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

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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.

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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)

as well as providing direct calcium uptake. Calcium-induced mitochondrial arrest therefore directs provision of these functions to synapses as required. Mitochondrial stopping is regulated by calcium via the calcium-sensing activity of the MIRO proteins (Cai and Sheng, 2009). In neurons the axonal protein SNPH is also involved (Kang et al., 2008). SNPH is recruited to hippocampal axonal mitochondria in response to neuronal firing-induced calcium ion influx. Here it binds to, and inactivates, mitochondrial kinesin via a mechanism involving the MIRO calcium sensor (Chen and Sheng, 2013).

3.2. DISC1 and mitochondrial trafficking

The perinuclear mitochondrial clustering induced by the presence of the DISC1 37W variant (Ogawa et al., 2014) or some of the aberrant chimeric DISC1 species (Eykelenboom et al., 2012) putatively arising from the t(1;11) translocation could be due to a trafficking defect whereby the mitochondria either cannot be forward trafficked, or are preferentially transported back to the cell soma and retained there. Consistent with this suggestion, we recently demonstrated a robust association between DISC1 and TRAK1 (Ogawa et al., 2014). Norkett et al. subsequently confirmed this association and also reported that DISC1 complexes with TRAK2 (Norkett et al., 2016). Overexpression studies in both laboratories found that DISC1 is recruited to mitochondria by the TRAK proteins (Norkett et al., 2016; Ogawa et al., 2014). Association with TRAK1 and TRAK2 involves the DISC1 head domain (Norkett et al., 2016; Ogawa et al., 2014), and for TRAK1 at least, this requires a conserved arginine-rich sequence within the head domain that encompasses the 37W sequence variant (Ogawa et al., 2014). DISC1 also associates with the MIRO proteins (Norkett et al., 2016; Ogawa et al., 2014), and for MIRO1 it is known that association with DISC1 is augmented by the presence of TRAK1 (Bradshaw et al., 2008). As with the TRAK proteins, MIRO1 overexpression recruits DISC1 to mitochondria (Norkett et al., 2016). DISC1 therefore robustly associates with mitochondrial trafficking complexes through multiple protein associations (Fig. 1), and likely is directly involved in mitochondrial transport.

Several studies have used time-lapse live cell imaging to track movements of individual mitochondria in hippocampal neurons and demonstrate that DISC1 does indeed modulate mitochondrial trafficking (Table 1). Following knock down of endogenous DISC1 in rat neurons, the proportion of moving axonal mitochondria is reduced, an effect that is rescued by overexpressing DISC1 (Atkin et al., 2011). Exogenous expression of the DISC1 head domain (amino acids 1–301) similarly impairs mitochondrial movement, presumably through disruption of protein associations such as with TRAK1/2 (Bradshaw et al., 2008; Ogawa et al., 2014). Moreover, DISC1 overexpression increases the proportion of motile mitochondria, both in axons and in dendrites (Norkett et al., 2016), as predicted by the association of DISC1 with both TRAK1 and TRAK2. Our own slightly different experimental approach using mouse neurons has not detected increased axonal mitochondrial motility overall in response to DISC1 overexpression, but does demonstrate that DISC1 promotes increased anterograde mitochondrial movement at the expense of retrograde transport (Bradshaw et al., 2008). DISC1 therefore increases mitochondrial motility, although discrepancies as to its precise effect have yet to be resolved.

While DISC1 expression levels clearly influence mitochondrial trafficking, effects of mutant DISC1 species have also been demonstrated (Table 1). The influences upon mitochondrial morphology of the DISC1 sequence variant 37W, and of the deleterious chimeric DISC1 species, CP60 and CP69, putatively arising from the t(1;11) translocation (Eykelenboom et al., 2012; Ogawa et al., 2014) have now been shown to likely be due, at least in part, to direct effects upon mitochondrial trafficking. The 37W variant, located within a region of DISC1 essential for TRAK1 association, dysregulates DISC1/TRAK1 and TRAK1/MIRO1 associations (Ogawa et al., 2014). In turn, it also abolishes the ability of DISC1 to promote anterograde mitochondrial movement in mouse hippocampal neuron axons (Ogawa et al., 2014). Similarly, an aberrant chimeric DISC1 species DISC1-Boymaw (Zhou et al., 2010), corresponding approximately to CP60/69, does not increase mitochondrial motility in rat hippocampal neuron axons, unlike wild type DISC1 (Norkett et al., 2016). These observations illustrate the adverse impact of putative psychiatric disorder-associated forms of DISC1 upon the efficient transport of mitochondria around neurons.

