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.

Keywords

DISC1, Miro1, Mitochondria, Mitochondrial trafficking, Mitochondrial dynamics, synapse

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

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. Figure 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) (Figure 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 (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 figure 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 and Dickman, 2013). Close proximity to synapses enables mitochondria to buffer Ca^{2+}, which plays an important role in neurotransmission at central synapses. Beyond spine morphogenesis, mitochondrial distribution is essential for correct neurite outgrowth, and thus development of the neuron and circuit connectivity (Chen et al., 2007; Fukumitsu et al., 2015; Norkett et al., 2016). Moreover, mitochondrial distribution is linked to neuronal differentiation and migration (Kim et al., 2015; Lin-Hendel et al., 2016). These processes are also well recognised to be influenced by DISC1 function, and known to be impaired in psychiatric disease (Brandon and Sawa, 2011; International Schizophrenia et al., 2009).

In addition to the trafficking and positioning of mitochondria, other aspects of mitochondrial function such as mitochondrial Ca^{2+} uptake or release, the production of superoxide and other ROS (reactive oxygen species) are also increasingly implicated in synaptic plasticity (Cheng et al., 2010; Levy et al., 2003; Santini et al., 2015; Vos, 2010). Interestingly, calcium overload or oxidative stress can significantly impair mitochondrial function and this form of dysfunction in specific brain regions are often correlated with major depressive disorder (Lin and Beal, 2006; Nicholls, 2009; Shao et al., 2008). Whilst psychiatric diseases do not present with classical mitochondrial dysfunction, as do multiple neurodegenerative disease including Alzheimer's disease, Parkinson's disease and Huntington's disease (Carvalho et al., 2015), mitochondria are essential to power and regulate neuronal development and function. Thus, there has been an effort to investigate the contribution of these organelles to the onset of major mental illness (as reviewed in (Clay et al., 2011; Deheshi et al., 2013; Manji et al., 2012; Rossignol and Frye, 2012)). Evidence for mitochondrial abnormalities has been described in post mortem tissue from patients with psychiatric disease. Electron microscopy has revealed a reduction in the number and density of mitochondria in the hippocampus, striatum and substantia nigra of schizophrenia patients (Kolomeets and Uranova, 2010; Kung and Roberts, 1999; Roberts et al., 2015).

2. Localisation of DISC1 at the mitochondrion

DISC1 is a multi-compartmentalised protein, which can localise to mitochondria as demonstrated by subcellular fractionation, immunocytochemistry and electron microscopy (James et al., 2004; Millar et al., 2005a; Millar et al., 2005b; Norkett et al., 2016; Ogawa et al., 2014; Park et al., 2010). It would seem this targeting is dependent upon the N terminus of DISC1 (Millar et al., 2005a). Immunocytochemistry shows a predominantly mitochondrial localisation in two neuroblastoma cell lines (U373 MG and SH-SY5Y), although puncta are also detected both in the periphery and the nucleus (James et al., 2004). Further studies in cortical neurons are consistent with this heterogeneous distribution of DISC1 (Brandon et al., 2005; Park et al., 2010). DISC1 lacks a classic mitochondrial targeting sequence, therefore other factors must allow this mitochondrial targeting, such as interaction with mitochondrial proteins. Those that have been studied in this way include trafficking proteins, Miro1, Miro2 and TRAK1 and TRAK2, and the mitochondrial fusion machinery Mitofusins, (Norkett et al., 2016; Ogawa et al., 2014; Park et al., 2010)– overexpression of each showing a marked redistribution of DISC1 to the mitochondria. Further, two studies show a redistribution of DISC1 away from mitochondria and into the cytosolic fraction upon destabilisation of microtubules with taxol or nocodazole (Brandon et al., 2005; James et al., 2004). These observations represent early indications of a role for DISC1 in microtubule based transport of mitochondria.

In addition to the outer mitochondrial membrane, ultrastructural and biochemical analyses have demonstrated the presence of both exogenous and endogenous DISC1 inside mitochondria in HEK cells and mouse brain (Park et al., 2010). Treatment of mitochondrial fractions with trypsin has shown specific DISC1 isoforms to be protected, while outer mitochondrial membrane proteins are digested, supportive of localisation at internal mitochondrial compartments (James et al., 2004; Park et al., 2010). Further investigation of localisation of multiple DISC1 isoforms has revealed the longer, 100kDa isoforms are degraded by this treatment, consistent with an outer mitochondrial membrane distribution whereas, the shorter, 71 and 75kDa isoforms were protected (James et al., 2004; Pinero-Martos et al., 2016).

The effects of schizophrenia associated DISC1 mutations on mitochondrial distribution of the protein are less clear. It has been shown that an R37W mutation leads to a more uniform distribution of DISC1 on the mitochondria, and induces mitochondrial clustering. In neurons, this mutation seems to increase colocalisation of DISC1 with the mitochondria (Ogawa et al., 2014). Further, the DISC1-Boymaw fusion protein has been shown to localise to the mitochondria to a greater extent than the wild type protein (Eykelenboom et al., 2012; Norkett et al., 2016). This altered distribution of mutant DISC1 confers defects in mitochondrial trafficking and function to be discussed in the following sections.

