Oligodendrocyte progenitors are present in the normal adult human CNS and in the lesions of multiple sclerosis

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Summary
In multiple sclerosis, partial remyelination is conspicuous in many lesions, but widespread and lasting myelin repair ultimately fails as disability and handicap accumulate. Thus far, the precise identity of the cell responsible for limited spontaneous myelin repair has remained obscure. In the rodent, the proliferative oligodendrocyte progenitor is the most efficient remyelinating cell; this has now been identified in cultures prepared from normal human brain, but has proved difficult to demonstrate in situ. We adapted techniques using antibodies against the human platelet-derived growth factor-α receptor to identify oligodendrocyte progenitors in human tissue sections. Small numbers of oligodendrocyte progenitors were found in normal adult human white matter. Progenitors were also demonstrable in acute and chronic lesions from patients dying with multiple sclerosis, but with no evidence of any marked reactive increase in cell numbers. Understanding the biology of the remyelinating cell, and in particular the reason for its apparent failure to repopulate demyelinated lesions, is important for the development of remyelination treatments.

Keywords: human oligodendrocyte progenitor; remyelination; multiple sclerosis; PDGF-α receptor

Abbreviations: GalC = galactocerebroside C; ORO = oil red O; PDGF = platelet-derived growth factor

Introduction
In multiple sclerosis, myelin sheaths and the oligodendrocytes responsible for their synthesis and maintenance are selectively damaged by repeated focal episodes of inflammatory attack (e.g. Scolding et al., 1994). Whilst axonal loss does occur (Trapp et al., 1998), the contribution of demyelination to neurological impairment and symptoms remains paramount (Smith, 1996). Ultrastructural studies beginning almost 30 years ago first suggested that remyelination occurs in multiple sclerosis lesions (Suzuki et al., 1969), and the significance and extent of spontaneous myelin repair has since been increasingly appreciated—approximately 40% of plaques exhibit remyelination extending over >10% of the lesion area during ongoing inflammation (Prineas et al., 1993; Raine and Wu, 1993).

Whilst the process of remyelination is therefore widespread, it is equally clear that much acute myelin damage is not repaired, and remyelination is particularly less conspicuous in chronic lesions. Furthermore, clinical experience emphasizes that myelin repair ultimately fails in many patients as disability and handicap accumulate. Nevertheless, these pathological observations provide a firm basis for the development of therapeutic strategies designed to encourage remyelination, redefining the goal as the promotion of an endogenous process rather than necessarily initiating repair de novo. Strategies for promoting remyelination in order to prevent, ameliorate or delay neurological impairment have attracted increasing interest recently (Scolding, 1997) as improved immunotherapies permit some control over the occurrence of repeated episodes of inflammation, especially since these treatments exert very little impact on the progression of disability (Rudick et al., 1997).

Understanding the biology of the remyelinating cell is clearly fundamental to the development of reparative
treatments. Studies in experimental animals indicate that the proliferative oligodendrocyte progenitor (Raff et al., 1983) is a highly efficient remyelinating cell, responsible for spontaneous myelin repair in various demyelinating models, and capable of remyelinating axons in exogenous tissue after transplantation (Godfraind et al., 1989; Carroll et al., 1990; Rodriguez, 1991; Reynolds and Wilkin, 1993; Warrington et al., 1993; Carroll and Jennings, 1994; Duncan, 1996; Franklin and Blakemo, 1997; Gensert and Goldman, 1997). A cell with properties equivalent to those of the bipolar, proliferative, bipotential rodent oligodendrocyte progenitor has been identified in cultures prepared from normal human white and grey matter (Scolding et al., 1995). However, the antibody markers (directed against surface gangliosides) conventionally used to identify this cell in vivo are not useful for studying tissue sections ex vivo: the A2B5 monoclonal antibody in particular does not specifically stain glial progenitors in the CNS.