The effect of common non-synonymous DISC1 sequence variants upon mitochondrial trafficking has also been examined (Atkin et al., 2011). This was carried out by determining whether variant forms of DISC1 can rescue the decreased mitochondrial trafficking that occurs in hippocampal neurons following DISC1 knockdown (Atkin et al., 2011). Of the variants examined (L607F and S704C) the DISC1 607F variant was unable to rescue the defect (Table 1). This is noteworthy because the 607F variant, present in approximately 10% of the population, influences brain structure and function (Thomson et al., 2013), and may therefore do so, at least in part, through adverse effects upon mitochondrial movement within neurons.

3.3. DISC1 interactors and mitochondrial trafficking

It will be clear from the foregoing that DISC1 does not function in isolation. Indeed, with multiple, directly interacting protein partners, DISC1 fits the description of a molecular scaffold (Camargo et al., 2007). Among its well-known binding partners are the dynein regulators LIS1, NDEL1 and NDE1 (Bradshaw et al., 2009; Brandon et al., 2004; Ozeki et al., 2003), and the kinase GSK3β (Mao et al., 2009). Like DISC1, all of these interactors modulate neuronal mitochondrial trafficking. Moreover, like DISC1 there is evidence pointing towards involvement of NDE1 and GSK3β in risk of developing major mental illness. For example, the NDE1 gene is encompassed by recurrent copy

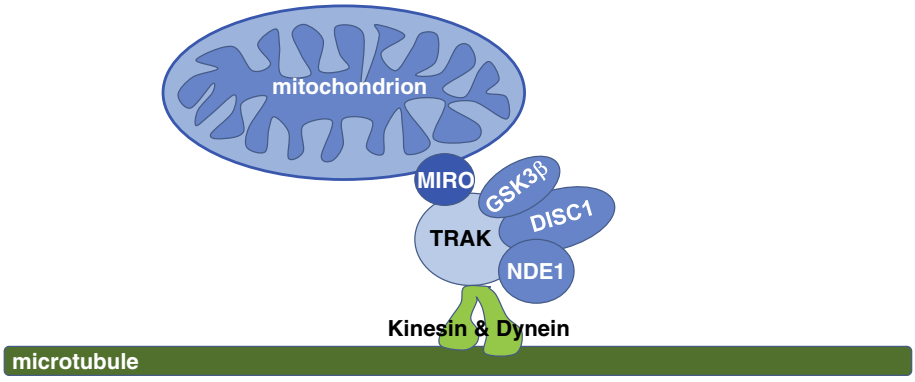

Fig. 1. Mitochondria are transported along microtubules by a multi-protein complex that links mitochondria to the molecular motors kinesin and dynein for transport to (retrograde) and from (anterograde) the cell body. TRAK1 and TRAK2 bind kinesin and/or dynein, as well as the MIRO proteins which are embedded in the outer mitochondrial membrane. DISC1 associates robustly with TRAK1 and TRAK2. The DISC1 binding partners NDE1 and GSK3β also associate with TRAK1 and may, by inference, associate with TRAK2 as well.

number variants, both deletions and duplications, that are significantly more common in psychiatric patients than in unaffected individuals (Malhotra and Sebat, 2012). GSK3β is a major target of the drug Lithium Chloride which is in clinical use as a mood stabiliser (Cole, 2013), and, like NDE1, is targeted by copy number variants that occur most frequently in psychiatric patients (Alkhaja et al., 2012).

