COMMENTARY

MOLECULAR PROFILE OF REACTIVE ASTROCYTES— IMPLICATIONS FOR THEIR ROLE IN NEUROLOGIC DISEASE

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Abstract—The central nervous system responds to diverse neurologic injuries with a vigorous activation of astrocytes. While this phenomenon is found in many different species, its function is obscure. Understanding the molecular profile characteristic of reactive astrocytes should help define their function. The purpose of this review is to provide a summary of molecules whose levels of expression differentiate activated from resting astrocytes and to use the molecular profile of reactive astrocytes as the basis for speculations on the functions of these cells. At present, reactive astrocytosis is defined primarily as an increase in the number and size of cells expressing glial fibrillary acidic protein. *In vivo*, this increase in glial fibrillary acidic protein-positive cells reflects predominantly phenotypic changes of resident astroglia rather than migration or proliferation of such cells. Upon activation, astrocytes upmodulate the expression of a large number of molecules. From this molecular profile it becomes apparent that reactive astrocytes may benefit the injured nervous system by participating in diverse biological processes. For example, upregulation of proteases and protease inhibitors could help remodel the extracellular matrix, regulate the concentration of different proteins in the neuropil and clear up debris from degenerating cells. Cytokines are key mediators of immunity and inflammation and could play a critical role in the regulation of the blood–central nervous system interface. Neurotrophic factors, transporter molecules and enzymes involved in the metabolism of excitotoxic amino acids or in the antioxidant pathway may help protect neurons and other brain cells by controlling neurotoxin levels and contributing to homeostasis within the central nervous system. Therefore, an impairment of astroglial performance has the potential to exacerbate neuronal dysfunction. Based on the synopsis of studies presented, a number of issues become apparent that deserve a more extensive analysis. Among them are the relative contribution of microglia and astrocytes to early wound repair, the characterization of astroglial subpopulations, the specificity of the astroglial response in different diseases as well as the analysis of reactive astrocytes with techniques that can resolve fast physiologic processes. Differences between reactive astrocytes *in vivo* and primary astrocytes in culture are discussed and underline the need for the development and exploitation of models that will allow the analysis of reactive astrocytes in the intact organism.

CONTENTS

1. INTRODUCTION

Astrocytes make up a substantial proportion of the CNS and participate in a variety of important physiologic and pathologic processes.[75] One of the most remarkable characteristics of astrocytes is their vigorous response to diverse neurologic insults, a feature that is well conserved across a variety of different species. The astroglial response (see section 2) occurs rapidly and can be detected within one hour of a focal mechanical trauma.[201] Prominent reactive

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Abbreviations: see over.

astrocytosis is seen in AIDS dementia,[65] a variety of other viral infections,[291] prion-associated spongiform encephalopathies,[88] inflammatory demyelinating disease,[60,253] acute traumatic brain injury,[28] and such neurodegenerative diseases as Alzheimer's disease.[20,66]

The prominence of astroglial reactions in various diseases, the rapidity of the astroglial response and the evolutionary conservation of reactive astrocytosis indicate that reactive astrocytes fulfill important functions for the CNS. Yet, the exact role reactive

Abbreviations: ACT, antichymotrypsin; AD, Alzheimer's disease; ADC, AIDS dementia complex; ALS, amyotrophic lateral sclerosis; APP, amyloid β protein precursor; βA4 (aa1–42), amyloid β protein (amino acids 1–42); BDNF, brain-derived neurotrophic factor; Ca²⁺ I, calcium ionophore; CA II, carbonic anhydrase II; CAD, carbamyl phosphate synthetase II/aspartate transcarbamylase/dihydroorotase; CD, cluster designation; CJD, Creutzfeld–Jakob disease; CMV, cytomegalovirus; conA sup, supernatant from concanavalin A-stimulated macrophages; CPM, central pontine myelinolysis; cpt-cAMP, 8-(4-chlorophenyl thio) adenosine 3′-5′-cyclic monophosphate; CS-PG, chondroitin-6-sulphate proteoglycan; dbcAMP, dibutyryl cyclic adenosine monophosphate; dbcGMP, dibutyryl cyclic guanosine monophosphate; DD, inflammatory demyelinating disease, particularly MS and EAE; DSD, Down's syndrome dementia; EAE, experimental autoimmune encephalomyelitis; EGF, epidermal growth factor; E-NCAM, embryonic neural cell adhesion molecule; exitotox.inj., intracerebral injection of excitotoxins such as kainic, quinolinic or ibotenic acid; FCS, fetal calf serum; a/bFGF (FGF-1/2) [Nomenclature of FGFs (*Ann. N.Y. Acad. Sci.* **638**, xiii–xvi).], acidic/basic fibroblasts growth factor; GDN, glia derived nexin; GFAP, glial fibrillary acidic protein; GHAP, glial hyaluronate adhesion protein; G(M)-CSF, granulocyte (macrophage)-colony stimulating factor; HD, Huntington's disease; HO, heme oxygenase; HSPG, heparin sulphate proteoglycans; HTLV, human T cell leukaemia virus; ICAM, intercellular adhesion molecule; IFAP, intermediate filament associated protein; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; LCMV, lymphocytic choriomeningitis virus; LPS, lipopolysaccharide; LT, lymphotoxin; MAO, monoamine oxidase; MAP, microtubule-associated protein; MCP, membrane co-factor protein; MHC, major histocompatibility complex; MHV, mouse hepatitis virus; MS, multiple sclerosis; Myel.mut., demyelinating/myelin deficient mutant strains of mice or rats; NDV, Newcastle disease virus; NE, norepinephrine; NGF, nerve growth factor; NSE, neuron-specific enolase; PA I, plasminogen activator inhibitor; PCA, polyribonucleotides/cyclohexamide/actinomycin; PD, Parkinson's disease; PDGF, platelet derived growth factor; PG, prostaglandin; PHA sup, supernatant from phytohaemagluttinin-stimulated macrophages; PIBD, polyglucosan inclusion body disease; PKC, protein kinase C; PMA, phorbol-12-myristate-13-acetate; PN, protease nexin; PTBBS, peripheral type benzodiazepine binding site; SGP, sulphated glycoprotein; SSPE, subacute sclerosing panencephalitis; sub P, substance P; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloprotease; TIS, TPA induced sequences; TMEV, Theiler's murine encephalomyelitis virus; TNF, tumour necrosis factor; TPA, 12-*O*-tetradecanoyl-phorbol-13-acetate; t-PA, tissue-type plasminogen activator; u-PA, urokinase-type plasminogen activator; trauma, focal mechanical or electrolytic destruction of CNS tissue; VIP, vasoactive intestinal peptide; VLA, β1 integrin family.

astrocytes play in the injured CNS has so far remained elusive. Assuming that the biological functions of reactive astrocytes are reflected in the proteins they express, this review aims to further our understanding of these cells by providing a synopsis of recent studies examining the molecular profile of activated astrocytes.

