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Review

RNA metabolism and dysmyelination in schizophrenia

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Abstract

Decreased expression of a subset of oligodendrocyte and myelin-related genes is the most consistent finding among gene expression studies of postmortem brain tissue from subjects with schizophrenia (SCZ), although heritable variants have yet to be found that can explain the bulk of this data. However, expression of the glial gene Quaking (*QKI*), encoding an RNA binding (RBP) essential for myelination, was recently found to be decreased in SCZ brain. Both oligodendrocyte/myelin related genes, and other RBPs that are known or predicted to be targets of QKI, are also decreased in SCZ. Two different *quaking* mutant mice share some pathological features in common with SCZ, including decreased expression of myelin-related genes and dysmyelination, without gross destruction of white matter. Therefore, although these mice are not a model of SCZ per se, understanding the similarities and differences in gene expression between brains from these mice and subjects with SCZ could help parse out distinct genetic pathways underlying SCZ.

Keywords: Gene expression; Myelin; Oligodendrocytes; Splicing factors; Quaking

Contents

1. Introduction

Gene expression studies have yielded multiple candidate genes for Schizophrenia (SCZ), yet proving that any of them contribute to disease susceptibility requires demonstration that they harbor both functional and heritable variants, a rare occurrence to date. This may be partly due to incomplete screening, as it is too costly and time consuming to perform such evaluations without a rational strategy for prioritizing candidates. However, delineating common regulatory mechanisms shared by differentially expressed genes might narrow the focus to those actually harboring SCZ susceptibility alleles. In this paper, we will briefly review the function and formation of myelin, as well as the microarray studies that have established decreased expression of oligodendrocyte/myelin-

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related genes in SCZ brain. We will then describe recent data from two independent SCZ gene expression studies suggesting that defects in RNA binding proteins (RBPs) lie upstream of the myelin-related gene findings and may also account for other gene expression changes seen in this disorder.

1.1. The function and formation of myelin

Oligodendrocytes produce myelin membranes that wrap around axons and are interspersed by unmyelinated nodes that permit saltatory conduction of nerve impulses. These cells progress through several stages characterized by the expression of particular myelin-related genes and cell surface markers before they are able to form myelin. DM20, a splice form of the proteolipid protein (*PLP*), and 2′,3′-cyclic nucleotide phosphodiesterase (*CNP*) are among the first myelin genes to be expressed in developing oligodendrocytes (reviewed in Baumann and Pham-Dinh, 2001). Subsequently, as oligodendrocytes mature, they express myelin basic protein (*MBP*), then the *PLP* splice form of PLP/DM20, followed by myelin-associated glycoprotein (*MAG*). MAG is a transmembrane protein important for initiating myelination and for axon–glial interactions (Schachner and Bartsch, 2000). Finally, expression of myelin oligodendrocyte glycoprotein (*MOG*), characterizes mature myelinating oligodendrocytes. The majority of myelin genes are alternatively spliced during development and some, like *MBP*, are bound, stabilized, and transported to specific cellular locations by RBPs including QKI. The formation of myelin begins during the second half of fetal life in humans, peaking in the first postnatal year but continuing until approximately 20 years of age in certain cortical fiber tracts. In mouse, myelin can first be detected surrounding axonal sheaths at embryonic day 16.5 (E16.5) (Hardy and Friedrich, 1996) and peaks at postnatal day 18 (P18).

Myelin is made up of 70% lipids, including cholesterol and glycosphingolipids, which contain very long-chain fatty acids (Baumann and Pham-Dinh, 2001). Structurally, myelin is composed of distinct subdomains, including compact myelin, from which cytoplasm has been extruded, and cytoplasm-containing loops, which are further subdivided into periaxonal, paranodal, and outer domains. Many myelin proteins are localized to these specific compartments. For instance, compact myelin contains the myelin structural proteins MBP and PLP, which together constitute about 80% of total myelin protein, as well as much smaller amounts of myelin-associated oligodendrocyte binding protein (MOBP). Importantly, several myelin proteins have extracellular domains that can interact with neurons. In fact, substantial evidence is accumulating that certain oligodendrocyte/myelin related proteins, including CNP and PLP, play a role in the growth and maintenance of axons in white matter (Lappe-Siefke et al., 2003; Edgar et al., 2004), and synapses in gray matter (Kaifu et al., 2003), that is distinct from their activities in myelination. Therefore, reduced expression of these genes could have wide-ranging deleterious effects on the efficiency of axonal conduction and synaptic connectivity, in keeping with the hypothesis that SCZ is a disease of impaired neural communication (Frankle et al., 2003; Spencer et al., 2004).

1.2. Pathological changes in myelin observed in SCZ brain

Documented abnormalities of oligodendrocytes in SCZ brain tissue correlate with the decreased expression of myelin-related genes. For instance, histological studies have shown an abnormal distribution and decreased density of oligodendrocytes in frontal regions of SCZ brains, as well as reduced cell numbers in certain cortical layers (Uranova et al., 2001; Hof et al., 2003; Flynn et al., 2003; Tkachev et al., 2003; Uranova et al., 2004). Reduced glial density has also been observed in the anterior cingulate cortex (Stark et al., 2004). Although it could be argued that the decreased expression of myelin genes might simply be related to cell loss, no one has observed decreases in total mRNA for one of the most abundant myelin proteins, *MBP*, making this an unlikely possibility (Hakak et al., 2001; Tkachev et al., 2003; Mimmack et al., 2004; Prabakaran et al., 2004; Katsel et al., 2005a). However, as postmortem samples are currently only available in significant numbers from SCZ cases with an average age of 50 years or more, the contribution of chronic neuroleptic treatment and/or duration of illness to oligodendrocyte/myelin pathology is difficult to measure.

Fortunately, diffusion tensor imaging (DTI) studies can provide sensitive in vivo data on the integrity of white matter tracts and have shown disorganization of oligodendrocytes in white matter from a variety of brain regions in subjects with chronic SCZ, including the frontal cortices (Buchsbaum et al., 1998; Lim et al., 1999; Ardekani et al., 2003; Minami et al., 2003). Two preliminary DTI studies in SCZ subjects performed at the first onset of illness (average age of subjects approximately 25 years) do suggest that white matter abnormalities are absent or very subtle in fronto-temporal regions at this stage, (Price et al., 2005; Szeszko et al., 2005) although larger sample sizes and more brain regions need to be studied before conclusions can be drawn. On the other hand, a microarray study of postmortem brain tissue from the temporal cortices of subjects with major depression who had never been exposed to neuroleptics also demonstrated decreases in oligodendrocyte/myelin-related genes (Aston et al., 2005). This data suggests that neuroleptics, at least, may not be the reason for similar observations in schizophrenia.

1.3. Decreased expression of myelin related genes in schizophrenia

The first group to report decreased expression of myelin genes in a microarray study of SCZ sampled postmortem prefrontal cortical brain tissue (Brodmann area (BA) 46) from a phenotypically homogeneous cohort of cases (Hakak et al., 2001). (Please see Table 1 for a list of microarray studies performed on SCZ brain tissue). The cases were long-term residents of a psychiatric hospital with no exposure to drugs of abuse, who died of natural causes and had extensively documented clinical histories prior to death. Matched controls from nursing homes had similar