Selection of Poly-α 2,8-Sialic Acid Mimotopes from a Random Phage Peptide Library and Analysis of Their Bioactivity*

Received for publication, April 8, 2004, and in revised form, May 5, 2004
Published, JBC Papers in Press, May 6, 2004, DOI 10.1074/jbc.M403952000

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Poly-α 2-8 sialic acid (PSA), attached to the neural cell adhesion molecule, is a permissive determinant for numerous morphogenetic and neural plasticity processes, making it a potential therapeutic target. Here, using a monoclonal antibody specific for PSA, we screened a phage-display library and identified two cyclic nine-amino acid peptides (p1, p2) that are PSA epitope analogues. We evaluated their bioactivity in vitro and in vivo. In culture, micromolar concentrations of the peptides promoted axon growth, defasciculation, and migration of neural progenitors. When injected into developing chicken retina, the peptides modified the trajectory of retinal ganglion cell axons. Moreover, they enhanced migration of grafted neuroblasts in mouse brain. These effects were selective and dependent upon the presence of PSA on transplanted cells. Our results demonstrate the feasibility and therapeutic potential of enhancing PSA biological activity.

The ability of a neuron to modify its cell surface interactions is a critical component of nervous tissue development, remodeling, and repair. Among candidate molecules that are potentially involved in such a process, the poly-α 2-8 sialic acid (PSA) carbohydrate polymer is of particular interest. PSA is found as a capsular polysaccharide of bacteria causing meningitis (1) and in mammals (including humans), it is found attached to the neural cell adhesion molecule (NCAM). Polysialylated NCAM isoforms (PSA-NCAM) are associated with morphogenetic changes during developmental processes such as cell migration, synaptogenesis, axonal growth, and branching, whereas PSA-NCAM persists in the adult brain only in structures that display a high degree of functional plasticity (2). Notably, PSA-NCAM is re-expressed during regeneration after damage to muscle (3) and neural tissue (4, 5). Several observations based upon either enzymatic destruction of PSA by endo
eraminidase (EndoN) (6) or the use of mutant mice for the polysialyltransferase enzyme responsible for PSA synthesis (7) indicate that PSA rather than the NCAM protein is required for morphogenesis and tissue remodelling (8, 9). For example, PSA is required in the adult brain for migration of developing neuroblasts in the rostral migratory stream (10, 11) or on activity-induced synaptic plasticity in the hippocampus (12). PSA also enhances the effect of brain-derived neurotrophic factor (BDNF) on cell survival (13) and regulates the directionality of migration of oligodendrocyte precursors in response to a gradient of platelet-derived growth factor (14). Thus, the PSA carbohydrate emerges as an important permissive factor underlying dynamic changes in cell-surface interactions and represents one of the potential targets for future therapeutic approaches to promote plasticity and functional recovery after brain damage.

As different peptides can assume diverse conformations, a large peptide library expressing random sequences should contain peptides that can conformationally mimic many ligands. This idea has been shown to have practical application with the demonstration that peptide mimics of antigenic specificities (mimotopes) can be efficiently identified using peptide libraries (15). Peptides mimicking polysaccharides can be readily produced and used in various ways (see, for example, Refs. 16–18). Unlike the polysaccharides themselves, such peptide mimics should be easier to manufacture and modify. Thus, the mimotopes may be useful as potential therapeutic compounds. Here, by biopanning a phage library with an anti-PSA monoclonal antibody (Ab), we characterized cyclic peptide inserts, which are mimotopes for PSA. We tested their bioactivity in several in vitro and in vivo tests and demonstrated their ability to enhance PSA biological activity.

**EXPERIMENTAL PROCEDURES**

Phage Library and Screening—Monoclonal anti-PSA Ab of the IgG2a isotype directed to Neisseria meningitidis B capsular polysaccharide (19) was immobilized on magnetic protein G beads (protein G Maga
bets; Europa Bioproducts, Ltd). A phagemid library, prepared as described by Felici et al. (20), was used. Briefly, the library comprises constrained random nonamer peptides presented on the surface of M13-like phage particles as fusion protein to the N terminus of pVIII major coat protein (100 copies/ phage). The random sequences are linked by a cysteine residue at one end and cysteine and glycine residues on the other (20). The library comprises ~10^10 peptides with constant sequence length. Three rounds of panning were carried out as described in Ref. 21. Monoclonal phages from all three rounds of panning were tested in enzyme-linked immu
nosorbent assay (ELISA) for reactivity with the anti-PSA Ab. For each clone, three wells of an ELISA plate (NUNC) were coated with 10^10
phage particles overnight at 4 °C. After blocking with Tris-buffered saline/2% nonfat dry milk, the wells were incubated with the anti-PSA monoclonal Ab (2 μg/ml in Tris-buffered saline/1% nonfat dry milk). Reactions were developed with a horseradish peroxidase-conjugated anti-mouse IgG secondary antibody. Monolocular phages reacting positively with the anti-PSA Ab and negatively with a control monoclonal from the same isotype were selected, DNA-isolated, and sequenced.