2. REACTIVE ASTROCYTOSIS

The CNS responds to neural injuries with an increase in the number and size of cells expressing glial fibrillary acidic protein (GFAP), a phenomenon generally referred to as reactive astrocytosis. GFAP is an intermediate filament cytoskeletal protein expressed primarily by astroglia[29] and represents the prototypic marker of astroglial activation.[28,60] However, despite its prominent upmodulation in response to diverse injuries, the precise function of the GFAP molecule remains unclear. Suppression of GFAP expression in glial cell lines with antisense mRNAs suggests that GFAP may be necessary for the formation of stable glial processes in response to neuronal signals.[279] It will be interesting to assess the functional role of GFAP *in vivo* by ablating GFAP in experimental animals with the help of homologous recombination, expression of anti-sense mRNAs or ribozymes.

It should be noted that it has not yet been established if an increased level of GFAP expression and/or turnover is, in fact, a reliable indicator of astroglial activity in general. For example, in normal rodent brains, astrocytes of the glial limitans and the hippocampal formation show higher levels of GFAP mRNA and GFAP immunostaining than astrocytes of other brain regions.[27,137,155,167,201] This raises the question whether these heterogenous levels of GFAP expression reflect particular functional demands placed upon specific astroglial subpopulations and whether they correlate with a general increase in the functional activity/metabolism of the strongly GFAP-positive cells. It should also be noted that using increased GFAP expression as the basis for the definition of astroglial activation will exclude any subpopulation of astrocytes that responds to neural injury without GFAP expression. Pending further experimental evaluation of these issues we have considered the induction of GFAP expression to be the main indicator of astroglial activation.

The origin of the increased number of GFAP-expressing cells that appear in response to neurologic insults has been the subject of intense discussion over the last decade. Specifically, the debate has focused on the question of whether reactive astrocytosis represents primarily the proliferation/migration of GFAP-positive cells or the phenotypic change of local astrocytes. Studies using double-labeling with GFAP antibodies and bromodeoxyuridine or tritiated thymidine to identify dividing astrocytes have shown that, at least in acute lesions, mitotic division (proliferation) of GFAP-expressing cells does not account

for the majority of GFAP-positive cells that appear in response to the injury (for review, see Ref. 211). Furthermore, we have been unable to find convincing *in vivo* evidence that mature GFAP-positive astrocytes of adult brains are able to migrate effectively. Hence, it is likely that the appearance of GFAP-positive astrocytes in regions of acute neural injury represents primarily a change in the phenotype of resident astroglia. It can, however, not be excluded that astroglial proliferation contributes more significantly to chronic astrocytosis.

In many instances, the phenotypic changes seen in reactive astrocytes may reflect a substantial increase in astroglial metabolism and protein synthesis, consistent with a "healthy" cellular hypertrophy in response to increased physiologic demands. In other situations, however, astroglial swelling may result from pathologic processes that afflict the astrocyte itself (for review, see Ref. 210).

3. STUDIES ON ACTIVATED ASTROCYTES

The current literature on reactive astrocytosis is extensive. We have attempted a comprehensive review of this subject using rigid selection criteria to produce a practical synthesis that will be easily amenable to consultation. To construct a list of molecules expressed by activated astrocytes we have included information drawn from two types of studies. The first are studies carried out *in vivo* where the expression of a particular molecule or its mRNA was co-localized to reactive astrocytes by immunochemical staining or *in situ* hybridization. For inclusion into the table clear evidence for astroglial expression was required, for example co-labelling with GFAP or demonstration of electron-microscopic features typical of astrocytes. This should ensure that the molecules in question were indeed found in astrocytes rather than in other injury-responsive CNS cells, in particular microglia. The combination of immunostaining with *in situ* hybridization can also help differentiate between accumulation in astrocytes of molecules actually synthesized by these cells and those produced elsewhere and subsequently taken up by the astrocyte. Many interesting leads on the induction of potential astroglial molecules, particularly enzymes, have come from studies on bulk brain extracts. However, because these studies usually do not provide direct proof that astrocytes form the main cellular source of the identified molecules in the pathologically altered CNS, they have not been included in this review.

The second class of information comes from *in vitro* studies. Since the isolation of enriched astrocyte cultures by McCarthy and de Vellis[192] and subsequent refinements, a great deal of experimental work on astrocytes has been carried out *in vitro*. Experiments indicating the upregulation of a molecule by a certain factor *in vitro* may offer clues as to what happens during reactive astrocytosis in the CNS, especially if this factor is known to occur in pathological

conditions. However, while tissue culture studies often provide important leads they can also sometimes be misleading. Therefore, because so much of our current knowledge on astrocytes is based on *in vitro* studies we would like to address a few caveats that should be kept in mind when considering the molecular profile of cultured astrocytes.

A major consideration is the imperfect purity of primary astrocyte cultures because current techniques for purifying astrocytes usually produce cultures of 90–99% purity. Contamination with microglia is particularly problematic because these cells also respond to neural injuries and secrete a number of biologically active molecules such as cytokines. At present, the most definitive assay for determining the cell source of most molecules is the combination of immunostaining with *in situ* hybridisation but this has been carried out only rarely (for an example, see Ref. 287). For inclusion into Table 1, we have favored studies that have addressed the issue of culture purity.

