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Regulation of mitochondrial dynamics by DISC1, a putative risk factor for major mental illness

Laura C. Murphy, J. Kirsty Millar *

Centre for Genomic and Experimental Medicine, MRC Institute of Genetic and Molecular Medicine at the University of Edinburgh, Crewe Road, Edinburgh EH4 2XU, UK

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ABSTRACT

Mitochondria are dynamic organelles that are essential to power the process of neurotransmission. Neurons must therefore ensure that mitochondria maintain their functional integrity and are efficiently transported along the full extent of the axons and dendrites, from soma to synapses. Mitochondrial dynamics (trafficking, fission and fusion) co-ordinately regulate mitochondrial quality control and function. DISC1 is a component of the mitochondrial transport machinery and regulates mitochondrial dynamics. DISC1's role in this is adversely affected by sequence variants connected to brain structure/function and disease risk, and by mutant truncation. The DISC1 interactors NDE1 and GSK3β are also involved, indicating a convergence of putative risk factors for psychiatric illness upon mitochondrial dynamics.

1. Introduction

In humans, around 20% of total energy consumption, at rest, is due to brain activity, despite the brain representing only a few per cent of total body mass (Harris et al., 2012; Raichle and Gusnard, 2002). This high energy consumption by the brain is largely accounted for by neurotransmission (Harris et al., 2012; Raichle and Gusnard, 2002). For example, neurons require large amounts of energy to power the ion pumps that restore ion gradients following the ion influx that accompanies neuronal firing, and to drive synaptic vesicle release (Harris et al., 2012; Raichle and Gusnard, 2002). These energy demands are met by mitochondria, which also power important neurodevelopmental processes such as neurite outgrowth (Kimura and Murakami, 2014; Morris and Hollenbeck, 1993), as well as all the energy-dependent functions that occur in most cell types. Mitochondria have additional roles, including calcium buffering, which is another process important for neuronal functioning, particularly at synapses (Cai and Sheng, 2009).

Although mitochondria are essential in almost every cell type, the particularly high energy demands of neurons render them especially sensitive to mitochondrial dysfunction. Altered mitochondrial homeostasis could result, for example, in synaptic vesicles not being efficiently released into the synaptic cleft, or in ion pumps being unable to restore ion gradients, post-neuronal firing, in readiness for the next action potential. Neurotransmission would be predicted to be suboptimal as a consequence. Moreover, neurons would be more susceptible to injury by excitotoxicity, a process by which glutamate-induced calcium influx through NMDA receptors triggers neuronal damage, or even death, if calcium levels are not adequately controlled (Rueda et al., 2016). This neuronal sensitivity to suboptimal mitochondrial function is exemplified by the strong link between mitochondrial defects and neurological disorders (Chaturvedi and Flint Beal, 2013), and there is increasing evidence that mitochondrial dysfunction also contributes to psychiatric disorders (Adzic et al., 2016; Bergman and Ben-Shachar, 2016; Machado et al., 2016). We discuss here the importance of mitochondrial dynamics to neuronal function and the potential contribution of DISC1 to major mental illness through disease mechanisms involving dysregulated mitochondrial dynamics, focussing particularly upon mitochondrial trafficking because that area has received most attention to date with respect to DISC1.

2. DISC1

2.1. DISC1 and psychiatric disorders

The DISC1 gene is directly disrupted by a balanced translocation between chromosomes 1 and 11 that substantially increases risk of schizophrenia, bipolar disorder and recurrent depression in a large Scottish

Abbreviations: DISC1, Disrupted in Schizophrenia 1; DISC1FP1, DISRUPTED in Schizophrenia 1 Fusion Partner 1; FEZ1, Fasciculation and Elongation Protein Zeta 1; $GABA_A$, Gamma-Aminobutyric Acid A; GSK3β, Glycogen Synthase Kinase 3 Beta; LIS1, Lissencephaly 1; MFN1/2, Mitofusin 1/2; MIRO1/2, Ras Homologue Family Member T1/2; NDE1, NudE Neurodevelopment Protein 1; NDEL1, NudE Neurodevelopment Protein Like 1; NMDA, *N*-Methyl-D-Aspartate; OPA1, Optic Atrophy 1; SNPH, Syntaphilin; TRAK1/2, Trafficking Protein, Kinesin Binding 1.

* Corresponding author.
E-mail address: kirsty.millar@igmm.ed.ac.uk (J.K. Millar).

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family (Blackwood et al., 2001; Millar et al., 2000; Thomson et al., 2016). The translocation decreases DISC1 expression by approximately half (Eykelenboom et al., 2012; Millar et al., 2005b), consistent with a haploinsufficiency model of associated risk. Moreover, the translocation results in fusion of *DISC1* on chromosome 1 to *DISC1FP1* (otherwise known as *Boymaw*) (Zhou et al., 2010) on chromosome 11, producing a variety of chimeric transcripts (Eykelenboom et al., 2012). Some of these chimeric transcripts encode aberrant C-terminally truncated forms of DISC1 fused to amino acids encoded by *DISC1FP1* exons (Eykelenboom et al., 2012). Although expression of these aberrant DISC1 protein species has yet to be demonstrated in translocation carriers (Eykelenboom et al., 2012), it is possible that they contribute to the translocation-induced disease mechanism.

In addition to the translocation, rare copy number variants, duplications and deletions, affecting *DISC1*, have been identified in Scottish and Swedish individuals diagnosed with schizophrenia or intellectual disability (Johnstone et al., 2015). Moreover an 'ultra-rare' non-synonymous DISC1 sequence variant, R37W, is present in a single schizophrenic individual (Song et al., 2008), as well as in three members of a Scottish family diagnosed with recurrent depression or anxiety (Thomson et al., 2014). These structural and sequence variants may conceivably be involved in DISC1-based disease mechanisms in psychiatry beyond the t(1;11) translocation family.

