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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 their role in neurologic disease. At present, reactive astroglosis 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.

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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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Astrocytosis is seen in AIDS dementia, a variety of other viral infections, prion-associated spongiform encephalopathies, inflammatory demyelinating disease, acute traumatic brain injury, and such neurodegenerative diseases as Alzheimer's disease. The prominence of astroglial reactions in various diseases, the rapidity of astroglial response and the evolutionary conservation of astrocytosis indicate that reactive astrocytes fulfill important functions for the CNS. Yet, the exact role reactive 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 and represents the prototypic marker of astroglial activation. 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. 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 whether 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. 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 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 astrocytes represent 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 vitro 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 immunocytochemical 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 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 astrogensis 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. 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. 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 cell lines 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 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\textsuperscript{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           | TNF\textsubscript{\gamma} | 132a     |
|                | GHAP                 | Wallerian degeneration    | 181      |
|                | HNK-1                | CPM                       | 95       |
|                | HSPG                 | FCS                       | 8        |
|                | ICAM-1               | IFN\textsubscript{\gamma} | 85, 240, 241 | 274 |
|                |                      | DD                        | 45a      |
|                |                      | PMA sup                   | 240      |
|                |                      | TNF\textsubscript{\alpha} | 241      |
|                |                      | IL-1                      | 85       |
|                |                      | IL-1\alpha                | 240      |
|                |                      | TNF\textsubscript{\alpha} | 85, 132a, 240 | 85  |
|                |                      | TNF\beta (LT)             | 85       |
|                |                      | LPS                       | 240      |
| Laminin        | TGF\textsubscript{\alpha} | 132a       | 95       |
|                |                      | Trauma                    | 23, 91, 101, | 169, 285 |
|                |                      | excitotox. inj.           | 169      |
|                |                      | FCS                       | 8        |
| Tenascin       |                      | Trauma                    | 159, 193 |
| (cytotactin)   |                      |                           |          |
| Thrombospondin| PDGF                 | 12                        |          |
|                |                      | TNF\textsubscript{\alpha} | 132a     |
|                |                      | IL-1\beta                 | 3        |
|                |                      | TNF\textsubscript{\alpha} | 3        |
|                |                      | IL-1\beta                 | 3        |
|                |                      | TNF\textsubscript{\alpha} | 3        |
| VLA-6          |                      | IFN\textsubscript{\gamma} | 3        |
| VLA-1          |                      |                           |          |
| VLA-2          |                      |                           |          |
| Antigen        | MHC class I          | IFN\alpha/\beta           | 264      |
| presentation   |                      | IFN\textsubscript{\gamma} | 283      |
|                |                      | Poly 1:C                  | 174      |
|                |                      | TNF                       | 157, 185 |
|                |                      | LPS                       | 185      |
|                |                      | conA sup                  | 241      |
|                |                      | measles particles         | 185      |
|                |                      | Coronavirus particles     | 262      |
|                |                      | Flavivirus infection      | 174      |
|                |                      | DD, PIBD                  | 268      |
|                | MHC class II         | IFN\textsubscript{\gamma} | 21, 77, 85, 125, | 274, 283 |
|                |                      |                           | 214, 187, 241, | 275, 283 |
|                |                      |                           |           |
|                |                      |                           |           |
|                |                      |                           |           |
|                |                      |                           |           |
|                |                      |                           |           |
|                |                      |                           |           |
|                |                      |                           |           |