The adult CNS is characterized by the close interaction of many different cell types both through actual cell contact and secretion of factors. Thus a further problem is that cells in nearly pure primary culture have been released from these interactions. This point is illustrated by the fact that astrocytes in tissue culture have different morphologies depending on whether they are cultured alone or with other neural cells. Cultured alone, they bear few processes, however when co-cultured with neurons they develop multiple processes.[110] The physiologic behavior of astrocytes is also dependent on the presence of other neural cells. Cocultivation of astrocytes with neurons induces calcium channel activity in astrocytes which is undetectable in pure astrocyte cultures or in astrocytes co-cultured with oligodendrocytes.[56] Many protocols for the establishment of primary astrocyte cultures include an early exposure of the cells to relatively high concentrations of serum. This represents a major difference from the situation *in vivo* where astrocytes are shielded from blood-derived factors by the blood–brain barrier. In essence there are numerous variables in culture conditions that could dramatically influence the molecular profile of astrocytes *in vitro* and alter the astroglial responsiveness to further stimulation.

Cloned lines of immortalized glial cells such as the rat glioma cell line C6 can circumvent the problem of culture impurity and have yielded an enormous amount of interesting data. However, they differ from astrocytes *in vivo* in many respects, even more so than primary astrocytes. As an example, astrocytes of the adult CNS have only a limited proliferative potential[172,211] and this is reflected to some extent in primary culture. In contrast, immortalized cell lines often proliferate vigorously having been released from many controlling influences, including in some cases contact inhibition. Therefore, findings obtained with immortalized glial cell lines have not been included in Table 1.

Lastly, cell cultures and cell culture-derived reagents (e.g. stocks of viruses) can easily become contaminated with mycoplasma. While very few *in vitro* studies address this possibility it is important not to underestimate mycoplasma as a source of complex artifacts. Recent studies[24] clearly demonstrate that mycoplasma contamination has marked effects on cultured CNS cells, including astrocytes, and is often difficult to detect unless highly sensitive assays are used.

4. Table 1. MOLECULES THAT ARE UPREGULATED DURING ASTROCYTE ACTIVATION: EVIDENCE FROM *IN VIVO* AND *IN VITRO*

Category	Upregulated molecule	Induced by	*In vitro*	*In vivo*
Adhesion	CD44	DD		92
	CS-PG	Trauma		193
	E-NCAM	Excitotox.inj.		161
	E-Selectin	TNFα	132a	
	GHAP	Wallerian degeneration		181
	HNK-1	CPM		95
	HSPG	FCS	8	
	ICAM-1	IFNγ	85, 240, 241	274
		DD		45a
		PHA sup	240	
		conA sup	241	
		IL-1	85	
		IL-1α	240	
		TNFα	85, 132a, 240	
		TNFβ (LT)	85	
		LPS	240	
	IG9	TNFα	132a	
	Laminin	CPM		95
		Trauma		23, 91, 101, 169, 285
		Excitotox. inj.		169
		FCS	8	
	Tenascin (cytotactin)	Trauma		159, 193
	Thrombospondin	PDGF	12	
	VCAM-1	TNFα	132a	
	VLA-1	IL-1β	3	
		TNFα	3	
	VLA-2	IL-1β	3	
		TNFα	3	
	VLA-6	IFNγ	3	
Antigen presentation	MHC class I	IFNα/β	264	
		IFNγ	283	
		Poly I:C	174	
		TNF	157, 185	
		LPS	185	
		conA sup	241	
		Measles particles	185	
		Coronavirus particles	262	262
		Flavivirus infection	174	
		DD, PIBD		268
	MHC class II	IFNγ	21, 77, 85, 125, 184, 187, 241, 275, 283	274, 283
		TNF + IFNγ	21, 85, 185, 275	
		TNF + paramyxovirus particles	185	
		Coronavirus particles	184, 186	
		Paramyxovirus particles	185	
		SSPE, PIBD		268
		Flavivirus infection	174	
		TMEV infection		235
		HTLV 1 infection	124	
		DD		123, 129, 162, 239, 268–270
		Around glioma		83
		conA sup	77, 241	

4. Table 1—*continued*

Category	Upregulated molecule	Induced by	In vitro	In vivo
		A23187 (Ca^{2+}I)	186	
		PMA	186	
		LPS	186	
		Adjuvant	186	
Calcium-binding proteins	S100β	AD/DSD		100
Cytokines/growth factors	aFGF (FGF-1)	AD		266
	bFGF (FGF-2)	Trauma		98, 176, 263
		AD		97
		Ischaemia		144
		IL-1β	6	
		IL-6	6	
		EGF	6	
		βA4 (aa1–42)	7	
	BNDF	TPA	290	
		Ionomycin	290	
		Forskolin	290	
		NE	290	
		Epinephrine	290	
		Dopamine	290	
		NE + quisqualate	290	
		NE + glutamate	290	
	Endothelin 1	LPS	73	
		NE	73	
		PMA	73	
		TNFα	73	
		Thrombin	73a	
		Sarafotoxin S6b	73	
	G-CSF	LPS	180	
		TNFα	4, 180	
		IL-1β	4	
		IL-1β + IFNγ	4	
		TNFα + IFNγ	4	
	GM-CSF	LPS	180	
		TNFα	180	
		IL-1β	4	
	IFNα	NDV infection	168	
		DD		268 [269]
	IFNα/β	PCA	264	
		Flavivirus infection	174	
		Poly I:C	174	
	IFNβ	NDV infection	168	
		DD		268
		SSPE, PIBD		268
	IFNγ	Trauma		246
		DD		268, 269
		SSPE, PIBD		268
	IGF-1	Cuprizone		149
		Ischaemia		94, 163
	IL-1	HIV-1	195	
		ADC		58
		AD/DSD		100
	IL-1α	LPS	168, 180 [89, 114]	
		βA4 (aa1–42)	7	
	IL-1β	LPS	168, 180 [89, 114]	
	IL-6	IL-1α	84	
		IL-1β	4, 22, 84	
		IL-1β + IFNγ	4	
		TNFα	4, 22, 84	
		TNFα + IFNγ	4	
		TNFα + TGFβ1	4	
		LPS	168	
		NDV infection	168	
		LCMV infection	84	

