLRMM	LGKRSAILRM	ILMYEEKNKE	HQKPTGPPAK	KAISELP...	BAA11533
Iba1-mouse-Imai-11/99	FSYSDFLRMM	LGKRSAILRM	ILMYEEKNKE	HKRPTGPPAK	KAISELP...	BAA86387
MRF-1-rat-Tanaka-5/99	FSYSDFLRMM	LGKRSAILRM	ILMYEEKNKE	HQKPTGPPAK	KAISELP...	BAA19189
Daintain-pig-Chen-12/98	FSYSIFLKMM	LGKRSAILKM	ILMYEEKARE	QEKPTGPPAK	KAISELP...	P81076

Fig. 1. Chromosomal location and homology of AIF family members. AIF-1 and splice variants are encoded within the HLA class III region on chromosome 6 (A). Comparison of AIF-1 sequences reveals a high degree of homology between the different species (B). AIF-1, Iba1, MRF-1 and daintain of rat, human, mouse and pig origin are identical proteins with only species-specific amino acid differences (C).

In the brain, a subset of microglial cells constitutively express AIF-1 [19]. Increased numbers of AIF-1-immunoreactive macrophages/microglial cells were observed in focal human brain infarctions [20], human and rat traumatic brain injury [21,22], in human gliomas [23], rat uveitis [24], following injection of immunostimulatory CpG nucleotides [25], and in inflammatory lesions of a rat model of autoimmune disease, autoimmune encephalomyelitis, neuritis, and uveitis [26]. During experimental therapy of these diseases with high doses of recombinant autoantigens or with dexamethasone, a prominent reduction of AIF-1-immunoreactive macrophages/microglial cells was observed [27].

Three other proteins share widespread identical amino acid sequences with AIF-1 but complete functional identity still remains to be established: Iba1, MRF-1 and daintain. Iba1 of both rat (DNA DataBank of Japan accession number D82069) and human (DNA DataBank of Japan accession number D86438) origin has been reported to be exclusively