3.1 DISC1 and mitochondrial function – ATP production

The presence of DISC1 both on the mitochondrial outer membrane and within internal compartments raises the possibility that DISC1 could act within the mitochondrion to regulate function of these organelles. Further, two independent yeast two hybrid screens have identified the inner mitochondrial membrane protein Mitofilin as a DISC1 interactor (Camargo et al., 2007; Park et al., 2010). Interaction with this protein has been confirmed at the protein level (Park et al., 2010) and is of particular interest as Mitofilin (also known as IMMT for inner membrane protein, mitochondrial) has been shown to regulate cristae formation as part of the mitochondrial contact site and cristae organizing system (MICOS) complex (John et al., 2005). These cristae (in-foldings) in the inner mitochondrial membrane serve as the site of ATP production via oxidative phosphorylation (OXPHOS). Mitofilin knockdown studies in HeLa cells showed less organised cristae, associated with an increase in reactive oxygen species (John et al., 2005). Thus, Mitofilin regulates mitochondrial function in terms of ATP production. The interaction between DISC1 and Mitofilin has been localised to the mitochondrial fraction of cell lysates and multiple experiments were carried out to investigate crosstalk of these two proteins in regulating mitochondrial function (see figure 2a). Knockdown of DISC1 both decreased NADH dehydrogenase activity and ATP production (Park et al., 2010; Pinero-Martos et al., 2016). These effects mimicked those obtained from Mitofilin knockdown cells. Further, expression of truncated DISC1 (amino acids 1-597, resulting from the Scottish mutation) also caused a decrease in these measures (Park et al., 2010). This phenocopy is likely due to the necessity of DISC1 in

stabilising the Mitofilin protein. Knockdown or expression of truncated DISC1 causes an increase in Mitofilin ubiquitination and subsequent proteasomal turnover (Park et al., 2010). Thus, DISC1 acts as a regulator of mitochondrial function via Mitofilin levels (see figure 2b).

In addition to DISC1, another of its interaction partners, CHCHD6 – a MICOS component - has been shown to regulate Mitofilin levels. This protein is localised to the inner mitochondrial membrane according to fractionation experiments and knockdown of this protein has similar, adverse, effects on cristae organisation as does Mitofilin. As with Mitofilin, knockdown of CHCHD6 leads to a decrease in mitochondrial ATP production (An et al., 2012). This raises the possibility that DISC1, Mitofilin and CHCHD6 exist together in a large complex involved in mitochondrial function by maintaining cristae integrity. Indeed, DISC1 knockdown leads to disassembly of the cristae organisation complex as well disassembly of OXPHOS complexes (see figure 2b), as demonstrated by blue native PAGE (Pinero-Martos et al., 2016), suggesting DISC1 may be acting as a scaffold for assembly of cristae organisation complexes, thus facilitating OXPHOS.

As well as DISC1 truncation, alternative outcomes of the Scottish mutation have been investigated with a focus on mitochondrial dysfunction (Eykelenboom et al., 2012). The distribution of DISC1-Boymaw fusion transcripts was investigated in COS7 cells and primary neurons. In both cases, the novel transcripts adopted a predominantly mitochondrial localisation, in contrast to truncated DISC1 1-597, which appeared diffuse throughout the cytosol. Thus, it appears the novel amino acids confer a gain of function in terms of distribution. It was notable that mitochondria of cells expressing fusion transcripts showed decreased mitotracker staining in comparison to cytochrome C labelling. This observation might suggest that the novel transcripts decrease mitochondrial membrane potential, as mitotracker is selectively taken up into functional mitochondria (Eykelenboom et al., 2012). Thus it would appear that DISC1-Boymaw fusion transcripts have deleterious effects on mitochondrial function, independent of wildtype DISC1, although endogenous DISC1 levels were not investigated in cells heterologously expressing the chimaeric proteins. Therefore, indirect effects via loss of DISC1 expression cannot be ruled out.

Consistent with these observations, the DISC1-Boymaw fusion protein (CP60 by the alternative nomenclature), was shown to localise to mitochondria in two recent studies (Ji et al., 2014; Norkett et al., 2016). Additionally, a decrease in NADH oxidoreductase activity was detected in total lysates and mitochondrial fractions of cells expressing the DISC1-Boymaw fusion protein. This may contribute to a decrease in ATP production via mitochondrial damage (Ji et al., 2014). The Boymaw gene itself has been recently suggested to encode a small protein (Ji et al., 2015). This is in contrast with earlier reports which suggested no open readings frames were present in this gene (Eykelenboom et al., 2012; Zhou et al., 2010; Zhou et al., 2008). When overexpressed in HEK293 cells, this small Boymaw protein localises to mitochondria and inhibits NADH oxidoreductase activity (Ji et al., 2015). Taken together, these data are supportive of mitochondrial damage, caused by the DISC1-Boymaw fusion protein, being a pathological feature of schizophrenia.