4. Table 1—*continued*

Category	Upregulated molecule	Induced by	*In vitro*	*In vivo*
	IL-8	IL-1β	4	
		TNFα	4	
	M-CSF (CSF-1)	IL-1β	4, 161a	
		TNFα	4, 161a	
	NGF	IL-6	84 [87, 287]	
		aFGF (FGF-1)	287, 288	
		aFGF + IL-1β	287	
		aFGF + TNFα	287	
		aFGF + dbcAMP	288	
		aFGF + TGFβ1	288	
		bFGF (FGF-2)	255, 287, 288	
		EGF	255, 287	
		IL-1β	87, 255, 287	
		TNFα	287 [87]	
		IL-1β + TNFα	87	
		TGFα	255	
		TGFβ1	171	
		FCS	255	
		Excitotox.inj		14
	TGFα	Trauma		136
	TGFβ	IL-1α	59	
	TGFβ1	IL-1α	58	
		ADC		58, 277
		EGF	170	
		FGF	170	
		TGFβ1	170, 171	
		TGFβ1 + FGF	170	
	TGFβ3	TGFβ1 + TGFβ2	170	
	TNF	DD		128
		SSPE		128
	TNFα	NDV infection	168	
		HIV-1	195	
		ADC		271
		DD		248
		LPS	53, 168, 243	
		LPS + IFNγ	53	
		IFNγ + IL-1β	53	
	TNFβ (LT)	NDV infection	168	
Cytoskeleton	IFAP	dbcAMP	1	
		Trauma		1
	MAP 2	Trauma		90
	Vimentin	dbcAMP	76, 96	
		DD		42, 43
		Myel. mut.		50
		CPM		95
		Ischaemia		223, 247
		Wallerian degen.		61
		Irradiation		244
		Ethylnitrosourea		244
		Ataxic CJD		153
		Trauma		38, 224, 285
Early response	AP-1	Endothelin 1	73	
		Sarafotoxin S6b	73	
	c-fos (TIS 28)	TPA	10, 11, 126	
		TGFβ1	171	
		EGF, FGF	10, 11, 126	
		Ganglioside GM₁	10	
		dbcAMP, forskolin	10, 126	
		Carbachol	9	
		NE	9	
		Isoproterenol	9	
		Phenylephrine	9	
	hsp68/70/72	Heat shock	71, 242	
	NGFIA	TPA	10, 11	
	(TIS8, egr-1,	EGF, FGF	10, 11	
	krox-24, zif268)	Ganglioside GM₁	10	

4. Table 1—*continued*

Category	Upregulated molecule	Induced by	*In vitro*	*In vivo*
		dbcAMP, forskolin	10	
		Carbachol	9	
		NE	9	
		Isoproterenol	9	
		Phenylephrine	9	
	NGF1B	TPA	10, 11	
	(nur77, TIS1)	EGF/FGF	10, 11	
		Ganglioside GM$_1$	10	
		dbcAMP, forskolin	10	
		Carbachol	9	
		NE	9	
		Isoproterenol	9	
		Phenylephrine	9	
	PC4 (TIS7)	TPA	10, 11	
		EGF, FGF	10, 11	
		dbcAMP, forskolin	10	
		Carbachol	9	
		NE	9	
		Isoproterenol	9	
		Phenylephrine	9	
	TIS10	TPA	10, 11	
		EGF, FGF	10, 11	
		dbcAMP, forskolin	10	
	TIS11	TPA	10, 11	
		EGF, FGF	10, 11	
		Ganglioside GM$_1$	10	
		dbcAMP, forskolin	10	
		Carbachol	9	
		NE	9	
		Isoproterenol	9	
		Phenylephrine	9	
	TIS21	TPA	10	
		EGF, FGF	10	
		Ganglioside GM$_1$	10	
		dbcAMP, forskolin	10	
		Carbachol	9	
		NE	9	
		Isoproterenol	9	
		Phenylephrine	9	
Eicosanoids	Leukotriene B4	A23187 (Ca^{2+}I)	108	
	Leukotriene C4	A23187 (Ca^{2+}I)	107, 109	
		TPA + A23187	107	
		IL-1β	109	
	Prostaglandin E	LPS	82, 106, 109	
		A23187 (Ca^{2+}I)	108, 109	
		TPA	106, 109	
		sub P	105	
		Physalaemin	105	
		IL-1β	109	
	Prostaglandin E2	LPS	89	
	Thromboxane A2	sub P	105	
		Arachidonic acid	203	
		A23187 (Ca^{2+}I)	203	
	Thromboxane B2	IL-1β	109	
		A23187 (Ca^{2+}I)	109	
		TPA	109	
Enzymes	CAD multidomain complex	Myel. mut.		40
	Ca^{2+}-ATPase	Cold lesion		139
	CA II	DD		42
		Myel. mut.		41, 44
		dbcAMP	143	
	Glutamine synthetase	aFGF (FGF-1)	221	
		bFGF (FGF-2)	221	
		dbcAMP	142	