Around glioma conA sup 77, 241
### 4. Table 1—continued

| Category                        | Upregulated molecule | Induced by              | \(\text{In vitro}\) | \(\text{In vivo}\) |
|--------------------------------|----------------------|-------------------------|----------------------|----------------------|
| Calcium-binding proteins       | S100β                | AD/ADSD                 | 100                  |                      |
| Cytokines/growth factors       | aFGF (FGF-1)         | AD                      | 266                  |                      |
|                                | bFGF (FGF-2)         | Trauma                  | 99, 176, 263         |                      |
|                                |                      | AD                      | 97                   |                      |
|                                |                      | Ischaemia               | 144                  |                      |
|                                |                      | IL-1β                   | 6                    |                      |
|                                |                      | IL-6                    | 6                    |                      |
|                                |                      | FGF                     | 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                   |                      |
|                                |                      | TNFz                    | 73                   |                      |
|                                |                      | Thrombin                | 73a                  |                      |
|                                |                      | Sarafotoxin S6b         | 73                   |                      |
|                                | G-CSF                | LPS                     | 180                  |                      |
|                                |                      | TNFz                    | 4, 180               |                      |
|                                |                      | IL-1β                   | 4                    |                      |
|                                |                      | IL-1β + IFNγ            | 4                    |                      |
|                                |                      | TNFz + IFNγ             | 4                    |                      |
|                                | GM-CSF               | LPS                     | 180                  |                      |
|                                |                      | TNFz                    | 180                  |                      |
|                                |                      | IL-1β                   | 4                    |                      |
|                                | IFNα                 | NDV infection           | 168                  |                      |
|                                | DD                   | 268 [269]               |                      |                      |
|                                | IFNα/β               | PCA                     | 264                  |                      |
|                                |                      | Flavivirus infection    | 174                  |                      |
|                                |                      | Poly 1:C                | 174                  |                      |
|                                | IFNβ                 | NDV infection           | 168                  |                      |
|                                | DD                   | 268                    |                      |                      |
|                                | IFNγ                 | Trauma                  | 246                  |                      |
|                                |                      | DD                      | 268, 269             |                      |
|                                | ISPE, PIBD           | 268                    |                      |                      |
|                                | IGF-1                | Cuprizone               | 149                  |                      |
|                                |                      | Ischaemia               | 94, 163              |                      |
|                                | IL-1                 | HIV-1                   | 195                  |                      |
|                                | ADC                  | 58                     |                      |                      |
|                                | AD/ADSD              | 100                    |                      |                      |
|                                | IL-1α                | LPS                     | 168, 180             |                      |
|                                |                      | [89, 114]               |                      |                      |
|                                | IL-1β                | LPS                     | 168, 180             |                      |
|                                |                      | [89, 114]               |                      |                      |
|                                | IL-6                 | LPS                     | 168                  |                      |
|                                |                      | NDV infection           | 168                  |                      |
|                                |                      | LCMV infection          | 84                   |                      |