Expression of the platelet-derived growth factor (PDGF)-α receptor is a widely accepted means of identifying oligodendrocyte progenitors (Pringle et al., 1992; Pringle and Richardson, 1993; Ellison and de Vellis, 1994; Hall et al., 1996; Nishiyama et al., 1996a). Differentiated oligodendrocytes do not express the receptor (Ellison and de Vellis, 1994; Butt et al., 1997). The R7 rabbit polyclonal antibody, raised against a synthetic peptide from the C-terminal end (amino acids 1066–1084) of the human PDGF-α receptor, fully characterized elsewhere (Chaudhry et al., 1992; Eriksson et al., 1992; Claesson-Welsh et al., 1989), has been used in numerous published studies to identify oligodendrocyte progenitors in the neonatal rat (e.g. Nishiyama et al., 1996a, b), the adult mouse (Rewine et al., 1997) and the foetal human nervous system (Hajihosseini et al., 1996); it has been used in adult human studies to identify the PDGF-α receptor in glioma tissue (Hermanson et al., 1992) and in gut neuroendocrine tumours (Chaudhry et al., 1992). Here, techniques using antibodies against the PDGF-α receptor to identify oligodendrocyte progenitors in human tissue sections are validated in studies of human glial progenitors in vitro. Both healthy white matter and lesions from patients with multiple sclerosis were interrogated and shown to contain small numbers of bipolar or non-processed PDGF-α receptor antibody-positive oligodendrocyte progenitors, cells not previously identified in normal adult or diseased human tissue.

Methods

Adult human glial cultures

Cells of the human oligodendrocyte lineage were cultured as previously described (Armstrong et al., 1992; Scolding et al., 1995) from normal-appearing white matter removed at the time of anterior temporal lobe resection for intractable epilepsy. Previous studies had confirmed that comparable tissue, dissected from sites distant from the epileptic focus, was histologically normal (Scolding et al., 1995). Briefly, small fragments of tissue were dissected to remove meninges and identifiable blood vessels, enzymatically digested and triturated as described, then cultured in uncoated plastic flasks or plated onto poly-L-lysine-coated glass coverslips. After overnight incubation in either DMEM (Dulbecco’s Modified Eagle Medium) with 10% FCS (foetal calf serum) or N2B3 medium (a 1 : 1 mixture of Ham’s F12 medium and DMEM with 0.5% FCS and defined additives) supplemented with PDGF-AA and bFGF (basic fibroblast growth factor), floating cells were removed and reseeded onto poly-L-lysine-coated coverslips; these cells represented a population enriched for the oligodendrocyte lineage.

Tissue sections and staining

Eight post-mortem brain and spinal cord samples from five patients with multiple sclerosis were obtained in collaboration with the Multiple Sclerosis Society Tissue Bank at the Institute of Neurology, London, UK (Newcombe and Cuzner, 1993). All patients had been clinically diagnosed as having multiple sclerosis, and this diagnosis had been confirmed histologically. Control brain tissue from three patients who had died from causes other than neurological disease was also studied (Table 1).

Cryostat sections (10 μm) were cut from each tissue block and stained with oil red O (ORO) to detect lipid-laden macrophages and with haematoxylin–eosin. Numbers of ORO-positive macrophages and haematoxylin-positive inflammatory cells were scored semiquantitatively on a scale from 0 to 5. Histological assessment of lesion development was based on these ORO and haematoxylin scores—demyelinated lesions with an ORO score of 0 were considered chronic and those scoring ≥3 as acute; the score for perivascular cuffs provided an index of inflammation.

Adjacent sections were studied immunocytochemically, stained as described below. Histology sections were evaluated and graded by two independent observers, and the assessment of immunocytochemical staining was performed blind with respect to histological evaluation.

Fluorescence immunocytochemistry staining of cultured cells and of tissue sections was performed by conventional techniques.