2.2. DISC1 influences mitochondrial distribution and morphology

DISC1 is targeted to multiple subcellular compartments including synapses, centrosomes, nuclei, endoplasmic reticulum (ER), Golgi and mitochondria (Park et al., 2015; Thomson et al., 2013), and plays important roles at each location. We have demonstrated that DISC1 normally associates with mitochondria as discrete puncta organised around the mitochondrial periphery (Ogawa et al., 2014). Intriguingly however, we have also found that variant and mutant forms of DISC1 become more homogeneously distributed at mitochondria (Eykelenboom et al., 2012; Millar et al., 2005a; Ogawa et al., 2014). They also alter mitochondrial morphology and distribution (Table 1). For example, artificial overexpression of only the DISC1 N-terminal head domain (amino acids 1–358) induces abnormal mitochondrial ring- or lariat-like structures (Millar et al., 2005a), while the presence of the 37W sequence variant in the head domain (Song et al., 2008), causes mitochondrial clustering in the perinuclear region (Ogawa et al., 2014). Moreover, when artificially overexpressed, some of the translocation-induced aberrant chimeric DISC1 species, those referred to as CP60 and CP69, are targeted to mitochondria where they induce perinuclear mitochondrial clustering together with mitochondrial dysfunction (Eykelenboom et al., 2012). The effects on mitochondrial distribution and morphology are consistent with altered mitochondrial dynamics as will be discussed later.

3. Mitochondrial trafficking

3.1. Molecular mechanisms underlying mitochondrial trafficking

To function as required, mitochondria must be present at the right place, in the required numbers and at the right time. This is achieved by actively transporting the mitochondria to their destination along microtubules. In neurons this process is of critical importance because their highly elongated structure means that mitochondria may need to be transported considerable distances, for example from the cell soma to synapses.

Mitochondrial trafficking is therefore a tightly regulated process that utilises the co-ordinated opposing actions of the microtubule-based anterograde and retrograde molecular motors kinesin and dynein, respectively. In neurons this results in a proportion of mitochondria moving in a saltatory fashion in both directions, while the rest are stationary. The trafficking process involves the adaptor proteins TRAK1 and TRAK2 (Ashrafi and Schwarz, 2013) which bind to kinesin and/or dynein. Specifically, TRAK1 binds both kinesin and dynein, while TRAK2 binds only dynein (van Spronsen et al., 2013). TRAK1 and TRAK2 also interact with MIRO1 and MIRO2, which are embedded in the outer mitochondrial membrane (Ashrafi and Schwarz, 2013). TRAK1 and TRAK2 therefore link mitochondria to the molecular motors that power their movements around cells. The TRAK proteins are differentially expressed within neurons (Loss and Stephenson, 2015; van Spronsen et al., 2013) in hippocampal and cortical neurons TRAK1 predominates in axons, but is also present in dendrites (Loss and Stephenson, 2015; van Spronsen et al., 2013). In contrast, the majority of TRAK2 is dendritic in hippocampal neurons (van Spronsen et al., 2013), while it is equally distributed between axons and dendrites in cortical neurons (Loss and Stephenson, 2015). Their differential expression and motor protein binding has led to the suggestion that TRAK1 mainly drives mitochondrial transport in axons, while TRAK2 regulates their transport in dendrites, at least in hippocampal neurons (van Spronsen et al., 2013). This is supported by the observation that knocks down of TRAK1, but not of TRAK2, inhibits axonal mitochondrial transport in hippocampal neurons (Brickley and Stephenson, 2011).

Mitochondrial motility is also regulated by signals that determine how many mitochondria are motile versus stationary, including signals that halt mitochondrial movement at specific locations. One of the most widely studied of these signals is calcium, which triggers local mitochondrial arrest in excitable cells (Schwarz, 2013). In neurons calcium influx occurs at synapses, where mitochondria are consequently required to power the ion pumps that restore pre-firing calcium levels,

Table 1
Summary of the known mitochondrial effects of DISC1 and variant or mutant DISC1 species.

Protein species	Mitochondrial trafficking	Mitochondrial fusion & fission	Mitochondrial morphology
DISC1	Knockdown impairs motility (Atkin et al., 2011), overexpression increases total (Atkin et al., 2011) or anterograde (Ogawa et al., 2014) movement		No effect (Ogawa et al., 2014)
DISC1-Boymaw, CP60/69	Impairs motility (DISC1-Boymaw) (Norkett et al., 2016)	Impairs fusion and decreases mitochondria-ER contacts which could affect fission (DISC1-Boymaw) (Norkett et al., 2016)	Induces perinuclear clustering and loss of membrane potential (CP60/69) (Eykelenboom et al., 2012), decreases segment size (DISC1-Boymaw) (Norkett et al., 2016)
DISC1-37W	Fails to promote anterograde movement (Ogawa et al., 2014)		Induces perinuclear clustering (Ogawa et al., 2014)
DISC1-607F	Fails to rescue effect of DISC1 knockdown (Atkin et al., 2011)		
DISC1-704C	No effect (Atkin et al., 2011)		
DISC1 N-terminus	Impairs motility (amino acids 1–301) (Norkett et al., 2016)	Probable effects (amino acids 1–358 and 1–301) (Millar et al., 2005a; Norkett et al., 2016)	Induces lariat and ring structures (amino acids 1–358) (Millar et al., 2005a), decreases segment size (amino acids 1–301) (Norkett et al., 2016)

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