4. Table 1—*continued*

Category	Upregulated molecule	Induced by	*In vitro*	*In vivo*
		dbcGMP	142	
		Hydrocortisone	142	
		DD		43
	Glutathione-S-transferase Y_b	DD		43
	HO-1	Heat shock	71, 72	
	MAO	AD		204
	NSE	Infarct		276
		Trauma		276
	PKC a	Infarct		54
		AD		54
	PKC a/b	Around glioma		233
Proteases	Calpain I	Excitotox. inj.		251
	Carboxypeptidase E	TPA	145	
	Cathepsin B	AD		205
	Cathepsin D	Scrapie		70
		Leupeptin	280	
		AD		205
	t-PA	Forskolin	267	
	u-PA	PMA	267	
Protease inhibitors	α1-ACT	AD		219
	APP (PN II)	Excitotox. inj.		251, 252
	PA I	Angiotensin II	213	
		IL-1β	236	
		PMA	267	
	PN I (GDN)	Ischaemia		127
	TIMP related protein	Angiotensin II	213	
Epitopes	J1-31	Trauma		226
		DD		179
	LN-1	AD		68
	M1	Trauma		154
	M22	Trauma		284
		TMEV infection		284
	X-hapten (Le^x) (3-fucosyl-*N*-acetyllactosamin)	CPM		95
Receptors	EGF receptor	Infarct		31
		Trauma		207
	Tissue factor	Scrapie infection		72a
	TNFα receptor	IFNγ	21	
	Transferrin receptor	Trauma		215
Transport	Apolipoprotein E	IFNγ	216	
		Scrapie infection		70
	Transferrin	CPM		95
		AD		55
Miscellaneous	α B-crystallin	Infarct/hypoxia		133
		ALS		133
		CJD		133
		Infectious diseases		133
		DD		133
		Leukodystrophies		133
	C3	LPS	165	
	Factor B	LPS	165	
	Galactocerebroside	DD		47
	G_{D3} ganglioside	Neuronal degeneration mutants		166
	LY-6A/E	conA sup	57	
		IFNγ	57	
	MCP (CD46)	CMV infection	99	
	Proenkephalin	IL-1β	206	
		Cold shock	206	
		Isoproterenol	194	
		cpt-cAMP	194	

4. Table 1—*continued*

Category	Upregulated molecule	Induced by	*In vitro*	*In vivo*
	SGP-2	Trauma		64
		Excitotox. inj.		218
	"ω3"-PTBBS	IL-1β	212	
		TNFα	212	

The assignment of molecules to a specific functional category was introduced to facilitate consultation of the table. Note, however, that this assignment is somewhat arbitrary as a number of molecules can exist in different forms or fulfill functions in different categories. For example, there is evidence that components of the amyloid β protein precursor (APP) could function as a protease inhibitor[214,273] or as a serine protease[225] while the structure of the whole precursor molecule resembles that of a cell-surface receptor[138]. In addition, it seems likely that other functions will be identified for many of the above molecules, some of which may be more relevant to the CNS than those they are currently assigned. Because GFAP is a well established marker for reactive astrocytes and colocalization with GFAP was required for inclusion into the table this molecule has not been listed. Separation of inducer molecules/conditions by commas indicates that each inducer was effective when tested in isolation, whereas a plus sign indicates that synergistic effects were observed when both inducers were combined. References in square brackets [ ] contradict the previously quoted reference. For definitions, see abbreviations list.

5. WHAT DIFFERENTIATES ACTIVATED FROM RESTING ASTROCYTES? TOWARDS A FUNCTIONAL CHARACTERIZATION OF REACTIVE ASTROCYTES

The transition of astrocytes from the resting to the activated state is associated with the expression of new molecules not normally detectable in quiescent astroglia as well as with the upmodulation of factors that are found in resting astrocytes at lower levels. Table 1 lists a number of molecules whose expression in astrocytes increases upon astroglial stimulation and, hence, may provide a molecular profile of reactive astrocytosis. From this table, it appears that reactive astrocytes are equipped with a large armamentarium of molecules that allows them to participate in many important biologic functions. In the subsequent sections we will speculate how the expression of specific groups of molecules could relate to the function of reactive astrocytes.

5.1. Mechanical functions and tissue repair

As outlined above astrocytes undergo dramatic changes upon activation which are likely to have functional consequences. It remains, however, controversial if the induced changes are generally beneficial or detrimental in nature (reviewed in Ref. 231). On one hand, it is conceivable that the increase in cytoskeletal proteins within reactive astrocytes may assist wound repair by stabilizing the tissue surrounding neural injuries. The glial scar formed by reactive astrocytes may also help to wall off areas of tissue necrosis, excluding non-neural cells from the CNS parenchyma and appears to fill in the space that results from neuronal loss.[230]

On the other hand, it has been suggested that the glial scar may form a barrier that could hinder regenerative processes such as neurite outgrowth.[230,232] Central neurons do not regenerate effectively after injury. The studies of Aguayo and colleagues indicate that this is due not to an intrinsic inability of these neurons to regenerate but to the environment present

within the CNS.[2] Electron-microscopic analysis of regenerating axons revealed that arrest of axonal growth in the CNS occurs in the immediate vicinity of reactive astrocytes.[175] This observation together with the finding that reactive astrocytes *in vivo* express molecules which inhibit neurite extension *in vitro*[193] suggests that astrocytes can actively inhibit regeneration.

While it is difficult to prove that dense gliotic scars do not mechanically block axonal growth, *in vitro* evidence suggests that astrocytes themselves are not necessarily inhibitory to regeneration (reviewed in Refs 111,182). Furthermore, reactive astrocytes do not prevent PC12 cells from extending neurites over glial scars in optic nerve explants.[63] Most conclusively, the *in vivo* experiments of Gage and Kawaja showed that in the presence of NGF (produced by transplanted fibroblasts), reactive astrocytes could, in fact, provide a substrate for the growth of sympathetic neurites.[140] These findings demonstrate that, at least in certain experimental situations, astrocytes do not inhibit but may even promote regeneration.

A role for reactive astrocytes in regeneration and tissue repair is also supported by their molecular profile (see Table 1) which suggests both a production of, and interaction with, the extracellular matrix. *In vivo* astrocytes express extracellular matrix molecules such as laminin, chondroitin-6-sulphate proteoglycan and glial hyaluronate adhesion protein, a hyaluronate binding protein. *In vitro*, they are also able to secrete glycosaminoglycans.[8,135] Reactive astrocytes may interact with extracellular matrix and other CNS cells via adhesion molecules such as embryonic neural cell adhesion molecule and cytotactin/tenascin.

Transforming growth factor (TGF)-β1 has been shown to be increased in reactive astrocytes after CNS stab wounds.[177] Logan and colleagues proposed that astroglial secretion of TGF-β1 may attract fibroblasts into the lesion site, regulate their deposition of extracellular matrix proteins and synthesis of degradative

enzymes, and play a role in controlling angiogenesis in the scar. Hence, astrocytes may be important in controlling the deposition of scar tissue after injury and its vascularization.[177]

The production of proteases and protease inhibitors might allow astrocytes to further remodel the extracellular matrix at sites of neural injury and to clear up the debris of degenerating cells. While the activity of these molecules would thus assist in wound repair it is also conceivable that astroglial proteases or protease inhibitors have detrimental effects in certain pathologic conditions. The production of calcium activated proteases by reactive astrocytes has, for example, been implicated in the degeneration of neurons after ischemia, and in the production of the amyloid β protein,[229] a protein that accumulates abnormally in the brains of patients with Alzheimer's disease.