After blocking with 5–10% phosphate-buffered saline or tissue culture medium, live glial cells in vitro were immunostained with monoclonal A2B5 immunoglobulin M (IgM) (culture supernatant 1 : 2), Ranscht monoclonal anti-GalC (galactocerebroside C) IgG3 (culture supernatant 1 : 4) or a variety of antibodies directed against human PDGF-α receptor, including the rabbit polyclonal antibody R7 (Nishiyama et al., 1996a) (diluted 1 : 20–1 : 50 for cell culture experiments; a dilution of 1 : 400 was used for all tissue section experiments) and three monoclonal antibodies: (i) one from Upstate Biotechnology, Lake Placid, NY, USA, diluted 1 : 50–1 : 200; (ii) one from Sigma Immunochemicals, Poole, UK, ascites fluid, diluted 1 : 50–1 : 200; and (iii)
Oligodendrocyte progenitors in multiple sclerosis lesions

**Table 1 Summary of histological data in multiple sclerosis and normal control cases**

<table>
<thead>
<tr>
<th>Block</th>
<th>Sample type</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Area</th>
<th>Histology</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>N</td>
<td>54</td>
<td>–</td>
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<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>MS</td>
<td>58</td>
<td>27</td>
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</tr>
<tr>
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<td>7</td>
<td>Parietal V</td>
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<tr>
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<td>N</td>
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<td>–</td>
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</tr>
<tr>
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<td>14</td>
<td>Temporoparietal V</td>
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</tr>
<tr>
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<td>14</td>
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<tr>
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<tr>
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</tr>
<tr>
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<td>37</td>
<td>10</td>
<td>Cervical SC</td>
<td>3.2</td>
</tr>
<tr>
<td>11</td>
<td>MS</td>
<td>37</td>
<td>10</td>
<td>Occipital V</td>
<td>0.2</td>
</tr>
</tbody>
</table>

MS = multiple sclerosis plaque tissue; N = normal control CNS; SC = spinal cord; SV = subventricular area tissue; V = ventricular area. Histological grading was scored on a scale 1–5 (see Methods): first numeral is the number of oil red O-positive macrophages; second numeral is the number of haematoxylin-positive periventricular inflammatory cell cuffs.

Results

**PDGF-α receptor antibody labels oligodendrocyte progenitors in vitro**

The PDGF-α receptor has been shown to be a useful marker of rodent oligodendrocyte progenitors in tissue sections (Pringle et al., 1992; Nishiyama et al., 1996a); we set out to establish whether the same is true of the human oligodendrocyte progenitor in vitro. A number of commercially obtained monoclonal antibodies (see Methods) failed, however, to label cultured A2B5-positive human cells either live or after prefixation, despite varying considerably both the concentrations of antibodies used and the duration of incubation. Other workers have also found these antibodies not to be useful for studying either human or rodent tissue (N. Pringle and R. Reynolds, personal communication); it may be that the recognition of a range of epitopes within the human PDGF-α receptor by the rabbit polyclonal antibody explains the superior staining ability of this reagent.

However, more success was obtained using the rabbit polyclonal R7 anti-PDGF-α receptor antibody. At concentrations of 1 : 20–1 : 50, exposing lightly prefixed (2% paraformaldehyde for 1–2 min) cells to this marker for 30 min at 37°C, the R7 antibody consistently stained human oligodendrocyte progenitors in vitro, co-staining positively with A2B5 (Fig. 1A–C). Double-labelling studies confirmed that astrocytes in vitro were not labelled by this antibody.

**Oligodendrocyte progenitors are present in multiple sclerosis lesions and in normal adult white matter**

Having shown the R7 anti-PDGF-α receptor antibody to be a useful marker of human oligodendrocyte progenitors...
cells with rimmed PDGF-α receptor staining were also apparent (Fig. 1D and E). These differences may simply reflect the orientation of labelled cells with respect to the tissue plane, and are consistent with the bipolar morphology disclosed by the occasional ‘capture’ of a cell in longitudinal section. PDGF-α receptor-positive cells with multiple processes were never observed. Small numbers of PDGF-α receptor-positive oligodendrocyte progenitors were identified in the normal human CNS, and in both acute and chronic lesions in the brain and spinal cord of patients with multiple sclerosis.