NDE1 associates robustly with TRAK1 (Ogawa et al., 2016) and is therefore a likely component of the mitochondrial transport machinery. Although LIS1 and NDEL1 have not yet been directly tested, it is probable that they too are associated with the trafficking complex since LIS1 functions together with NDE1 and/or NDEL1. NDEL1 and NDE1 are orthologous proteins that bind directly to each other, to LIS1 and to dynein (Cianfrocco et al., 2015). NDEL1 or NDE1 binding to LIS1 is considered necessary to activate dynein (Li et al., 2005; Liang et al., 2004; McKenney et al., 2010; Yan et al., 2003) and to maintain a persistent force-producing state (Cianfrocco et al., 2015). Indeed, it is thought that LIS1 and NDE1 together enable dynein to adapt to transportation of high-load cargo (Cianfrocco et al., 2015; Reddy et al., 2016), a category that mitochondria fall into. Knockdown of LIS1 or NDEL1 inhibits axonal mitochondrial transport in both directions, or just in the retrograde direction, respectively (Shao et al., 2013), while in separate experiments NDE1 overexpression was found to promote retrograde axonal mitochondrial movement (Ogawa et al., 2016). These observations are consistent with a role for these proteins in activating and maintaining force production of the retrograde motor dynein at mitochondria. In the absence of LIS1 or NDEL1 it is possible that dynein activity is minimal, or insufficient for transportation of high-load cargo, thus mitochondria are effectively slowed or halted. On the other hand, NDE1 overexpression is predicted to increase dynein activation (or perhaps dynein recruitment to the mitochondrial transport complex) and augment its ability to move large cargo, in turn, increasing retrograde mitochondrial movement (Ogawa et al., 2016). This latter effect is reduced by mutation of an amino acid within the LIS1 binding site on NDE1 that disrupts LIS1/NDE1 interaction (Bradshaw et al., 2011), further supporting the evidence that NDE1 binding to LIS1 activates dynein and facilitates its ability to maintain movement of high-load cargo (Cianfrocco et al., 2015; Reddy et al., 2016). Overall then, the available evidence points towards inclusion of the DISC1 interactor NDE1, and probably NDEL1 and LIS1 also, in the mitochondrial trafficking machinery in order to regulate dynein activity and retrograde mitochondrial movement.

GSK3β also associates with TRAK1 (Ogawa et al., 2016). Although its role within the mitochondrial trafficking complex is unknown at present, there are many studies demonstrating involvement of GSK3β in regulation of mitochondrial trafficking. Overexpression of GSK3β fused to Enhanced Green Fluorescent Protein (EGFP) was found to decrease the proportion of anterograde-moving mitochondria, and their movement lengths, in cortical neuron axons and dendrites (Morel et al., 2010), suggesting that GSK3β inhibits anterograde mitochondrial movement. Moreover GSK3β inhibition by α-4-Dibromoacetophenone reportedly increases mitochondrial velocity and anterograde motility in hippocampal neurons (Chen et al., 2007). In contrast, it has been reported that in hippocampal neurons GSK3β overexpression increases overall (Llorens-Martin et al., 2011), or only anterograde (Ogawa et al., 2016), mitochondrial movement. Moreover, a dominant-negative form of GSK3β, lacking kinase activity, decreases axonal mitochondrial motility, and specifically decreases mitochondrial run length and velocity in the anterograde direction in hippocampal neurons (Llorens-Martin et al., 2011). Despite the discrepancies, these data collectively point towards a role for GSK3β in modulating mitochondrial motility, and, although its precise effect remains controversial, on balance the data suggest that GSK3β regulates the number of motile mitochondria, and their velocity of movement, primarily in the anterograde direction. It is therefore noteworthy that the non-synonymous DISC1 variant that interferes with DISC1's role in trafficking, 607F (Atkin et al., 2011), disrupts DISC1/GSK3β interaction (Singh et al., 2011). On this basis we speculate that the molecular scaffold DISC1 helps to recruit GSK3β to the mitochondrial transport complex, and that this function is disrupted by the 607F variant. This could restrict incorporation of GSK3β into the complex and its ability to activate mitochondrial movement could be curtailed as a result.

In addition to the above confirmed interactors, a potential novel association of DISC1 with SNPH was recently reported (Park et al., 2016) Overexpression or knock down of DISC1 or SNPH was found to have opposing effects upon mitochondrial motility. Moreover, deletion of the region of SNPH required for exogenous association with DISC1 increases the inhibitory effect of SNPH overexpression upon mitochondrial motility. Finally, treatment of neurons with KCl to mimic neuronal firing-induced calcium influx normally induces mitochondria to stop moving, a mechanism that is blocked by DISC1 overexpression. Altogether, it is proposed that DISC1 modulates the interaction between SNPH and kinesin to regulate mitochondrial pausing in response to neuronal firing, with DISC1 counteracting the inhibitory effect of SNPH upon mitochondrial movement (Park et al., 2016). These observations suggest that the mechanism by which DISC1 promotes mitochondrial movement (Atkin et al., 2011; Ogawa et al., 2014) may involve blocking the mitochondrial anchoring function of SNPH (Amiott et al., 2008).

As well as interacting with the dynein regulators LIS1, NDE1 and NDEL1, DISC1 is also known to complex with dynein (Kamiya et al., 2005) and kinesin (Tsuboi et al., 2015), although neither association has yet been examined in the context of mitochondria. Moreover, the DISC1 binding partner FEZ1 regulates mitochondrial trafficking (Fujita et al., 2007; Ikuta et al., 2007) and may in the future be shown to do so together with DISC1.