Destruction or degeneration of white matter tracts in the CNS leads to the release of large quantities of myelin lipids. Apolipoprotein E (apoE) is a major constituent of both low- and high-density lipoproteins and plays an important role in lipid transport and metabolism. Within the CNS apoE is constitutively produced by astrocytes,[35,202,259] and the astroglial expression of apoE has been found to be upmodulated during reactive astrocytosis.[70] Astrocyte-derived apoE may help deliver lipids to other CNS cells for membrane biosynthesis and facilitate the removal of cholesterol into the periphery. Consistent with the latter possibility is the increase in plasma apoE levels observed during the active phase of experimental allergic encephalomyelitis (EAE),[250] a demyelinating disease of the CNS.

5.2. Immune responses

One of the major functions proposed for reactive astrocytes is the initiation of immune responses within the CNS (e.g., see Ref. 112). When treated with factors such as interferon-γ, astrocytes in vitro are induced to express molecules involved in immune responses, for example major histocompatibility complex (MHC) antigens and adhesion molecules such as intercellular adhesion molecule 1. Cultured astrocytes are able to present antigens to MHC class I and to MHC class II restricted T lymphocytes[80,81,174,261] and to produce many different cytokines. In addition, a number of in vivo immunohistochemical studies have reported the expression of MHC molecules on small numbers of reactive astrocytes in different pathologic conditions (see Table 1). Taken together, these findings support speculations that (i) antigen presentation by MHC expressing astrocytes and astroglial production of cytokines might play a crucial role in CNS-immune interactions; and that (ii) astrocyte responses could be causally involved in the pathogenesis of various immune-mediated neurologic diseases (reviewed by Refs 78,86,112).

However, recent in vivo experimental evidence has called the postulated immunologic functions of astrocytes into question. While injection of interferon-γ into the CSF space produces extensive induction of MHC class I and II on microglia, only a limited induction of MHC molecules was found on astrocytes.[274,283] Systemic injection of interferon-γ[156,257] or intracerebral injection of lipopolysaccharide[5] also induced MHC class II expression primarily on microglia. Furthermore, studies on EAE, amyotrophic lateral sclerosis and intracerebral transplantation of allografts have provided ample evidence that CNS-immune interactions are mediated primarily by microglia rather than by astrocytes.[93,121-123,141,156,158,188] These studies indicate that astrocytes probably do not function as the main antigen presenting cells in the CNS and argue against a major role for astrocytes in the initiation of immune-mediated neurologic diseases. However, as outlined below, astrocytes may still have important regulatory effects on inflammatory and immune responses directed at the CNS.

5.3. Blood–central nervous system interface

The interaction of the CNS with blood-borne factors and cells is of paramount importance in the pathogenesis of a number of neurologic diseases. This interaction is controlled, in part, by the blood–brain barrier which is formed by the unique properties of the CNS endothelial cells. Astrocytes are in intimate contact with these cells by their endfeet processes[222] and several lines of evidence suggest that they may participate in the control of the blood–CNS interface.

Astrocytes could influence the entry of hematogenous cells into the CNS as well as their intraparenchymal activity through the secretion of cytokines. As indicated in Table 1, astrocytes appear to produce a large number of cytokines and inflammatory mediators in vitro. Unfortunately, in vivo confirmation of these findings is lacking in most cases and the possibility of microglial contamination of astrocyte cultures has not always been addressed rigorously. However, the few in vivo studies that are available support the postulate that astroglial cytokine production may be involved in the pathogenesis of viral and immune mediated neurologic diseases. For example, Wahl and colleagues[277] have shown that reactive astrocytes in HIV-1 infected brains express TGFβ and speculate that this cytokine enhances the recruitment of HIV-1-infected monocytic cells. Hence, the astroglial TGFβ production could both contribute to the inflammatory changes seen in HIV-1 associated encephalomyelitis and also increase the spread of cell-borne virus in(to) the CNS. It should be noted in this context, however, that many cytokines appear to fulfill a multitude of functions (for review see Ref. 265) and that their effects in the intact adult CNS are only now beginning to be defined.[45] It is, therefore, perhaps not too surprising that the effects of cytokines in specific neurologic diseases have been difficult to predict.[30,39,134,146]

Proteases and protease inhibitors could be used by astrocytes to regulate the concentration of a variety of proteins in the parenchyma, including cytokines and proteases derived from the blood or from other brain cells. Such a role has recently been suggested for protease nexin I,[51,127] a protease inhibitor found to be increased in reactive astrocytes.[127] *In vitro* data indicate that protease–protease inhibitor complexes can induce the synthesis of acute phase proteins in response to injury[148,152] and stimulate the directed migration of neutrophils.[15] Because reactive astrocytes express both cathepsin G-like protease and alpha1-antichymotrypsin-like protease inhibitor activities (Abraham *et al.*, unpublished observations) such complexes may form around reactive astrocytes where they would directly or indirectly increase the release of cytokines and acute phase proteins from astrocytes, endothelial cells, microglia or blood derived cells.

In head trauma and intracerebral hemorrhage the blood–CNS interface is acutely disrupted. This disruption causes red blood cells to extravasate, lyse and release iron-containing compounds into the CNS. Consequences of such lesions include focal encephalomalacia, hemosiderin deposition and occasionally the development of recurrent seizures. Studies in experimental animals suggest that some of the clinical sequelae of brain trauma are related to the induction of free radicals by the iron moieties within extravasated blood, and the subsequent peroxidation of lipids.[282] The expression of transferrin, which mobilizes and transports iron, and its receptor in reactive astrocytes[55,95,215] suggests that these cells may help diminish excess iron loads around sites of tissue injury.