The sequences of the random peptide insert were obtained by BigDye Terminator cycle-sequencing with standard M13–40 primer on an Applied Biosystems 877/377 system using double-stranded, purified DNA (QIAprep).

**Peptide Synthesis**—Peptides were synthesized in our peptide synthesis facility using Fmoc (N-(9-fluorenylethoxycarbonyl) chemistry in a solid-phase synthesizer. The peptides were purified by high performance liquid chromatography, and their sequence and structure were confirmed by mass spectrometry.

**Animals**—Green fluorescent protein (GFP) (22) and NCAM-deficient (11) mice have been described previously. Animal experimentation conformed to European Community guidelines.

**Immunohistochemistry**—Fixed dorsal root ganglion (DRG) explants were incubated at 4 °C for 2 h with anti-neurofilament (mouse IgG, SMI-31, dilution 1:800, Sternberger Monoclonals). Brain sections were incubated at 4 °C overnight with MenB anti-PSA Ab (mouse IgM, dilution 1:2000 (23) and 5 min at room temperature in Hoescht (Sigma, dilution 1:100). Revelation was performed by 1-h incubation with the corresponding fluorescent-labeled secondary Abs.

**SVZ Explant Culture**—Cultures of subventricular zone (SVZ) explants were performed as described in Chazal et al. (11). Briefly, 1-day-old mice were killed by rapid decapitation. Brains were dissected and sectioned by Vibratome (Leica). The SVZ from the lateral wall of the anterior lateral ventricle horn was dissected in Hanks’ balanced salt solution medium (Invitrogen) and cut into 200- to 300-μm diameter explants. The explants were mixed with Matrigel (BD Biosciences) and cultured in four-well dishes. After polymerization, the gel was overlaid with 400 μl of serum-free medium containing B-27 supplement (Invitrogen) in the presence of 40 μm peptides (p1, p2, reverse p1, and/or 70 units of EndoN/ml. **SVZ Explant Cultures**—DRGs were dissected from 13.5-day-old mouse embryos in Hanks’ balanced salt solution medium and seeded on glass coverslips coated with polylysine. Explants were cultured in the presence or absence of the peptides (40 μm) in 2 ml of neurobasal medium supplemented as described in Chazal et al. (11).

**Cell Migration, Neurite Outgrowth, and Fasciculation**—After 48 h in culture, explants were examined directly (SVZ) or after overnight fixation in 4% paraformaldehyde in phosphate-buffered saline (PBS) and immunostaining (DRGs). Observation was done using an Axiosvert 35M (Zeiss, Germany). Images were collected with a video camera (Cool View, Photonic Science) and analyzed using an image-processing software (Visiolas 1000, Biocom). Mean migration distance (calculated on five independent experiments, including at least five explants per condition) or mean length of the neurites (based on three independent experiments, including at least eight explants per condition) was the distance (in μm) between the explant edge and the border of the cell or axon migration front. Four measurements were performed for each explant.

Fasciculation was estimated by drawing a circle at 1500 μm for p1 and 1150 μm for reverse p1 from the explant center and by counting for each explant (eight explants/condition examined) the total number of single axons and bundles crossing the circle. Fasciculation index was calculated as the ratio of the number of bundle/single axons for each explant analyzed.

**Intravitreal Injections and Retinal Whole Mount**—Injections were performed as described in Monnier et al. (24). Briefly, a 2 × 2-mm window was cut into the shell over E3 embryos. p1 or reverse peptide (10 μm) was injected in 1 μl of Fast green into the right eye vitreous body using a capillary. After a 5-day incubation at 37 °C (embryonic day 8 (E8)), retinae were dissected, spread onto nitrocellulose filters (Millipore, 0.45 μm), and fixed with 4% paraformaldehyde in PBS. Two- and three-dimensional 3,3'-3,3'-tetracarbocyanine perchlorate (DiI) crystals were applied dorsally to the optic fissure. Retinae were stored in the dark at 37 °C for 10 days until the dye reached the axonal growth cones in the fissure, mounted in glycerol/PBS (9:1), and analyzed using confocal microscopy. Three experiments were done, including at least three retinae per condition.