*continued overleaf*
### 4. Table 1—continued

| Category       | Upregulated molecule | Induced by                                                                 | \textit{In vitro} | \textit{In vivo} |
|----------------|----------------------|-----------------------------------------------------------------------------|-------------------|-----------------|
| IL-8           | IL-1β                | 4                                                                           | 4                 |                 |
|                | TNFα                 | 4                                                                           |                   |                 |
| M-CSF (CSF-1)  | IL-1β                | 4, 161a                                                                     | 4, 161a           |                 |
|                | TNFα                 |                                                                             |                   |                 |
| 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                                                                         |                   |                 |
|                | IL-1β                | 87, 255, 287                                                                |                   |                 |
|                | TNFα                 | 387 [87]                                                                    |                   |                 |
|                | IL-1β + TNFα         | 87                                                                          |                   |                 |
|                | TGFβ2                | 255                                                                         |                   |                 |
|                | TGFβ1                | 171                                                                         |                   |                 |
|                | FCS                  | 255                                                                         |                   |                 |
|                | Excitotoxin inj      | 14                                                                          |                   |                 |
| TGFβ2          | Trauma               | 136                                                                         |                   |                 |
| TGFβ1          | IL-1z                | 59                                                                          |                   |                 |
|                | IL-1z                | 58                                                                          |                   |                 |
|                | ADC                  | 58                                                                          | 277               |                 |
|                | EGF                  | 170                                                                         |                   |                 |
|                | FGF                  | 170                                                                         |                   |                 |
|                | TGFβ1                | 170                                                                         | 171               |                 |
|                | TGFβ1 + FGF          | 170                                                                         |                   |                 |
| TGFβ3          | TGFβ1 + TGFβ2        | 170                                                                         |                   |                 |
| TNFα           | DD                   | 128                                                                         |                   |                 |
|                | SSPE                 | 128                                                                         |                   |                 |
|                | NVD infection        | 168                                                                         |                   |                 |
|                | HIV-1                | 195                                                                         |                   |                 |
|                | ADC                  | 271                                                                         | 248               |                 |
|                | DD                   | 248                                                                         |                   |                 |
|                | LPS                  | 53, 168, 243                                                                |                   |                 |
|                | LPS + IFNγ           | 53                                                                          |                   |                 |
|                | IFNγ + IL-1β         | 53                                                                          |                   |                 |
| TNFβ (LT)      | NVD infection        | 168                                                                         |                   |                 |
|                | Aphasia              | 168                                                                         |                   |                 |
| Cytoskeleton   |                      |                                                                             |                   |                 |
|                |                      |                                                                             |                   |                 |
| IFAP           |                      | dbcAMP                                                                      | 1                 |                 |
|                |                      | Trauma                                                                      | 1                 |                 |
| MAP 2          |                      | Trauma                                                                      | 90                |                 |
| Vimentin       |                      | dbcAMP                                                                      | 76, 96            |                 |
|                |                      | Trauma                                                                      |                   |                 |
|                |                      | dbcAMP                                                                      |                   |                 |
|                |                      | Myel. mut.                                                                  | 42, 43            |                 |
|                |                      | CPM                                                                         | 50                |                 |
|                |                      | Ischaemia                                                                   | 95                |                 |
|                |                      | Wallerian degen.                                                            | 223, 247          |                 |
|                |                      | Irradiation                                                                 | 244               |                 |
|                |                      | Ethynitrosourea                                                             | 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 GM,                                                             | 10                |                 |
|                |                      | dbcAMP, forskolin                                                           | 10, 126           |                 |
|                |                      | Carbachol                                                                   | 9                 |                 |
|                |                      | NE                                                                           | 9                 |                 |
|                |                      | Isoproterenol                                                               | 9                 |                 |
|                |                      | Phenylephrine                                                               | 9                 |                 |
|                |                      | heat shock                                                                  | 71, 242           |                 |
| hsp68/70/72    |                      | Heat shock                                                                   | 71, 242           |                 |
| NGF1A          |                      | TPA                                                                         | 10, 11            |                 |
| (TIS8, egr-1,  |                      |                                                                             |                   |                 |
|                 | krox-24, zif268)      |                                                                             |                   |                 |
|                |                      |                                                                             |                   |                 |

\[continued\]
### 4. Table 1—continued

| Category | Upregulated molecule | Induced by | In vitro | In vivo |
|----------|----------------------|------------|----------|---------|
| NGF1B    |                      |            |          |         |
| (nur77, TIS1) |                      |            |          |         |
| Eicosanoids |                      |            |          |         |
| Leukotriene B4 | A23187 (Ca²⁺1)      | 108        |          |         |
| Leukotriene C4 | A23187 (Ca²⁺1)      | 107, 109   |          |         |
|            | TPA + A23187        | 107        |          |         |
|            | IL-1β               | 109        |          |         |
| Prostaglandin E | LPS                  | 82, 106, 109 |          |         |
|            | A23187 (Ca²⁺1)      | 108, 109   |          |         |
|            | TPA                 | 106, 109   |          |         |
|            | sub P               | 105        |          |         |
|            | Physalaemin         | 105        |          |         |
|            | IL-1β               | 109        |          |         |
| Prostaglandin E2 | LPS                  | 89         |          |         |
| Thromboxane A2 | sub P               | 105        |          |         |
| Thromboxane B2 | Arachidonic acid    | 203        |          |         |
|            | A23187 (Ca²⁺1)      | 203        |          |         |
|            | IL-1β               | 109        |          |         |
|            | A23187 (Ca²⁺1)      | 109        |          |         |
|            | TPA                 | 109        |          |         |
| Enzymes   | CAD multidomain complex | Myel. mut. | 40       |         |
| Ca²⁺-ATPase | Cold lesion         |            | 139      |         |
| CA II     | DD                  |            | 42       |         |
|           | Myel. mut.         |            | 41, 44   |         |
|           | dbcAMP              |            |          |         |
| Glutamine synthetase | aFGF (FGF-1) | 221        |          |         |
|           | bFGF (FGF-2)        | 221        |          |         |
|           | dbcAMP              | 142        |          |         |

