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Mitochondrial roles of the psychiatric disease risk factor DISC1

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ABSTRACT

Ion transport during neuronal signalling utilizes the majority of the brain's energy supply. Mitochondria are key sites for energy provision through ATP synthesis and play other important roles including calcium buffering. Thus, tightly regulated distribution and function of these organelles throughout the intricate architecture of the neuron is essential for normal synaptic communication. Therefore, delineating mechanisms coordinating mitochondrial transport and function is essential for understanding nervous system physiology and pathology. While aberrant mitochondrial transport and dynamics have long been associated with neurodegenerative disease, they have also more recently been linked to major mental illness including schizophrenia, autism and depression. However, the underlying mechanisms have yet to be elucidated, due to an incomplete understanding of the combinations of genetic and environmental factors contributing to these conditions. Consequently, the DISC1 gene has undergone intense study since its discovery at the site of a balanced chromosomal translocation, segregating with mental illness in a Scottish pedigree. The precise molecular functions of DISC1 remain elusive. Reported functions of DISC1 include regulation of intracellular signalling pathways, neuronal migration and dendritic development. Intriguingly, a role for DISC1 in mitochondrial homeostasis and transport is fast emerging. Therefore, a major function of DISC1 in regulating mitochondrial distribution, ATP synthesis and calcium buffering may be disrupted in psychiatric disease. In this review, we discuss the links between DISC1 and mitochondria, considering both trafficking of these organelles and their function, and how, via these processes, DISC1 may contribute to the regulation of neuronal behavior in normal and psychiatric disease states.

1. Introduction

Disrupted in schizophrenia 1 - DISC1 - was first identified as a candidate susceptibility factor for psychiatric disease in a Scottish pedigree. In this study, it was found that a balanced chromosomal translocation co-segregated with psychiatric diagnoses including schizophrenia, bipolar disorder and major depression (St Clair et al., 1990). Analysis of the interrupted regions on these chromosomes (1 and 11) led to the discovery of the DISC1 gene on chromosome 1, encoding a protein proposed to have a large, globular, N terminus and a coiled coil rich C terminus (Millar et al., 2000). The gene on chromosome 11 was termed Boymaw or DISC1FP1 for DISC1 fusion partner 1. Fig. 1a shows a schematic of the DISC1 protein structure with the position of psychiatric disease associated variants marked. The balanced chromosomal translocation has been proposed to have three potential outcomes. It may give rise to abnormal transcripts encoding DISC1 1-597 plus 60 or 69 novel amino acids derived from the gene on chromosome 11 (known as DISC1-Boymaw fusion protein or CP60/69 for chimaeric protein 60 or 69) or a truncated DISC1 transcript, ending at the break point (Brandon and Sawa, 2011). Alternatively, the abnormal transcript may not be expressed, giving rise to a haploinsufficiency (Brandon and Sawa, 2011) (Fig. 1b). Beyond the balanced chromosomal translocation, multiple other linkage analyses and sequence analyses have proposed DISC1 as a risk factor in psychiatric illness. For example, polymorphisms in DISC1 such as a 4-base pair deletion, or point mutations giving rise to amino acid substitutions R37W, S704C and L607F segregate with schizophrenia and other major mental illness (Callicott et al., 2005; Hodgkinson et al., 2004; Sachs et al., 2005; Thomson et al., 2014). The 4-base pair deletion results in the loss of 46 C terminal amino acids of wild type DISC1, and instead, the inclusion of 9 novel amino acids (Sachs et al., 2005). From work in patient derived neurons, we now know this transcript to be expressed at the protein level and to contribute to a defect in presynaptic function – perhaps via increased turnover of wildtype DISC1 (Wen et al., 2014). R37W and L607F have been described to impair mitochondrial trafficking, to be discussed below (Atkin et al., 2011; Ogawa et al., 2014). Further work into the functional effects of these, and other, mutations remains to be carried out, but, at the biochemical level, DISC1 is linked to sporadic schizophrenia. It has been shown to form insoluble aggregates in post mortem schizophrenia tissue, perhaps induced by cellular stress

Abbreviations: DISC1, disrupted in schizophrenia 1; Miro, mitochondrial Rho GTPase; ATP, adenosine triphosphate; OXPHOS, oxidative phosphorylation; KIF, kinesin family; TRAK, trafficking kinesin binding protein; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane.