4. Mitochondrial fission and fusion

4.1. Importance of mitochondrial fission and fusion

Since temporal-spatial provision of mitochondrial function is so critical in neurons, the number of available mitochondria, as well as mitochondrial quality control, is of prime importance. Mitochondrial biogenesis and mitophagy (mitochondrial clearance) contribute to this. These processes are complimented by the capability of mitochondria to join and increase mitochondrial mass (fusion), or to divide and increase mitochondrial numbers (fission). Damaged or suboptimal mitochondria may undergo fusion with healthy mitochondria to create fully functioning daughter mitochondria in which the damage has been diluted out through exchange of materials (Chen and Chan, 2009; Schwarz, 2013). Such material exchanges may also enable communication between mitochondria (Chen and Chan, 2009; Schwarz, 2013). Increasing the number of mitochondria by fission may facilitate distribution of mitochondria along the length of the neurites (Berthet et al., 2014; Chen and Chan, 2009; Schwarz, 2013). Fission can also serve to segregate damaged mitochondrial components for later clearance by mitophagy (Ashrafi and Schwarz, 2013; Chen and Chan, 2009; Otera and Mihara, 2011; van der Bliek et al., 2013). It follows that, if motility is defective or numbers are reduced, mitochondria may meet less often, causing fusion rates to be suppressed, or slowing clearance of isolated damaged mitochondria, and ultimately decreasing the health of the mitochondrial pool.

In mammalian cells mitochondrial fusion is primarily carried out by the dynamin family members MFN1 and MFN2 (outer mitochondrial membrane fusion) and OPA1 (inner membrane fusion) (Chen and Chan, 2009). MFN1 and MFN2 interact with both MIRO1/2 and TRAK1/2, and MFN2 has been shown to regulate mitochondrial trafficking independently of its membrane fusion function (Misko et al., 2010).

Mitochondrial fission is initiated at mitochondria-associated endoplasmic reticulum (ER) Membranes (MAMs). MAMs are points of contact between the two organelles where ER tubules can wrap around mitochondrial tubules causing a constriction at which the dynamin family member DRP1 assembles and subsequently severs the mitochondrial membranes (van der Bliek et al., 2013). MAMs are not

exclusively involved in this process however, and also regulate ER-mitochondria cross-talk including calcium transfer, and autophagosome (mitophagosome for mitochondria) formation, for example (van der Bliek et al., 2013).

4.2. DISC1 and mitochondrial fusion

The abnormal mitochondrial lariat or ring-like structures induced by over-expression of the DISC1 head domain (Millar et al., 2005a) suggest that mitochondrial tubule fission/fusion is abnormal under these circumstances. Interestingly, therefore, DISC1 has been shown to associate with MFN1 and MFN2, although only MFN1 association has been confirmed so far using endogenous proteins in brain (Norkett et al., 2016). While these novel associations could be related to mitochondrial trafficking (Misko et al., 2010), they prompted an investigation into whether DISC1 is involved in mitochondrial fusion. It was found that exogenous expression of the DISC1 N-terminal head domain (amino acids 1–301), or the DISC1-Boymaw fusion protein, in neurons reduces the average size of mitochondria, indicating a probable fission/fusion defect (Table 1) (Norkett et al., 2016). A possible decrease in mitochondrial fusion in the presence of DISC1-Boymaw was then demonstrated (Norkett et al., 2016). To do this COS7 cells carrying either red or green-labelled mitochondria were fused using polyethylene glycol. Subsequent convergence of the two fluorophores was assessed on the assumption that red and green co-localisation represents mitochondrial fusion. Red and green fluorescence co-localisation was found to be decreased in cells expressing DISC1-Boymaw, most likely indicating decreased fusion. The aberrant chimeric DISC1 species may therefore dysregulate mitochondrial fusion (Norkett et al., 2016), but it remains to be seen whether wild-type DISC1 normally plays a role in this process.

4.3. DISC1 at the mitochondria-ER interface, a role in fission?

DISC1-associated proteins MIRO and MFN2 are present at mitochondria-ER contact sites (Kornmann et al., 2011; Lee et al., 2016). DISC1 also localises to MAMs (Norkett et al., 2016). The DISC1-Boymaw fusion protein localises to these sites as well. Indeed it does so more abundantly than the wild-type protein, and decreases the total area of contact between the two organelles (Norkett et al., 2016). Since MAMs are involved in many processes it therefore follows that DISC1, and mutant DISC1, may impact upon these processes. Although there is no evidence for this at present, we speculate that DISC1 may be involved in the MAM-dependent process of mitochondrial fission in light of the regulation of the fission factor DRP1 by the DISC1 binding partner GSK3β (Loh et al., 2015).