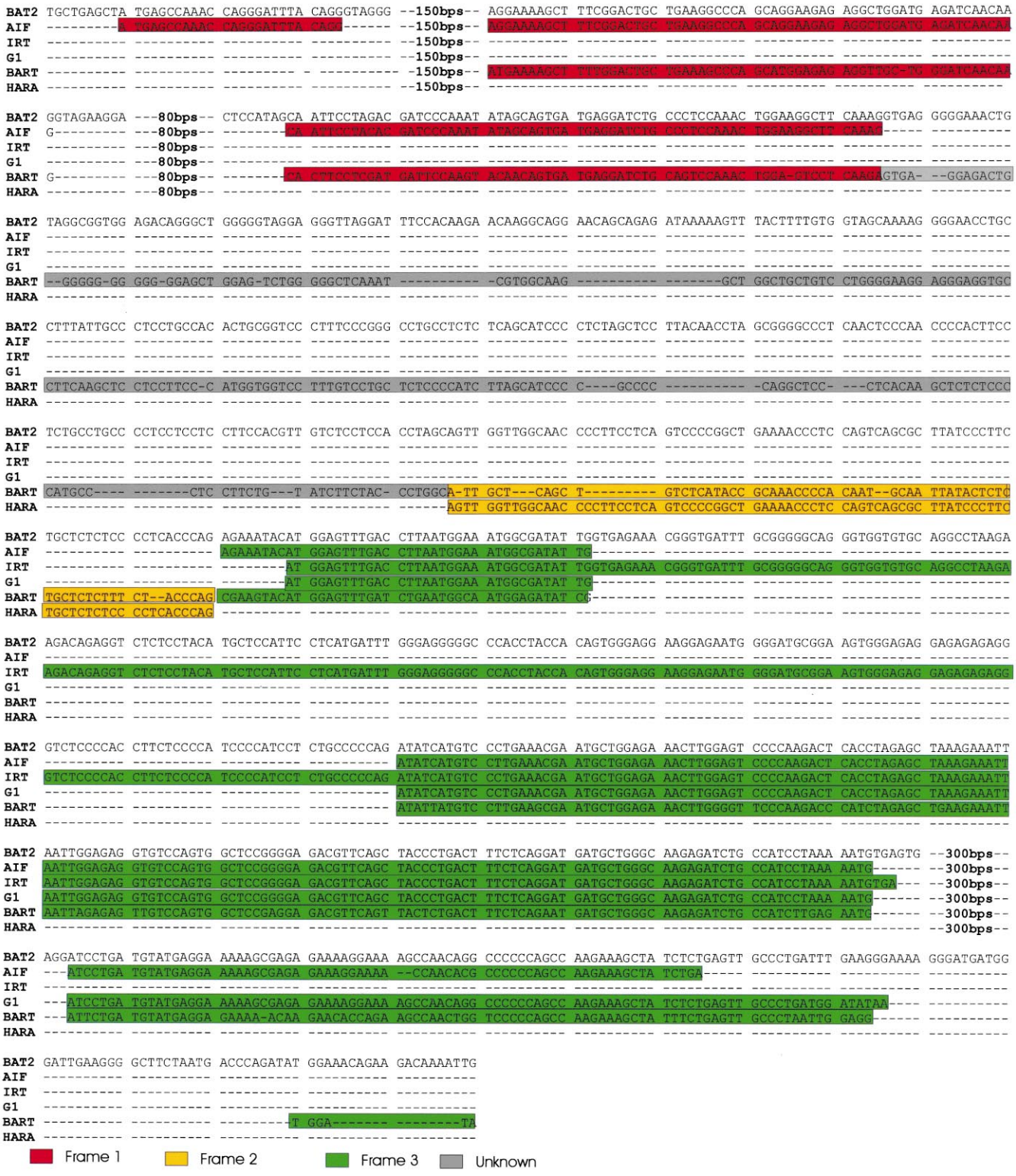


Fig. 2. AIF splice variants IRT-1, G1, BART-1 and the transcript described by Hara et al. [8] are encoded in the same region of the BAT2 gene on chromosome 6. The modular architecture suggests that differential splicing mechanisms are responsible for the production of individual proteins. All variants contain a varying number of exons and transcripts. Frameshift mechanisms appear to at least in part participate in the production of the different variants.

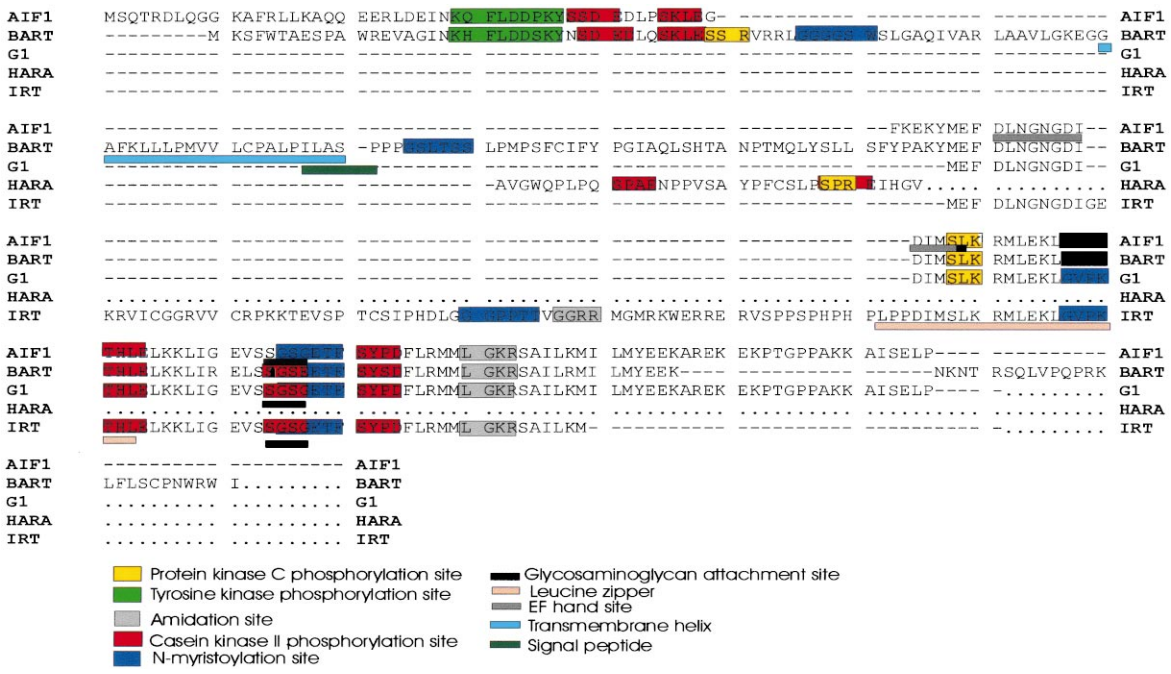


Fig. 3. AIF family members encode proteins that are characterized by a wide range of biologically active sites.