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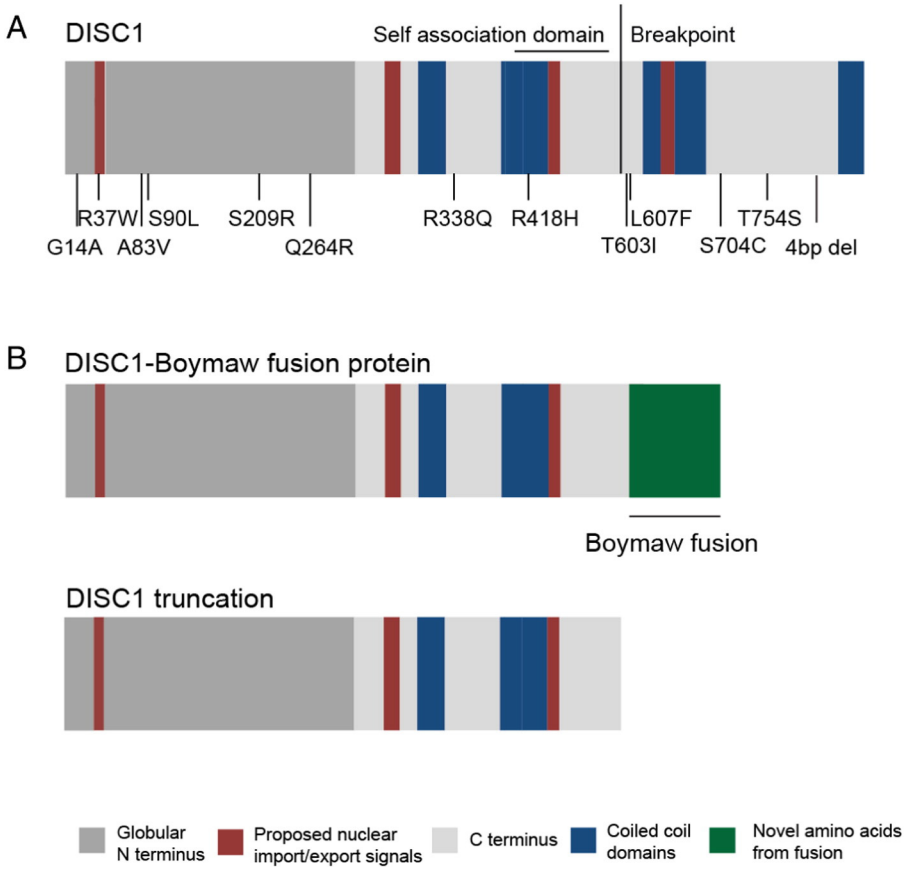

Fig. 1. Schematic of the DISC1 protein. A Structure of the DISC1 protein showing globular N terminus, Coiled coil rich C terminus and sites of psychiatric disease associated mutations. B Possible outcomes of the balanced chromosomal translocation at the protein level. The translocation may give rise to a fusion protein between DISC1 and Boymaw/DISC1 fusion partner 1, or a truncated DISC1.

(Leliveld et al., 2008). It should be noted that DISC1 fails to appear as a genetic risk factor in genome wide association studies (International Schizophrenia et al., 2009; O'Donovan et al., 2008). However, DISC1 is known to influence endophenotypes associated with psychiatric disease such as cortical thickness and anhedonia (Callicott et al., 2005; Tomppo et al., 2009). Thus, thorough analysis of DISC1 function could give rise to deeper understanding of pathways interrupted in these diseases.

Since its discovery, the function of DISC1 in the neuron has undergone intense study, revealing roles in intracellular trafficking, neuronal development and intracellular signalling. Yeast two hybrid studies have suggested over 100 potential interaction partners (Brandon and Sawa, 2011; Camargo et al., 2007). These include kinesin motor proteins (Taya et al., 2007; Tsuboi et al., 2015), and dynein motor complex components Lis1, Nde1 and Ndel1 (Kamiya et al., 2006). Interaction with components of molecular motor complexes highlights potential roles in intracellular trafficking (see (Devine et al., 2016b) for a more detailed review). Interaction with Nde1/Ndel1 has led to elucidation of DISC1 as a regulator of neuronal differentiation, migration and integration during neuronal development (Brandon and Sawa, 2011; Duan et al., 2007; Enomoto et al., 2009; Narayan et al., 2013; Singh et al., 2011). Further, interactions with GSK3 beta and phosphodiesterases suggest roles in intracellular signalling (Ishizuka et al., 2011; Millar et al., 2005b). Beyond these functions, DISC1 has been localised to mitochondria in multiple studies via electron microscopy, immunocytochemistry and biochemical fractionation experiments (James et al., 2004; Millar et al., 2005a; Norkett et al., 2016; Park et al., 2010) and found to interact with mitochondrial proteins mitofilin and CHCHD6 – which influence mitochondrial function (Park et al., 2010; Pinero-Martos et al., 2016). Along with its interaction with trafficking machinery this has suggested DISC1 as a crucial regulator of mitochondrial trafficking and function which will be further discussed below.

Mitochondria are considered as the powerhouses of cells, generating ATP to facilitate key cellular functions such as ion pumping, cellular trafficking, and neuronal communication. They are comprised of an outer membrane, inter membrane space and highly selective inner mitochondrial membrane, preventing free diffusion of ions and small molecules, thus compartmentalising the matrix from the cytosol (see Fig. 2a). This inner membrane is intricately folded into cristae to increase surface area and is the site of oxidative phosphorylation for ATP production. The inner membrane surrounds the mitochondrial matrix (Cogliati et al., 2016). Besides ATP production, mitochondria are known to buffer Ca^{2+} during release of neurotransmitters or post-synaptic receptor activation which, in turn, regulates neural signalling (McBride et al., 2006; Sheng and Cai, 2012; Szabadkai and Duchen, 2008; Werth and Thayer, 1994; Zucker, 1999). In order to achieve this, mitochondria must be precisely situated within neuronal processes at sites of high ATP or calcium buffering demand, such as the pre and post synapse. Therefore, mitochondria must be trafficked to, and docked at these sites to allow correct neuronal function and development (MacAskill et al., 2010; MacAskill and Kittler, 2010).

Several studies have demonstrated that physical proximity between mitochondria and synapses is dependent on neuronal activity (Courchet et al., 2013; Macaskill et al., 2009b; Sheng and Cai, 2012). Neural activity consumes energy in terms of ATP which is provided by the mitochondria. Studies suggested that ATP derived from mitochondria is important for long-term potentiation (LTP) and dendritic spine morphogenesis (Li et al., 2004; Lowe et al., 2013). Synaptic plasticity has a key role in both short- and long-term memory and is often linked to a variety of psychiatric disorders (Takeuchi et al., 2013; Wondolowski

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