Co-staining with the R7 polyclonal anti-PDGF-α receptor antibody and with antibodies against either mature oligodendrocytes (with anti-GalC antibody or with the RIP antibody), astrocytes (GFAP) and neurons (β-tubulin) yielded consistently negative results, excluding the possibility that the PDGF-α receptor-positive population included any of these cell types. [It has been reported that, in the rat, neuronal subpopulations may express PDGF-α receptor (Vignais et al., 1995), though this has not been observed in other rodent studies (Pringle et al., 1992), and neuronal PDGF-α receptor expression was not reported in (foetal) human tissue (Hajihosseini et al., 1996).]

Quantification of PDGF-α receptor-positive oligodendrocyte progenitors in multiple sclerosis lesions and in normal white matter

We attempted to elucidate whether the numbers of PDGF-α receptor-positive oligodendrocyte progenitors varied substantially in different lesion types and between lesions and normal control tissue. Tissue sections were stained with the fluorescent nuclear dye Hoechst 33258 (Sigma), allowing the total numbers of cells per field to be established; the number of PDGF-α receptor-positive oligodendrocyte progenitors per 100 nuclei was counted; 1–3000 cells per section were studied, avoiding perivascular inflammatory cell cuffs. (No progenitors were seen within inflammatory cuffs in any of the sections studied.)

The number of progenitors was in all cases low, the mean in every section (normal control tissue, acute inflammatory demyelinating lesions and chronic inactive plaques) falling between 1 and 3 cells/100 nuclei, or of the order of 1 cell every 10–15 high-power fields (×100 objective). There was some variation within normal tissue and in within different lesions, but these changes were not consistent, and the overall numbers were too low to allow any meaningful quantitative comparison. There was, however, no indication of strikingly increased cell numbers within or in the immediate vicinity of perivascular inflammatory cell cuffs, although rare fields containing small clusters of cells were observed in acute lesions (Fig. 1F and G), raising the possibility of limited and localized proliferative activity, an observation we are currently pursuing.

Fig. 1 PDGF-α receptor-positive adult human oligodendrocyte progenitors in culture and in situ in multiple sclerosis. (A–C) A single human glial cell in vitro is shown (A, phase-contrast) stained immunofluorescently with A2B5 monoclonal antibody (B, tetramethyl rhodamine isothiocyanate-anti-mouse IgM conjugate, rhodamine optics); the same cell stained live also expresses PDGF-α receptor, disclosed with the R7 polyclonal antibody (C, fluorescein isothiocyanate-anti-rabbit IgG, fluorescein optics) (×400). (D–G) High-power (×1000) fields of normal post-mortem brain (D and E) and of an acute inflammatory demyelinating lesion from a patient with multiple sclerosis (F and G). Tissue sections were stained with the blue fluorescent Hoechst dye 33258 to disclose all cell nuclei (E and G), and with the R7 polyclonal anti-PDGF-α receptor antibody (D, F). Occasional bipolar cells were seen (arrows) (D and E), but a rounded morphology was more common (F and G). Rare clusters of progenitors were observed (F and G).

in vitro, we used the same reagent to interrogate frozen normal adult CNS tissue, and lesions from patients with multiple sclerosis. Small numbers of cells exhibiting cell surface staining were apparent (Fig. 1D–G). Usually these were rounded in morphology (Fig. 1F and G), while bipolar
Discussion

We have shown that the rabbit polyclonal R7 anti-PDGF-α receptor antibody (Nishiyama et al., 1996a) serves as a useful marker of bipolar proliferative human oligodendrocyte progenitors in vitro, and that this antibody may also be used specifically to identify oligodendrocyte progenitors in human CNS tissue sections. Small numbers of progenitors are present in normal adult CNS white matter, and in acute and chronic lesions of both brain and spinal cord from patients with multiple sclerosis.