*continued overleaf*
Table 1—continued

| Category            | Upregulated molecule                                                                 | Induced by                  | In vitro | In vivo |
|---------------------|--------------------------------------------------------------------------------------|-----------------------------|----------|---------|
| **Proteases**       |                                                                                      |                             |          |         |
|                     | Glutathione-S.-transferase Y$_y$                                                     | dbcGMP                      | 142      | 43      |
|                     | HO-1                                                                                  | Heat shock                  | 71, 72   |         |
|                     | MAO                                                                                   | AD                          |          | 204     |
|                     | NSE                                                                                   | Infarct                     |          | 276     |
|                     | PKC a                                                                                  | Infarct                     |          | 276     |
|                     | PKC a/b                                                                               | Around glioma               |          | 233     |
|                     | Calpain I                                                                              | Excitotox. inj.             |          | 251     |
|                     | Carboxypeptidase E                                                                   | TPA                         | 145      |         |
|                     | Cathepsin B                                                                           | AD                          |          | 205     |
|                     | Cathepsin D                                                                           | Scrapie                     |          | 70      |
|                     | t-PA                                                                                   | Leupeptin                   | 780      |         |
|                     | u-PA                                                                                   | AD                          |          | 205     |
|                     | APP (PN II)                                                                           | AD                          |          |         |
|                     | PA I                                                                                   | Angiotensin II              | 213      | 251     |
|                     | APP I                                                                                 | IL-1$\beta$                 | 236      | 252     |
|                     | PN I (GDN)                                                                             | PMA                         | 267      |         |
|                     | TIMP related protein                                                                  | Ischaemia                   | 127      |         |
| **Epitopes**        | J1-31                                                                                 | Trauma                      |          | 226     |
|                     | LN-1                                                                                   | AD                          | 68       |         |
|                     | M1                                                                                     | Trauma                      | 154      |         |
|                     | M22                                                                                   | Trauma                      | 284      |         |
|                     | X-hapten (Le*) (1-fucosyl-N-acetyllactosamin)                                           | CPM                         | 95       |         |
| **Receptors**       | EGF receptor                                                                           | Infarct                     | 31       |         |
|                     | Tissue factor                                                                          | Trauma                      | 207      |         |
|                     | TNF$\alpha$ receptor                                                                  | Scrape infection            | 72a      |         |
|                     | Transferin receptor                                                                   | IFN$\gamma$                 | 21       |         |
| **Transport**       | Apolipoprotein E                                                                      | IFN$\gamma$                 | 216      |         |
|                     | Transferrin                                                                           | Scrape infection            | 70       |         |
| **Miscellaneous**   | $\alpha$-B-crystallin                                                                  | Infarct/hypoxia             | 133      |         |
|                     | C3                                                                                     | INF$\gamma$                 | 133      |         |
|                     | Factor B                                                                              | INF$\gamma$                 | 133      |         |
|                     | Galactocerebroside                                                                     | INF$\gamma$                 | 133      |         |
|                     | GD$_{10}$ ganglioside                                                                  | INF$\gamma$                 | 133      |         |
|                     | LY-6A/E                                                                               | conA sup                    | 57       |         |
|                     | MCP (CD46)                                                                             | CMV infection               | 99       |         |
|                     | Protoceratid                             | IL-1$\beta$                 | 206      |         |
|                     |                                                                   | Cold shock                  | 206      |         |