**Selection of Phage Clones and Analysis of Their Binding Properties**—Biopanning of a phage library displaying constrained random nonamer cyclic peptides with 30H12 anti-PSA Ab-coated magnetic beads (see “Experimental Procedures”) readily enriched for Ab-specific phage clones. Thirty-four monoclonal bound to the Ab after three cycles of biopanning, and they did not bind to an irrelevant Ab of the same isotype.

DNA from 13 of these monoclonal were prepared and sequenced (Fig. 1A). For MK3, the random insert is only eight amino acids long. Most likely, this results from a deletion, but the phage still represented a specific binder. MK3, -5, and -9 exhibited the same sequence, and the WP motif was found in 5 of 13 clones. Although the peptide inserts are most likely responsible for the binding of the phage particles to the Ab, it is possible that other parts of the phage protein may also be critical for binding. To directly investigate the role of the peptide inserts, the corresponding peptides were synthesized, coupled to bovine serum albumin (BSA), and tested for binding to the PSA Ab in ELISA. All 13 BSA-linked peptides bound to the 30H12 Ab. Peptides p1, which corresponds to phage MK6, and p2, which corresponds to phage MK11 (Fig. 1B), were chosen for further studies. These peptides are PSA mimotopes, as pre-incubation of the 30H12 Ab with 0.1 μM of either peptide prevented its binding to PSA-NCAM expressing cells (Fig. 1, E versus C), whereas pre-incubation with similar concentrations of the reverse peptides had no effect upon the antibody binding to cells (data not shown). PSA is a long polymer known to adopt a helical conformation (26) and to form filament bundles (27), thus exhibiting several epitopes. The binding specificity was examined in greater detail by testing peptide recognition by another anti-PSA Ab (MenB of the IgM class) (23). The peptides bound only to 30H12, which is the monoclonal Ab used for the selection, and pre-incubation of anti-MenB with the peptides did not prevent recognition of PSA-NCAM (Fig. 1D). Thus, the peptide mimotopes seem to be specific for a unique (idiotype) determinant.

**PSA Mimotope Peptides Modulate Fasciculation and Axon Outgrowth**—The two cyclic peptides, p1 and p2, were tested for their ability to modulate axonal growth and fasciculation, two events known to involve PSA (2, 9). Mouse DRG explants were cultured in the presence of the peptides added in soluble form to the culture medium. Reverse peptides were used as controls. The effects of the peptides on neurite outgrowth and fasciculation were analyzed qualitatively and quantitatively (Fig. 2). Whereas their respective reverse peptides had no effect, both p1 and p2 induced striking defasciculation of axon bundles (Fig. 2, B versus A and D versus C) and stimulation of neurite outgrowth (Fig. 2, B versus A). Quantitative analysis showed that p1 and p2 increased neurite outgrowth by 34 and 21%, respectively, compared with the reverse peptide controls (Fig. 2, E and F), whereas they decreased the fasciculation index (0.51 for reverse p1 versus 0.24 for p1; p < 0.05) (Fig. 2G).

These experiments demonstrated that the PSA mimotope peptides exhibit bioactivity in in vitro tests. To examine further whether p1 and p2 peptides were able to
exert the same effects in vivo, we chose to test their action upon
the guidance of ganglion cell axons toward the optic fissure in
the chicken retina, an event shown to be dependent upon PSA
expression (24). The mimetic peptides or the control reverse
peptides were injected into chicken embryo eyes at E3, and the
trajectory of retinal ganglion cell axons was observed at E9, as
described under "Experimental Procedures." The presence of
PSA mimotope peptides during retina development altered
axon guidance and fasciculation (Fig. 3). Several fibers defas-
ciculated from axon bundles, even running perpendicularly to
them (Fig. 3, E and F). These guidance errors were never
detected after injection of control peptides (Fig. 3, C and D).
These experiments demonstrated that the PSA mimotope pep-
tides exhibit bioactivity in vivo.