expressed in cells of the monocytic lineage and to be associated with microglial activation in the brain (Fig. 1C) [3,4]. Iba1 expression was observed in a microglilal cell line [28], in ramified microglia of adult rat brain and in the normal mouse olfactory bulb [29]. Accordingly, Iba1 was used to differentiate activated macrophages/microglial cells in brain tumors [30], following axotomy [31], facial nerve axotomy [4], manganese toxicity [32], ischemic axonal death in periventricular leukomalacia [33], influenza A virus infection [34], spinal cord injury in the rat [35] and focal cerebral ischemia [36].

MRF-1 (DNA DataBank of Japan accession number AB000818) cloned from rat tissues has been reported to be upregulated in microglial cells following apoptotic neuronal cell death [5]. Again, MRF-1 has been used to identify activated macrophages/microglial cells during their transformation to the ramified type [37], following cerebral ischemia in the rat brain [38], and following neurodegeneration after mechanical nerve injury in the rat [39].

Functional studies revealed that AIF-1 is secreted into the blood stream during experimental autoimmune neuritis [40]. When injected intravenously in mice, daintain/AIF-1 inhibited lower-dose glucose-stimulated insulin secretion with a concomitant impairment of the glucose elimination, whereas at higher doses daintain/AIF-1 potentiated glucose-stimulated insulin secretion and enhanced the glucose elimination [41]. In an in vitro model of rat muscle regeneration, addition of recombinant AIF-1 to the culture medium of satellite cells (myogenic precursors) resulted in a significant concentration-dependent and reversible reduction of the total number of cells expressing M-cadherin, a mediator of the differentiation process of skeletal muscle cells, the proliferation-associated

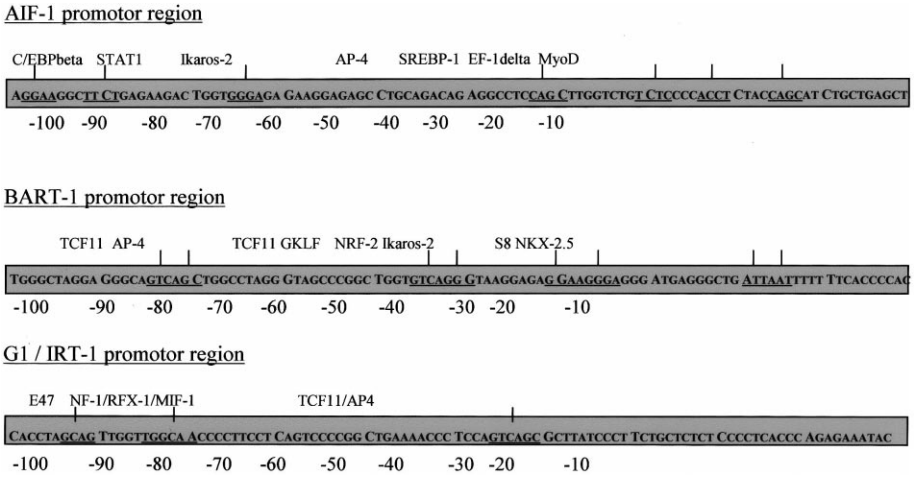


Fig. 4. Splice variant-specific promoter region analyses revealed binding sites for a wide range of transcription factors suggesting that distinct transcription factors are involved in the production of AIF splice variants.