The blood–brain barrier shields the CNS from toxic metals present within the blood. However, in a number of locations the blood–brain barrier is leaky.[25] Surrounding these sites one finds a class of GFAP-positive cells termed Gomori astrocytes (reviewed in Ref. 245) which may have an important role in controlling metal toxicity. These cells increase in number after irradiation[256] and accumulate silver, mercury and lead after systemic administration of these compounds.[245] Gomori astrocytes express metallothionein,[289] a protein which can bind to heavy metals such as cadmium and mercury, detoxifying them in the process. The protein is inducible by heavy metals in various tissues and there is some evidence that this occurs in astrocytes after cadmium administration.[208]

Tissue factor or tissue thromboplastin is a transmembrane glycoprotein that functions as the initiator of the coagulation protease cascade. In the brain tissue factor is expressed predominantly in astrocytes.[72a] In view of the apposition of astroglial endfeet with CNS endothelial cells (see above), tissue factor could help astrocytes form a "hemostatic envelope" around the vascular system of the CNS. The upregulation of tissue factor expression by reactive astrocytes in nonhemorrhagic conditions such as scrapie suggests that tissue factor may fulfill additional functions within the CNS.

5.4. Neurotrophic support

While it has long been realized that astrocytes secrete factors that promote the growth and prolong the survival of neurons in explant culture,[16] so far only a limited number of astroglial molecules that exert trophic effects on neurons have been identified. However, it seems likely that this small group represents the tip of the iceberg. As outlined below some astroglial neurotrophic factors may act directly on neurons whereas others could benefit neurons indirectly through the support of other CNS cells.

Both nerve growth factor (NGF) and basic fibroblast growth factor (bFGF) act as survival and neurite extension factors for some types of cultured neurons.[199,278,286] Astrocytes, in contrast to microglia, are ablear to secret NGF *in vitro*.[287] After trauma, NGF levels are increased in both the optic nerve[178] and the hippocampus,[160,281] and in a separate study, the cellular source of NGF was shown to be astrocytes.[14] Astrocytes also produce bFGF *in vitro* in response to various factors, and in Alzheimer's disease and lesioned brain bFGF has been localized to reactive astrocytes (see Table 1). Recent evidence from tissue culture studies suggests that growth factors such as NGF and bFGF are able to protect central neurons against hypoglycemic/excitotoxic insults by stabilizing neuronal calcium homeostasis.[48,190,191] Reactive astrocytes produce insulin-like growth factor-1 (IGF-1) after ischemia.[94,163] Because IGF-1 has neurotrophic effects,[46,94] this astroglial response may help diminish neuronal loss.

IGF-1 also stimulates oligodendrocyte development and myelination *in vitro*.[200] Work with mice transgenic for IGF-1 supports a similar role for the molecule *in vivo*.[47a] Consistent with the postulated role of IGF-1 in myelination, both IGF-1 and its receptor decrease to minimal levels in the adult brain.[13,18,33] Reactive astrocytes have recently been shown to express IGF-1[149] concomitant with the expression of the IGF-1 receptor by immature oligodendrocytes around the lesion.[149] This raises the possibility that reactive astrocytes play an important role in the remyelination of the adult CNS. However, reactive astrocytes expressing tumor necrosis factor α (TNFα) have been identified in multiple sclerosis lesions.[128,248] While there is no direct evidence for a role of astrocyte-derived TNFα in demyelination *in vivo*, this cytokine has been shown to be toxic to oligodendrocytes in culture.[234,249] Consequently, it remains undecided at this point if the role of astrocytes in inflammatory demyelinating diseases is beneficial or detrimental.

5.5. Control of neurotoxins

High concentrations of excitatory neurotransmitters are extremely toxic to neurons (reviewed in Ref. 52).

Evidence is increasing that the neuronal death or impairment that follows acute neurologic insults (e.g. hypoxia/ischemia, mechanical trauma, prolonged seizures) may, in the large part, be mediated by an increase in the extracellular concentration of excitatory amino acids such as glutamate. A role for glutamate toxicity has also been proposed in more chronic neurologic diseases such as Alzheimer's disease,[147,189] AIDS dementia (reviewed in Ref. 173), sulfite oxidase deficiency, Guam amyotrophic lateral sclerosis and Huntington's disease (reviewed in Ref. 52).

In the presence of high glutamate levels, removal of astrocytes from mixed cultures quickly leads to neuronal cell death.[237,238,260] *In vitro* studies suggest that amino acid transmitters may be removed from the extracellular space by astrocytic uptake mechanisms (reviewed in Refs 79,113,132). Astrocytes also contain glutamine synthetase which converts glutamate to glutamine and helps detoxify ammonia in the CNS. This enzyme has been shown to be upmodulated in reactive astrocytes in pathologic conditions.[43,209] Hence, it is possible that astrocytes participate in the removal of neurotoxins by both enhanced uptake and metabolic turnover. The recent cloning of the transporters for GABA and the amines, noradrenalin, serotonin and dopamine (for review see Refs 254,272) should supply molecular tools that will help in understanding the role of reactive astrocytes in regulating other neurotransmitters.

In a number of recent studies, Heyes and his colleagues have provided evidence that the NMDA receptor agonist quinolinic acid is involved in the pathogenesis of the neurologic dysfunction that can be associated with HIV-1 infection and other inflammatory diseases of the nervous system.[104,115,120] Because the quinolinic acid metabolizing enzymes, 3-hydroxyanthranilic acid oxygenase and quinolinic acid phosphoribosyltransferase, have been localized to astrocytes *in vivo*,[150,151] it is conceivable that the expression of these enzymes increases in astrocytes responding to inflammatory lesions. While an upmodulation of these enzymes in reactive astrocytes has apparently not yet been documented in the literature such an astroglial response could serve important protective functions in a variety of neurologic diseases.