PSA Mimotope Peptides Increase the Migration of PSA- posi-
tive Cells in a PSA-dependent Fashion—In a second set of
experiments, we evaluated the ability of the PSA mimotope
peptides to influence cell migration, another PSA-regulated
event (Fig. 4). Neuronal precursor cell migration from the SVZ
toward the olfactory bulb is severely impaired in PSA-NCAM-
deficient mice (10, 11). The role of PSA in migration was fur-
ther evidenced when SVZ explants were cultured in the pres-
ence of EndoN, which prevented neuroblasts to exit from the
 explant and to migrate in a chain-like fashion (Fig. 4, B and E,
and Ref. 11). To test the effect of PSA mimotope peptides upon
cell migration in vitro, we analyzed mouse SVZ explants cul-
tured in Matrigel in the presence of p1 or p2 or the reverse
peptides. We observed that addition of the mimotope peptides
to the culture increased the distance of migration of neuronal
precursors from the core explant (Fig. 4, C and F). This effect
was not found with the reverse peptides (Fig. 4, A and D). The
dose-response curve of p1 showed that a maximal effect upon
cell migration was observed starting from and above concen-
trations of 0.4 M peptide (Fig. 4 I). Moreover, we showed that
cyclization was a prerequisite for the promoting effect of p1
peptide because the corresponding amino acid sequence in a
linear form, either N-acetylated or not, was unable to stimulate
cell migration (Fig. 4 J). When PSA was removed from the
cultures by EndoN treatment, the peptides were no longer able
to modulate cell migration, indicating that their bioactivity is

A

| Phage (a) | Peptide sequence (b) |
|-----------|----------------------|
| MK 2      | cYPLNPEVYHcg         |
| MK 3      | cWPLSHSVIVcg         |
| MK 5      | cWPLSHSVIVcg         |
| MK 6 (p1) | cSSVTAWTTGcg         |
| MK 8      | cYMASGVFLcg          |
| MK 9      | cWPLSHSVIVcg         |
| MK 10     | cWPLGPRSTYlgc        |
| MK 11 (p2)| cSLIASMETGcg         |
| MK 12     | cYPLNPEVYHcg         |
| MK 13     | cYGDPENPcg           |
| MK 14     | cWPLGDSTVlgc         |
| MK 15     | cPLRALTFGcg          |
| MK 16     | cTRMSHGYWlgc         |

B

FIG. 1. Selection and characterization of PSA mimotope peptides. A, the names of phage clones and sequences of clones from nonapeptide
insert phage library after biopanning by 30H12 antibody are shown. Flanking sequences are shown in small letters and inserted sequences are
shown in capital letters. B, reactivity of BSA-coupled peptides with 30H12 anti-PSA Ab in ELISA tests. BSA-coupled MK6 and MK11 reverse
peptides have values of A < 0.1 (data not shown). C, 30h12 Ab staining of PSA-NCAM-expressing cells. Preincubation of 30H12 or MenB (1 
Mg/ml) with p1 (0.1 mM) inhibits the binding of 30H12 (E) but not MenB (D) anti-PSA Ab to the PSA-expressing cells. Bar, 20 
m.
Likewise, quantitative analysis (Fig. 4, G and H) demonstrated that p1 and p2 induced a significant increase in the distance the neuronal precursors migrated from the explant (+40 and +26%, respectively, at 40 μm, compared with the control), whereas EndoN decreased it both in the presence and absence of the peptide (−21% compared with the control).

To ascertain the PSA-dependence of the peptide effect upon migration, we performed the same experiments using SVZ...
FIG. 4. PSA mimotope peptides stimulate cell migration in vitro. Subventricular zone explants from 1-day-old mice were cultured in the presence of reverse p1 (A), EndoN (B), or p1 (C). D, E, and F, higher magnifications of selected areas in A, B, and C, respectively. D, arrowhead points to an example of neuroblast chains. G, quantification of the effect of the peptides upon the mean distance of cell migration. The condition without any peptide (mean distance of migration 160 μm) is taken as 100%. The mean ± S.E. of five independent series of experiments are indicated. H, cumulative distribution plot of the mean distance of migration. I, dose-dependent effect of the p1 peptide on the mean distance of cell migration. J, effects of different modifications of the p1 peptide (cyclic, linear, linear, and acetylated) (in two series of independent experiments) on its ability to enhance cell migration. Note that the linear form is not bioactive. K, effect of p1 on the migration of neuronal precursors from heterozygous (NCAM +/-) and homozygous (NCAM -/-) NCAM-deficient mice (two series of independent experiments). **, p < 0.01; ***, p < 0.001. Note that p1 is not able to enhance migration of PSA-NCAM-deficient cells by comparison to its effect upon PSA-NCAM-expressing (NCAM +/+ ) cells. Bars: A, 100 μm; D, 20 μm.
explants from PSA-NCAM-deficient mice (11). As expected (11), a significant reduction of precursor cell migration was observed in the PSA-NCAM−/− explants by comparison to the control PSA-NCAM+/+ explants. The presence of p1 did not restore migration of PSA-NCAM-deficient cells (Fig. 4K). Moreover, the data were similar in EndoN-treated PSA-NCAM+/+ and PSA-NCAM−/− explants. Altogether, these experiments revealed a co-dependence between PSA expression and the stimulatory effect of the mimotope peptides.