continued
that this is due not to an intrinsic inability of these
excluding non-neural cells from the CNS parenchyma
wound repair by stabilizing the tissue surrounding
versial if the induced changes are generally beneficial
It remains, however, contro-
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neural injuries. The glial scar formed by reactive astro-
changes upon activation which are likely to have func-
tional consequences. It remains, however, contro-
Table 1 lists a number of molecules whose expression
function of reactive astrocytes.
5. WHAT DIFFERENTIATES ACTIVATED FROM
RESTING ASTROCVTES? TOWARDS A FUNCTIONAL
CHARACTERIZATION OF REACTIVE ASTROCVTES
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 astroglosis. From this table, it appears that
reactive astrocytes are equipped with a large armamen-
tarium 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 func-
tional consequences. It remains, however, contro-
versial 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 cyto-
skeletal proteins within reactive astrocytes may assist
wound repair by stabilizing the tissue surrounding
neural injuries. The glial scar formed by reactive astro-
cytes 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.~~
On the other hand, it has been suggested that the
glial scar may form a barrier that could hinder re-
generative 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 vitro193
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.64 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 glectaminoglycans.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/tenasin.
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 extra-
cellular 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 astrogial 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,35,202,299 and the astrogial expression of apoE has been found to be upmodulated during reactive astrogliosis.30 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).270 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 lymphocytes80,91,174,201 and to produce many different cytokines. In addition, a number of in vivo immunohistoechemical 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 astrogial 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.274,289 Systemic injection of interferon-γ154,257 or intracerebral injection of lipopolysaccharide 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.75,131,123,141,156,158,188 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 processes222 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 astrogial cytokine production may be involved in the pathogenesis of viral and immune mediated neurologic diseases. For example, Wahl and colleagues277 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 astrogial TGFβ production could both contribute to the inflammatory changes seen in HIV-1 associated encephalomyelitis and also increase the spread of cell borne virus into 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.49 It is, therefore, perhaps not too surprising that the effects of cytokines in specific neurologic diseases have been difficult to predict.30,39,144,146
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.\textsuperscript{51,127} A protease inhibitor found to be increased in reactive astrocytes.\textsuperscript{17} In vitro data indicate that protease-protease inhibitor complexes can induce the synthesis of acute phase proteins in response to injury.\textsuperscript{148,162} and stimulate the directed migration of neutrophils.\textsuperscript{11} Because reactive astrocytes express both cathepsin G-like protease and alphalantichymotrypsin-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, hemoisiderin 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.\textsuperscript{282} The expression of transferrin, which mobilizes and transports iron, and its receptor in reactive astrocytes\textsuperscript{25,95,215} 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.\textsuperscript{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\textsuperscript{256} and accumulate silver, mercury and lead after systemic administration of these compounds.\textsuperscript{245} Gomori astrocytes express metallothionein,\textsuperscript{200} 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.\textsuperscript{200}

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.\textsuperscript{724} In view of the apposition of astroglial endfoot 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,\textsuperscript{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.\textsuperscript{190,278,281} Astrocytes, in contrast to microglia, are able to secrete NGF in vitro.\textsuperscript{287} After trauma, NGF levels are increased in both the optic nerve\textsuperscript{74} and the hippocampus,\textsuperscript{160,281} and in a separate study, the cellular source of NGF was shown to be astrocytes.\textsuperscript{42} 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 hemo-

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,147,149 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.237,238,240 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, noradrenaline, 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 vitro,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 astrogial 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 system102,103 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 yet been documented in the literature such an astrogial response could serve important protective functions in a variety of neurologic diseases.

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 function. While little evidence exists that the activity of reactive astrocytes is directly detrimental to the nervous system, it is conceivable that an impairment of astrogial performance could exacerbate neuronal dysfunction. This pathogenetic scenario may, for example, exist in hepatic encephalopathy (see Ref. 210 for review), scrapie in which priors appear to accumulate first in astrocytes24 or in AIDS dementia where viral or macrophage-derived products could interfere with astrogial functions such as neurotrophic support and/or elimination of excitotoxins.214,215,217,225

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 slice preparations. 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 slice preparations. 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 molecular117,194,195,197 and functional167,227 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 Ca2+ oscillations within astrocytes in hippocampal slice preparations. Astrocytes themselves are also capable of responding to neurotransmitters (reviewed in Refs 19,26). Because of their close association with nodes of Ranvier,32,166 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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