5. Other roles of mitochondrial DISC1

Although this review focuses upon the role of DISC1 in regulating mitochondrial dynamics, it is important to note that DISC1 has additional mitochondrial functions. DISC1 interacts with IMMT, a protein located within mitochondria (Park et al., 2010) that regulates mitochondrial inner membrane/cristae organisation (Zerbes et al., 2012). Indeed DISC1 is a component of the Mitochondrial Contact Site and Cristae Organising System (MICOS) (Pinero-Martos et al., 2016). Moreover, altered DISC1 expression has multiple effects upon mitochondrial metabolic functions, including upon mitochondrial oxidative phosphorylation (Park et al., 2010; Pinero-Martos et al., 2016). This is consistent with the localisation of the oxidative phosphorylation complexes to the mitochondrial inner membrane, and their dependence upon correct inner membrane organisation (Park et al., 2010; Pinero-Martos et al., 2016). Although these metabolic effects do not directly impact upon mitochondrial motility, there is evidence that mitochondrial dysfunction affects their movements (Miller and Sheetz, 2004), thus DISC1 may influence mitochondrial trafficking indirectly as well as directly through its association with the mitochondrial transport machinery (Norkett et al., 2016; Ogawa et al., 2014).

6. Conclusions

DISC1 is an integral component of the multiprotein complexes that control neuronal mitochondrial transport to meet energy demands and other mitochondrial functions. Consistent with this, there are a number of studies demonstrating that DISC1 is a key regulator of mitochondrial trafficking, and emerging evidence for roles in modulation of mitochondrial halting, as well as in fusion and possibly fission. DISC1 may also indirectly regulate mitochondrial dynamics through effects upon mitochondrial metabolism. As these fundamental properties of mitochondrial DISC1 are established it next becomes important to understand the mechanisms by which DISC1 exerts these effects upon mitochondrial dynamics. It is likely to do so via its binding partners, recruiting an array of regulatory molecules to control, for example, kinesin and dynein activity.

Crucially, it is now abundantly clear that altered DISC1 function, due either to changed expression levels or to mutant protein species, is likely to compromise the ability of neurons to access mitochondrial processes as required. In turn, this scenario is predicted to adversely affect neurotransmission. A major challenge now is therefore to determine whether mitochondrial trafficking and function are indeed compromised in psychiatric patients, or at risk individuals, where DISC1 function is known to be altered. Such work could utilise, for example, neurons derived by the induced pluripotent stem cell route from carriers of the t(1;11) translocation, the DISC1 37W or 607F sequence variants, or from carriers of a DISC1 frameshift mutation (Wen et al., 2014) that has not so far been investigated with respect to mitochondrial function, or indeed neurons cultured from mouse models of these genomic events. The question as to whether the ectopically expressed aberrant chimeric DISC1 species shown to affect DISC1 mitochondrial distribution and mitochondrial dynamics are expressed physiologically at any point or place during brain development currently remains open.

Although recent comprehensive genome-wide association studies (GWAS) indicate that the DISC1, NDE1 and GSK3β genes are unlikely to harbour common risk variants (Schizophrenia Working Group of the Psychiatric Genomics, 2014), it is conceivable that genes that do carry common risk variants could impact upon mitochondria or their ability to supply energy and other functions to neurons. The relevance of exceptional cases of rare presentations of psychiatric disorder linked causally to single genes, such as DISC1 or NDE1, has been debated, but the studies summarised here demonstrate the generic value of convergent genetic and biological evidence. In the same way that a subset of GWAS loci for schizophrenia point towards calcium ion transport as a plausible target of genetic variation, so the convergence of DISC1, NDE1 and GSK3β on mitochondrial motility provides a promising focus for further investigation of disease mechanisms in psychiatry.

Finally, it is important to point out that DISC1's role in neuronal trafficking extends well beyond mitochondria, and could be a general role in regulation of neuronal cargo transport. As well as mitochondria, DISC1 controls trafficking of synaptic vesicles (Flores et al., 2011), messenger RNA molecules involved in synaptic plasticity (Tsuboi et al., 2015) and $GABA_A$ receptors (Wei et al., 2015). The diversity of these cargos suggests that many more await discovery, thus dysregulated DISC1 function could have wide-ranging effects upon neuronal cargo transport and neurotransmission.

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Conflict of interest
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