PSA Mimotope p1 Increases the Migration of Transplanted Neural Progenitors—Peptide p1 was taken forward for testing in in vivo models. We set up transplantation experiments (Fig. 5A) to test its ability to stimulate migration of PSA-expressing cells. We grafted calibrated pieces of SVZ tissue from 1-day-old GFP-expressing mice (22) into the anterior SVZ area of adult mice and compared the migration of GFP-labeled progenitors toward the olfactory bulb in the presence of p1, reverse p1 (0.5 µl at 10 µl co-injected with the grafted tissues), or in the absence of peptide. After grafting, GFP-positive cells were observed along the rostral migratory stream, a pathway known to depend upon PSA. All of these cells were both GFP- and PSA-positive and integrated among host cells (Fig. 5B). No significant difference was found between experiments in the absence of peptide (data not shown) and with reverse p1. The number of migrating cells was dramatically increased by p1 (Fig. 5, F versus D). This effect was observed as early as 3 days after engraftment (Fig. 5, E versus C). Quantitative analyses were made by counting the total number of GFP-positive and GFP/PSA double-positive cells reaching the olfactory bulb 3 days after grafting. The number of GFP-positive cells in the bulb was 17-fold higher in the presence of p1 (Fig. 5, E and G), and no significant difference could be found between the numbers of GFP- and GFP/PSA-positive cells (Fig. 5G) at this stage in the bulb whatever the experimental condition. These data further confirm bioactivity of the PSA mimotope peptides and support its PSA-dependent enhancing effect upon migration.

DISCUSSION

Until now, PSA function could be manipulated only by reducing its expression. This has been achieved by genetic engineering (7), EndoN enzymatic digestion (6, 10, 28), or by the use of a small molecule, N-butanoylmannosamine, which is able to reversibly inhibit PSA synthesis in vitro (29, 30). However, the feasibility of enhancing PSA activity has not yet been demonstrated either in vitro or in vivo. Here, we characterized oligopeptide mimotopes of PSA and evaluated their bioactivity. The selected peptides do not seem to have the characteristics of
polysialic acid such as negatively charged amino acids. Indeed, because of its polyanionic nature, PSA epitopes would be expected to employ marked electrostatic components in their binding events. A possibility is that the binding is based upon hydrogen bonding and Van der Waals interactions, none of which involves charged groups. Peptide p1 contains two S and three T amino acids, all with a hydroxyl group on their side chains which can be involved in hydrogen bonding (31). In a recent study, however, Hayrinen et al. (32) studied the effects of cations on antibody binding properties and affinities. Interestingly, their results show that the interaction is influenced by divalent cations (such as Ca$^{2+}$ or Mn$^{2+}$) and polyamines. One possible explanation for this could be that under physiological conditions, Ca$^{2+}$ neutralizes the carboxyl groups and plays a significant role in the regulation of the PSA epitopes presentation in vivo. In culture, the peptides promoted axon growth and defasciculation and migration of neural progenitors. In vivo the peptides modified the trajectory of retinal ganglion cell axons and dramatically enhanced migration of grafted neuronal progenitors.

So far, the prevailing idea is that PSA could be viewed as a steric regulator of membrane-membrane apposition, which serves to attenuate a variety of cell-cell interactions, thus allowing movement. Through selective elimination of PSA on NCAM by EndoN, it has been possible to demonstrate in many different systems that PSA-NCAM favors defasciculation, axon growth, branching, and synapse formation. In the neuromuscular system for example, removal of PSA results in numerous defects, such as innervation of inappropriate muscles and a reduction in nerve branching and the number of synapses (33–35). Similarly, removal of PSA on NCAM was found to be associated with aberrant mossy fiber innervation and ectopic synaptic boutons in the hippocampus (36). Our selected mimotope peptides are able to stimulate neurite outgrowth in vitro and to dramatically increase axon defasciculation and cell migration both in vitro and in vivo. Therefore, our observations support a PSA mimetic function of the selected peptides.