The bipolar oligodendrocyte progenitor was first identified in cell cultures prepared from the neonatal rodent optic nerve (Raff et al., 1983), and was subsequently described in the adult rodent CNS (ffrench-Constant and Raff, 1986; Wolswijk and Noble, 1989). Studies of other mammals are few, but Carroll, in a series of experiments investigating remyelination in the cat optic nerve, described a proliferative polar small glial cell with ultrastructural similarities to the rodent progenitor; this, or a more immature immediate precursor, was found to be responsible for myelin repair after antibody-mediated demyelination (Carroll et al., 1990; Carroll and Jennings, 1994).

Studying the human CNS, Armstrong et al. (1992) provided the first demonstration of the immediate progenitors of oligodendrocytes (the pre-oligodendrocyte) in human white matter, based on an 04-positive GalC-negative immunophenotype. This group, having identified pre-oligodendrocytes in vitro, later showed expression of PDGF-α receptor messenger RNA (not peptide) in normal adult human white matter as well as expression of the MyT1 transcription factor—both markers of immature oligodendrocyte lineage cells (Gogate et al., 1994). PDGF-α receptor peptide expression was not examined, and morphological characterization of cells was not feasible; also, neuronal markers were not applied [in the rat, PDGF-α receptor message is also expressed by certain neuronal populations (Vignais et al., 1995)]. However, in definitive immunochemical (and molecular) studies of foetal human spinal cord, Dubois-Dalcq and colleagues have described in some detail the appearance and distribution of 04-positive/GalC-negative oligodendrocyte progenitors, and have also shown surface expression of PDGF-α receptor peptide by 04-positive cells using the same antibody that we have used (Hajihosseini et al., 1996).

Very recently, Wolswijk (1998) applied the 04/GalC double staining approach to study chronic multiple sclerosis lesions. Small numbers of 04-positive/GalC-negative oligodendrocyte precursor cells were identified; these were process-bearing and not proliferating. The technique did not allow similar examination of normal white matter areas replete with 04-positive/GalC-positive (fully differentiated) oligodendrocytes (Wolswijk, 1998).

The A2B5-positive bipolar progenitor is a more immature cell than the processed 04-positive/GalC-negative oligodendrocyte precursor (Pfeiffer et al., 1993). Cultured adult human A2B5-positive progenitors are, like their rodent counterparts, commonly bipolar, though occasionally unipolar or tripolar; in their morphology they therefore differ from 04-positive/GalC-negative pre-oligodendrocytes, which have three or more longer, branched processes (Scolding et al., 1995). Human pre-oligodendrocytes do not stain with A2B5, and have not been found to proliferate, unlike A2B5-positive adult human progenitors (Armstrong et al., 1992; Prabhakar et al., 1995; Scording et al., 1995). The confirmation that adult human A2B5-positive progenitors may be identified using anti-PDGF-α receptor antibody therefore allows the exploration with this reagent of normal and diseased human brain tissue in order to identify immature, potentially proliferative oligodendrocyte progenitors.

The current studies of normal adult tissue, demonstrating the expression of PDGF-α receptor peptide by early oligodendrocyte progenitors in vitro and in situ, showing that at least some of these cells exhibit a bipolar morphology in vivo and confirming that labelled cells are not neuronal, therefore help to consolidate and extend the observations on normal human tissue of Gogate, Armstrong and Dubois-Dalcq (Hajihosseini et al., 1996). The very small number of such cells in our studies of normal adult human white matter, both in vitro and in vivo (of the order of 1%) is comparable with the 1–2% quoted by Gogate et al. and with the figure of ~2% quoted for the rodent optic nerve (Fulton et al., 1992). Interestingly, larger numbers of PDGF-α receptor mRNA-positive cells were present in periventricular areas (Gogate et al., 1994).

Our studies of multiple sclerosis tissue also help to confirm and significantly to extend the findings of Wolswijk (1998). In contrast to the 04-positive/GalC-negative oligodendrocyte precursor, the PDGF-α receptor-positive progenitor is not a multiprocessed cell, again helping to confirm its more immature stage. PDGF-α receptor staining is useful for identifying precursors in both diseased (oligodendrocytopenic) and normal tissue, allowing a useful comparison of cell numbers. Finally, we have been able to study acute as well as chronic lesions, which is particularly useful in the current context in that pathological studies have consistently shown that remyelination is most conspicuous, if not confined to, acute lesions in multiple sclerosis (Prineas et al., 1993).

