

# INCREASED OLIGODENDROGLIAL EXPRESSION OF THE CELL PROLIFERATION-CONTROLLING PROTEIN PROHIBITIN IN SCHIZOPHRENIA. A HINT FOR CELL CYCLE ABNORMALITIES?

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## Abstract

Oligodendrocytes (OLs) are in many ways implicated in the pathophysiology of schizophrenia. However, very little is currently known about possible OL cell cycle disturbances in schizophrenia, a phenomenon which has been described for the birth of new hippocampal neurons in schizophrenics. When morphometrically analyzing the density of prohibitin-expressing OLs in different prefrontal white matter areas of patients with schizophrenia, we found a significantly increased density of this OL subpopulation in the anterior cingulate cortex. Prohibitin is a mitochondrial protein, which is expressed both in neurons and OLs. Among many other functions, this protein plays an important role in the control of cell proliferation and apoptosis by regulating the GTPase OPA1. Hence, our data might be taken as possible hint for disease-related cell cycle abnormalities.

## Introduction

To the key findings in the neuropathology of schizophrenia belong decreases in OL density as well as an altered spatial distribution, deviant cell morphology and protein expression patterns of these cells, which manifest themselves in an impaired chemical composition of myelin, aberrant communication between different brain regions and other white matter

abnormalities (reviewed in refs. 1 and 2). The reasons for reduced OL number and myelin-specific gene expression impairments in schizophrenia are yet poorly understood. When analysing what signalling pathways may elicit these deficits, Katsel *et al.*<sup>1</sup> found that especially genes associated with canonical cell cycle pathways were affected in the anterior cingulate gyrus (ACG), the region exhibiting the most profound myelin-specific gene expression changes in schizophrenia. Thus, while almost all other studies have focused on seeking abnormalities that impede OL maturation at the level of migration, myelination, and survival<sup>1,2</sup>, the results of Katsel's group<sup>3</sup> provide the first experimental evidence that not only neurons, but also OLs (or, more precisely, OL progenitor cells), may suffer from cell cycle disturbances in schizophrenia.

Our group has recently shown that the neuronal expression of prohibitin is upregulated in schizophrenia, which might be an indication of disease-related synaptic pathology<sup>4</sup>. Subsequent analysis revealed that the protein is also abundantly expressed in white matter OLs<sup>5</sup>. Emerging evidence in favour of a prominent role of prohibitin in the control of cell cycle (ref. 6 and others) encouraged us to analyse the OL expression of prohibitin in different brain white matter areas patients with schizophrenia.

## Material and methods

All brains were obtained from Magdeburg brain bank. Brains of six individuals with clinically confirmed schizophrenia and seven matched controls without neurological or psychiatric disorders were studied. The tissue preparation was as described earlier<sup>7</sup>.

Prohibitin immunoreactivity was detected with a monoclonal antibody using the nickel-enhanced avidin-biotin technique<sup>4</sup>. Prohibitin is present in multiple mature OLs as well as in progenitor cells located in the subventricular zone. The density of prohibitin-expressing OLs was determined in left and right dorsolateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex as recently described<sup>8</sup>.

## Results

Qualitatively, prohibitin was found to be expressed in a majority of white matter OLs and some gray matter OLs. The intracellular immunostaining was confined to granule-like organelles, which were distributed within the cytoplasm and are most probably mitochondria. Prohibitin-immunoreactive cells were also observed in the subventricular zone. Morphometrically, a significant ( $p=0.035$ ) increase in the numerical density of prohibitin immunoreactive OLs was found in the right dorsolateral prefrontal cortex. In all other brain areas under study no differences between schizophrenics and controls were seen. A limitation of this study is the small number of cases.

### Discussion

Although a nuclear localization of prohibitin has also been reported, there is yet consensus that this protein is predominantly localized to the mitochondria, where it might have roles in the maintenance of mitochondrial morphology and function, protection against senescence, tumor suppression, apoptosis and the regulation of cell-cycle progression<sup>6,9</sup>. Previously, the latter function was seriously questioned, because it is hard to imagine how a mitochondrial protein might manage this. A recent paper has convincingly shown that mitochondria-located prohibitin is indeed capable of controlling cell cycle by coupling cell proliferation to mitochondrial morphogenesis through the GTPase OPA1<sup>6</sup>. Thus, the observed increased expression of the anti-proliferative protein prohibitin

in dorsolateral prefrontal OLs might well be part of a disturbed signalling cascade which finally leads to an OL impaired cell cycle activity in schizophrenia<sup>3</sup>. However, since prohibitin is involved in a plethora of different regulatory mechanisms, our data cannot be taken as an evidence for this, and further studies are clearly needed to learn more about OL cell cycle abnormalities in schizophrenia. Therefore, studies are in progress to co-stain prohibitin with the proliferation marker Ki67.

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