Free radicals form another group of chemicals that could be extremely toxic to the nervous system[102,103] and the ability to eliminate or control these entities may be critical after neurologic insults such as cerebral hemorrhage.[282] While this issue does not appear to have been directly studied in reactive astrocytes, there is evidence that astrocytes may play a role in the antioxidant defense system. The biopigments biliverdin and bilirubin are potent antioxidants.[258] They are synthesized by a pathway which is rate-limited by the heme oxygenase isozymes HO-1 and HO-2. HO-1 is expressed by astrocytes in culture[72] and induced in glial cells after heat shock to the rat brain.[74] Apolipoprotein D, proposed also to be involved in the production of antioxidants,[220] appears to be expressed by astrocytes in the normal CNS[34] and increases in the peripheral nervous system after injury.[34] Antioxidant enzymes such as superoxide dismutase and catalase have been proposed to be induced in reactive astrocytes in Alzheimer's disease.[217] If the above studies are confirmed by double-labeling of reactive astrocytes it would be interesting to know if the antioxidant enzymes are induced solely to protect the astrocytes themselves or whether they are also secreted to influence the environment of other neural cells.

6. CONCLUSIONS AND FUTURE STUDIES

In this review we have constructed a molecular profile of reactive astrocytes and drawn conclusions from this profile on the functions reactive astrocytes may fulfill in neurologic diseases. As a result we have hypothesized that activated astroglia may benefit the damaged nervous system by participating in several important biologic processes such as the regulation of neurotransmitter levels, the repair of the extracellular matrix, control of the blood–CNS interface, transport processes, and trophic support of other CNS cells. The detectability of specific molecules depends not only on their absolute levels but also on the sensitivity of the assays used, i.e. the inability to detect certain markers does not necessarily exclude their presence. Consequently, it cannot be excluded that "resting" astrocytes also fulfill some of the functions assigned to reactive astrocytes but at a lower level.

We would like to emphasize that our extrapolation of the functions of reactive astrocytes from the molecules they express is speculative and based on current knowledge. It seems likely that other functions will be identified for many of these molecules, some of which may be more relevant to the CNS than the ones they are currently assigned. We also expect that the ongoing discovery of CNS-specific genes (see Ref. 198 for review) and the development of novel molecular probes/assays will significantly expand the molecular profile of reactive astrocytes.

In the majority of CNS diseases clinical signs and symptoms are related most directly to an impairment of neuronal functions. While little evidence exists that the activity of reactive astrocytes is directly detrimental to the nervous system, it is conceivable that an impairment of astroglial performance could exacerbate neuronal dysfunction. This pathogenetic scenario may, for example, exist in hepatic encephalopathy (see Ref. 210 for review), scrapie in which prions appear to accumulate first in astrocytes[69] or in AIDS dementia where viral or macrophage-derived products could interfere with astroglial functions such as neurotrophic support and/or elimination of excitotoxins.[36,37,49,173,228]

An inspection of Table 1 reveals that reactive astrocytes express a number of molecules that are typically produced by hematogenous cells. This observation could reflect the evolutionary response of

the CNS to two different types of selective pressures. There appears to be a need for the CNS to restrict the access of hematogenous cells as evidenced by the blood–brain barrier and the delayed invasion of neutrophils and monocytes after injections of LPS into the brain parenchyma when compared with peripheral sites.[5] On the other hand, early stages of wound repair within the CNS may depend on the fast action of those factors which are released into peripheral wounds by hematogenous cells. Recent evidence suggest that astrocytes are able to respond to neural injury with great rapidity.[130,131,201] Therefore, astrocytes may fulfill some of the functions that are carried out by invading hematogenous cells during wound repair in peripheral sites. We would like to emphasize at this point that the response of the CNS to neurologic injury involves many cell types in addition to astrocytes and that the assignment of certain functions to astrocytes by no means excludes the participation of other cells. An assessment of the relative contributions of microglia and astrocytes to early wound repair within the CNS should be a particularly fruitful subject for future studies.

Recent data indicate that subpopulations of astrocytes can be distinguished both at the molecular[17,164,183,197] and functional[67,227] levels. In leukocyte research the development of molecular markers has revealed a great functional diversity among cells that appear morphologically very similar. It seems likely that future molecular studies will also reveal a functional heterogeneity of reactive astrocytes that far surpasses their morphologic differences. It will be particularly interesting to find out whether there are subpopulations of astrocytes that respond to some neurologic disease processes but not to others. In a similar vein, it needs to be determined whether diverse neurologic diseases provoke the expression of the same set of astroglial molecules or whether the astroglial response is specific, with different molecules being expressed by astrocytes responding to different neurologic insults.

It should also be pointed out that the response of astrocytes to neurologic insults has so far been documented primarily by immunohistochemical staining and in situ hybridization. This methodologic approach provides a static image of the molecular profile of reactive astrocytes and does not allow the resolution of fast physiologic changes. Recent evidence suggests that astrocytes participate in neurophysiologic processes that occur within seconds. For example, the response of neurons to electrical stimulation was shown to be accompanied by rapid Ca^{2+} oscillations within astrocytes in hippocampal slice preparations.[62] Astrocytes themselves are also capable of responding to neurotransmitters (reviewed in Refs 19,26). Because of their close association with nodes of Ranvier,[32,196] perinodal astrocytes may be in a particularly suitable position to influence neurophysiologic processes. It is possible that rapid responses of astrocytes are of greater functional importance in neurologic diseases than the molecular changes that occur over hours or days. Yet, this type of response cannot be detected with conventional histopathologic methods. The application of novel neurophysiologic and cell biologic techniques should allow a high chronologic and spatial resolution of astroglial responses and is expected to substantially further our understanding of astroglial functions in health and disease. We suspect that this type of analysis will reveal "reactive astrocytosis" to be a much more dynamic process than is currently conceptualized.

We would like to end this Commentary by pointing out the imbalance between in vitro and in vivo studies in astroglial research. Judged by the number of in vitro vs in vivo studies (see Table 1), much greater efforts appear to have been placed on the extensive analysis of astrocytes in culture than on the in vivo confirmation of existing in vitro findings. However, reactive astrocytes in the adult brain and primary astrocytes in cell culture differ in many respects and results obtained in vitro and in vivo often do not overlap (see Table 1 and, for an example, Ref. 170). It is, therefore, to be hoped that future research will complement the vigorous efforts made in cell culture systems with the development and exploitation of models that allow the analysis of reactive astrocytes in the intact organism.

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