PCNA and the initiator of muscle differentiation myogenin [42]. Intricate and widespread cellular functions of AIF-1 have been described in VSMCs. Transfection and constitutive expression of AIF-1 in a primary and a rat VSMC line results in enhanced growth of those cells as measured by cell number and is proportional to the amount of AIF-1 expressed. Constitutive expression of AIF-1 results in a shorter cell cycle. AIF-1 overexpression also permits growth of these cells in serum-reduced media. Here, it was shown that the growth-enhancing effects of AIF-1 in VSMCs are dose-dependent and mediated by its ability to bind calcium [43,44]. Iba1 was shown to colocalize with F-actin in membrane ruffles induced by macrophage colony-stimulating factor and in phagocytic cups formed during zymosan phagocytosis. Expression of mutant Iba1 carrying either N- or C-terminal deletions or carrying a substitution in the calcium-binding domain suppressed the membrane ruffling and the phagocytosis. Furthermore, Iba1 colocalized with a small GTPase Rac in the membrane ruffles and the phagocytic cups. The Iba1 mutants also suppressed membrane ruffling induced by dominant active Rac1V12, but do not affect microspikes by Cdc42V12 and stress fibers by RhoAV14 [45]. Moreover, Iba1 possesses actin-binding and -cross-linking activities. Inhibitory mutant Iba1 that suppresses membrane ruffling had lost the actin-cross-linking activity, and it inhibited the cross-linking activity of intact Iba1 [46]. Interestingly, a new single nucleotide polymorphism within the promoter region of the human AIF-1 gene has recently been described. The polymorphism, defined by GenBank accession number AF097515, was characterized as a C/T single base pair substitution at position −932. The T allele is associated with both HLA-DR2 and HLA-B7. Also, this allele creates the consensus binding site for the E-box that has high affinity for the basic helix-loop-helix family of transcription factors [47]. Using differential display reverse-transcription polymerase chain reaction (RT-PCR), Iba1 was identified during rat testis development. Iba1 was detected in spermatogonia, spermatocytes, and round spermatids in adult rat testis but was specifically expressed in the cytoplasm of elongate spermatids as well as in residual bodies that are ultimately engulfed by Sertoli cells first at week 4 in postnatal development and then increased up to adulthood [48].

3. The AIF-1 splice variants IRT-1, BART-1, G1, and others

A range of proteins that share considerable but not complete sequence identity with AIF-1 have been described (Fig. 2). IRT-1 encodes a basic protein that contains a leucine zipper motif, a core nuclear localization sequence, and a single strongly hydrophobic region. Constitutive IRT-1 mRNA expression in human peripheral blood lymphocytes is reduced

Table 1
Proposal for a new nomenclature of the AIF family of proteins

New name	Species	Old name	Date	Type	Authors	Accession number	Description
AIF-1	Human	AIF-1	28.10.95	complete cds	Utans, U., Arceci, R.J., Yamashita, Y., Russell, M.E.	U17919	AIF-1
?	Human	AIF-1	16.03.96	complete cds	Utans, U., Arceci, R.J., Yamashita, Y., Russell, M.E.	U49392	Differs from AIF-1 at N-terminal end: TGPPAKKAISELP > TPPSQESPI
AIF-1	Mouse	AIF-1	15.05.98	complete cds	Watano, K., Iwabuchi, K., Fujii, S.	AB013745	AIF-1
AIF-1	Pig	Daintain	15.12.98	protein	Chen, Z.W., Ahren, B., Ostenson, C.G., Cintra, A., Bergman, T., Moller, C., Fuxe, K., Mutt, V., Jornvall, H., Efendic, S.	P81076	AIF-1
AIF-1	*Chrysophrys major*	AIF-1	09.01.99	complete cds	Miyata, M., Iinuma, K., Miyazaki, T.	AB019540	AIF-1
AIF-1	Rat	MRF-1	05.02.99	complete cds	Tanaka, S.	AB000818	AIF-1
AIF-1	Rat	Iba1	06.02.99	complete cds	Imai, Y.	D82069	AIF-1
AIF-1	Human	Iba1	07.02.99	complete cds	Imai, Y.	D86438	AIF-1
AIF-1	Mouse	Iba1	11.11.99	complete cds	Imai, Y., Ohsawa, K., Kohsaka, S.	D86382	AIF-1
AIF-1	Pig	AIF-1	10.12.00	partial cds	Mentschel, J., Deininger, M.H.	AF299326	AIF-1
AIF-1	*Bos taurus*	AIF-1	08.04.01	complete cds	Glover, M.D., Seidel, G.E. Jr.	AF348450	AIF-1
AIF-2	Human	IRT-1	26.06.98	complete cds	Autieri, M.V., Agrawal, N.	U95213	AIF-1 splice variant IRT-1
AIF-2	Human	IRT-1	27.06.01	complete cds	Iris, F., Bougueleret, L., Prieur, S., Caterina, D., Primas, G., Perrot, V., Jurka, J., Rodriguez-Tome, P., Claverie, J., Cohen, D., Dausset, J.	NM_004847	AIF-1 splice variant IRT-1
AIF-3	Pig	G1	10.12.00	complete cds	Mentschel, J., Deininger, M.H.	AF299325	AIF-1 splice variant G1
AIF-3	Human	G1	10.12.00	complete cds	Deininger, M.H., Trautmann, K.	AF299327	AIF-1 splice variant G1
AIF-3	Rat	G1	10.12.00	complete cds	Deininger, M.H., Schluesener, H.J., Trautmann, K.	AF299328	AIF-1 splice variant G1
AIF-3	Human	G1	27.06.01	complete cds	Iris, F., Bougueleret, L., Prieur, S., Caterina, D., Primas, G., Perrot, V., Jurka, J., Rodriguez-Tome, P., Claverie, J., Cohen, D., Dausset, J.	NM_032955	AIF-1 splice variant
AIF-4	Human	none	10.12.00	partial cds	Deininger, M.H., Trautmann, K., Schluesener, H.J.	AF299329	AIF-1 splice variant originally described by Hara et al.
AIF-5	Human	none	Biol. Chem. 380 (1999) 1333–1336	partial cds	Hara, H., Ohta, M., Ohta, K., Nishimura, M., Obayashi, H., Adachi, T.	None	AIF-1 splice variant originally described by Hara et al.