We have not yet determined whether the PDGF-α receptor-positive progenitor is responsible for generating remyelinating oligodendrocytes in multiple sclerosis. Several studies have suggested that oligodendrocyte proliferation occurs in multiple sclerosis lesions (Raine et al., 1981; Prineas et al., 1989; Luchinetti et al., 1996). Markers of mitosis were not employed in these investigations, nor were the currently employed means of identifying progenitors available, and the inference of proliferation was based on the observation of increased numbers of oligodendrocytes. These cells could have arisen, as explicitly discussed in these reports, through proliferation of more immature progenitors and/or their inward migration. Whilst the presence of increased numbers of oligodendrocytes in lesions has been correlated with...
remyelination (Lucchinetti et al., 1996), it is clear from studies in experimental animals that the bipolar, proliferative oligodendrocyte (or O2A) progenitor is the most successful and efficient remyelinating cell for achieving both spontaneous and post-transplantation myelin repair (Godfraind et al., 1989; Carroll et al., 1990; Reynolds and Wilkin, 1993; Warrington et al., 1993; Carroll and Jennings, 1994; Rosenbluth, 1996; Franklin and Blakemore, 1997; Gensert and Goldman, 1997). It is also clear that, in marked contrast to the observations described here, substantial oligodendrocyte progenitor proliferation is found in experimental remyelination (Rodriguez, 1991; Gensert and Goldman, 1997; Kierstead and Blakemore, 1998). It is indeed suggested that proliferation is a prerequisite for remyelination (Blakemore et al., 1997), so that the paucity of progenitors present in multiple sclerosis lesions, with little evidence of a reactive change in their numbers [perhaps related to the very limited in vitro capacity for proliferation (Armstrong et al., 1992; Scolding, 1997)], is at least commensurate with the far from perfect remyelination observed in multiple sclerosis. This said, we have not yet had the opportunity to study hyperacute lesions, which might conceivably contain larger numbers of progenitors.

However, that a human oligodendrocyte precursor may be cultured, can divide (and indeed shares many other properties of the rodent O-2A progenitor) and has now been identified in normal brain and in affected tissue in multiple sclerosis has implications not only for spontaneous remyelination in this disorder but also for the development of strategies designed to promote remyelination (Duncan, 1996; Rosenbluth, 1996; Scolding, 1997). Clearly, to contemplate therapeutic repair of the (typically) very large numbers of lesions present throughout the brain and spinal cord of patients with chronic multiple sclerosis is unrealistic. However, many such areas are essentially asymptomatic; conversely, a small number of eloquently sited discrete demyelinated lesions, in such areas are essentially asymptomatic; conversely, a small number of eloquently sited discrete demyelinated lesions, in contrast to the observations described here, substantial oligodendrocyte progenitor proliferation is found in experimental remyelination (Rodriguez, 1991; Gensert and Goldman, 1997; Kierstead and Blakemore, 1998). It is indeed suggested that proliferation is a prerequisite for remyelination (Blakemore et al., 1997), so that the paucity of progenitors present in multiple sclerosis lesions, with little evidence of a reactive change in their numbers [perhaps related to the very limited in vitro capacity for proliferation (Armstrong et al., 1992; Scolding, 1997)], is at least commensurate with the far from perfect remyelination observed in multiple sclerosis. This said, we have not yet had the opportunity to study hyperacute lesions, which might conceivably contain larger numbers of progenitors.

Further examination of the role of the adult human oligodendrocyte progenitor in endogenous remyelination, together with in vitro studies identifying the precise factors responsible for stimulating proliferation and investigating its relations with axons may offer explanations for the failure of more widespread and permanently successful remyelination in multiple sclerosis, and may indicate whether therapeutic strategies designed to challenge this failure and promote myelin repair in patients with this common and disabling disease are realistic.

Acknowledgements

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