What are the mechanisms underlying misguidance of retinal ganglion cell (RGC) axons after p1 peptide injection? Both axon defasciculation and cell migration involve decreased adhesion between axons and between migrating cells and their substrates. If we consider that the peptides modulate the classical steric function of PSA, p1 on PSA-positive axon tracts would modify the balance of interactions, and its effect has to be explained by the nature of the environment. Indeed, the environment could exhibit powerful and stable adhesive attractants, functionally affected by the presence of the peptide. This in turn could induce axons to follow more independent, less fasciculated pathways. Alternatively, we can consider a non-steric function of PSA during axon outgrowth of the RGC. As suggested by Monnier et al. (24), in the chick retinae, PSA could be involved in the recognition or could be part of the receptor complex for a soluble guidance cue playing a role in orienting the growth cones. PSA could bind to this secreted component, thus keeping it at a high concentration at the surface of RGC cells. Peptide p1 might interfere with the binding of this diffusible cue or titrate it, thus modifying signaling and inducing a misrouting of the PSA-positive axons. Among diffusible candidate molecules are FGF, netrin-1, and slit, which have been shown to play a role in the development of the RGC (37).

In support of this idea, additional mechanisms for PSA action have recently been proposed that suggest an instructive role for PSA in cell interactions (13, 14, 38). For example, the BDNF neurotrophin receptor TrkB has been proposed as an interacting partner at synapses. The addition of BDNF rescued the deleterious effect of PSA removal on differentiation and survival of cultured cortical neuron (13) and the defect in hippocampus synaptic plasticity associated with elimination of PSA by EndoN (12). In support of possible cross-talk between PSA and BDNF signaling, the level of TrkB phosphorylation was found to be decreased in NCAM-deficient mice and EndoN-treated cultures (13). It is tempting to propose that mimotope peptides influence BDNF signaling. Another possibility is that they influence glial-derived neurotrophic factor signaling as it has been shown recently that the PSA carrier NCAM can function as a signaling receptor for members of the GDNF ligand family and that migration of neuroblasts toward the bulb is influenced by glial-derived neurotrophic factor, although the effect of PSA has not yet been examined in this interaction (39).

Experiments using tissue either from NCAM-deficient mice or EndoN-treatment showed that the effect of the mimotope peptides depends upon the cellular expression of PSA. This intriguing observation invites further speculation on the mechanisms of peptide action. It is possible that the peptides are recognized as ligands by still unidentified PSA receptors. If this were the case, the peptides should have improved migration of PSA-NCAM-deficient neuroblasts, unless expression of putative PSA receptors is also perturbed in the deficient mice. Alternatively, the cyclic mimotope which forms a small molecular ring with little conformational freedom and can assume only a restricted set of conformations (31) may bind to PSA chains themselves, and, by changing their conformation or binding properties, may potentiate PSA effects. More studies will be required to examine these possibilities.

Whatever their mode of action, the characterized peptides might prove useful in central nervous system regenerative strategies. From a therapeutic perspective, these mimetic peptides exhibit many advantages. They act extracellularly, they are biocompatible, and their stability seems to be sufficient to detect observable effects after in vivo delivery. This happened to be true for injection in the developing eye, in which perturbations of axon guidance could be observed as late as 5 days after the injection, as well as for cell grafting, in which a dramatic effect was observed 4 days after the graft. After central nervous system injuries, one of the most important challenges is to design ways to promote the intrinsic capacity of the sprouting and growth of the lesioned axons. Such lesioned axons, at least in the central nervous system, very often reexpress PSA-NCAM (4, 5). Notably, the PSA-dependence of the mimetic peptides will be an asset, as their effect will be confined to the cells to be stimulated.

In central nervous system neurodegenerative diseases, grafting neuronal precursors in the patient’s brain to replace lost neurons is presently considered to be a promising medical advance (40). One important step in such an approach is to speed migration of the grafted precursors toward the damaged areas. In the context of this research, a clinically important feature relates to our observation that the mimotope peptides could be powerful adjuvants in cell therapy to increase migration of grafted PSA-positive cells. Here again, the PSA-mimotope peptide co-dependence might be considered to be an advantage, as most of the progenitors selected for grafting into patients should be PSA-positive. In addition to their therapeutic use, PSA mimetic peptides might also prove to be useful complementary tools to uncover mechanisms of action and unknown functions of PSA.

Acknowledgments—We thank C. Giribone and S. Nicolas for excellent technical assistance and Drs. V. Castellani and C. Henderson for helpful discussions.
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*J. Biol. Chem.* 2004, 279:30707-30714.
doi: 10.1074/jbc.M403935200 originally published online May 6, 2004

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