when these cells are stimulated to proliferate. Overexpression of IRT-1 protein in VSMCs alters their morphology and dramatically reduces their proliferative capacity [6].

Following balloon angioplasty of rat carotid arteries, the BART-1 transcript was described. This message is undetectable in undamaged vessels, reaches maximal levels 3 days post procedure, and reduces to half-maximal expression by 14 days post angioplasty. Northern analysis of various rat tissues reveals tissue specificity and possible differential processing. BART-1 mRNA therefore appears to represent an inducible, tissue-specific transcript encoding a putative integral membrane protein transiently expressed in response to vascular trauma [7].

A recent report has described the cloning of two novel alternatively spliced variants of AIF-1 by RT-PCR in peripheral blood leukocytes and in macrophages [8]. One variant encodes an AIF-1 protein that lacks 14 amino acids corresponding to one exon. The other variant encodes a truncated AIF-1 protein due to a frameshift introduced by an 85-bp insertion, and its C-terminal region differs from that of AIF-1.

4. Characterization of AIF-1 and its splice variants

AIF-1 is a IFN-γ-inducible Ca^{2+}-binding EF-hand protein encoded within the HLA class III genomic region on chromosome 6 termed BAT2. Several proteins including Iba1 and MRF-1 share amino acid homology with AIF-1 but their relationship remained unresolved. Using database analyses, we confirmed that AIF-1, Iba1, MRF-1 and daintain have identical cDNA sequences. Inversely, AIF-1-related variants IRT-1, BART-1, G1 and Hara-1 appear to be AIF-1 splice variants that contain up to seven exons within the AIF-1 genomic locus. Interestingly, frameshifts appear to be at least in part involved in the production of the different transcripts. It is of note that splicing results in the differential inclusion of EF-hand, leucine zipper and hormone precursor sites suggesting diverse and widespread biological functions (Fig. 3). Analyses of the sequences immediately adjacent to the transcription start site revealed binding sites for a wide variety of transcriptional promoters and repressors thus giving evidence for widespread modulation of transcriptional regulation (Fig. 4).

5. Proposal for a new nomenclature of the AIF-1 protein family

Because a recent US patent has cloned a novel member of the AIF-1 family termed AIF-3 (accession number E29047), we think the most useful and practicable way to rename AIF-1 family proteins is by chronological assignment of the first description of a coding cDNA. According to this system (Table 1), AIF-1 is a 147-aa protein described first by Utans et al. AIF-2 is the 132-aa protein previously assigned IRT-1 first described by Autieri et al. AIF-3 is a 93-aa protein that was initially described by Menschel et al. AIF-4 is the 57-aa partial sequence first described by Hara et al., and first submitted by Deininger et al. AIF-5 is the second variant initially described by Hara et al., which has not yet been submitted to a database. It is of note that both sequences submitted by Hara et al. are partial cDNAs that encode a stretch of the AIF-encoding gene that has never before been described to encode an individual protein. The aberrant AIF-1 sequence (accession number U49392) initially described by Utans et al. is not included in this system, because confirmation is still lacking. In addition, a range of patented sequences that were assigned either AIF-1 or AIF-1 variant can be found in the databases. Because their functional and sequence confirmation is still lacking, they are not included in this system, either.

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