3.2 Calcium Buffering

In addition to ATP production, DISC1 may influence mitochondrial calcium buffering. Upon DISC1 or Mitofilin knockdown, mitochondria were shown to buffer calcium more slowly than control cells using a fluorescent calcium reporter (GCAMP) in differentiating CAD cells. This was exemplified by an increase in the time taken for intra mitochondrial calcium levels to return to baseline after ionomycin treatment. Therefore, DISC1, in conjunction with Mitofilin, can regulate both the bioenergetic and calcium buffering capabilities of mitochondria (Park et al., 2010).

Beyond mitochondrial calcium handling, DISC1 has also been localised to the ER and shown to interact with the IP_3 receptor – a component of ER-mitochondria contact sites (Csordas et al., 2010; Park et al., 2015). In addition to the IP_3 receptor, DISC1 interacts with Miro (Norkett et al., 2016; Ogawa et al., 2014)– itself shown to be a component of ER-mitochondria sites in *Saccharomyces* and *Drosophila* (Kornmann et al., 2011; Lee et al., 2016). In neurons cultured from a DISC1 knockout mouse model, ER calcium dynamics were shown to be perturbed with the knock out cells displaying higher calcium uptake than wild type – a phenotype which could be reversed by antipsychotics (Park et al., 2015). This dual action of DISC1 in contributing to calcium dynamics in both mitochondrial and ER compartments raises

the possibility that DISC1 might coordinate crosstalk of these organelles via ER mitochondria contact sites. Indeed, super resolution microscopy studies have found DISC1 to be present at these sites (Norkett et al., 2016). Furthermore, when comparing distributions of wild type DISC1 and a schizophrenia associated DISC1 mutant (the DISC1-Boymaw fusion protein), it appears the mutant DISC1 localises to these sites more than the wild type. Crucially, this mutant form of DISC1 decreased the area of mitochondria-ER contact (Norkett et al., 2016). Thus, dysregulation of ER-mitochondria calcium signalling could be a contributory factor in the onset of psychiatric disease.

4. DISC1 as a regulator of mitochondrial trafficking

Beyond mitochondrial function, there are many lines of evidence supporting DISC1 as a mitochondrial trafficking regulator. In order to properly distribute mitochondria throughout the neuron, the mitochondrial population is trafficked in both anterograde and retrograde directions along microtubule tracks using motor proteins and adaptors found on mitochondrial surfaces (MacAskill and Kittler, 2010). The motor proteins involved are Kinesins (specifically Kinesin-1/KIF5 family members and KIF1Bbeta) for anterograde trafficking (towards the microtubule plus end) and Dynein (towards the microtubule minus end) (Macaskill et al., 2009b; Nangaku et al., 1994; Pilling et al., 2006).

Major players of this trafficking are Miro proteins, or Mitochondrial Rho-GTPases, anchored into the outer mitochondrial membrane, facing the cytosol. The Miro GTPases tether mitochondria to motor proteins and adaptors to enable long range transport in dendrites and axons (Birsa et al., 2013; Devine et al., 2016a; Lopez-Domenech et al., 2016; Macaskill et al., 2009b; Wang and Schwarz, 2009). The actin cytoskeleton and different myosin motors may also be involved in short range trafficking of this dynamic organelle (Quintero et al., 2009). Adaptor proteins involved include TRAK1 and TRAK2 (Milton in *Drosophila Melanogaster*). The TRAKS have been shown to form complexes with mammalian Miro proteins and indirectly regulate mitochondrial trafficking in both axons and dendrites (Brickley and Stephenson, 2011; MacAskill et al., 2009a; van Spronsen et al., 2013).

Multiple studies have confirmed protein-protein interactions between DISC1 and components of molecular motor complexes. These proteins include the molecular motors themselves kinesin-1 family members and the adaptor proteins TRAK1 and 2 (Norkett et al., 2016; Ogawa et al., 2014; Taya et al., 2007). Moreover, DISC1 interactions have been shown with dynein complex proteins Lis1 and Ndel1 (Kamiya et al., 2005), required for dynein based, retrograde trafficking of mitochondria (Shao et al., 2013). Recently, DISC1 interactor and dynein complex component Nde1 has been shown to associate with TRAK1 in a phospho-dependent manner (Ogawa et al., 2016). This phosphorylation is itself dependent upon DISC1 via interaction with phosphodiesterase 4 (Bradshaw et al., 2011). Crucially, immunoprecipitation experiments have demonstrated interactions between DISC1, Miro1 and TRAKs in cell lysates and brain tissue (Norkett et al., 2016; Ogawa et al., 2014). These interactions have been mapped onto DISC1 both biochemically and by immunofluorescence. Immunoprecipitation experiments with DISC1 deletion constructs and Miro/TRAK show the globular N-terminus to be necessary for interaction with Miro1 and TRAK, whilst the coiled-coil rich C-terminus is dispensable. Within the N-terminus, an arginine rich sequence has been shown to mediate the DISC1-TRAK interaction – deletion or mutation of this sequence decreased the DISC1-TRAK interaction and decreased mitochondrial DISC1 (Norkett et al., 2016; Ogawa et al., 2014). Importantly, the DISC1-Miro/TRAK interaction has been shown to be essential for mitochondrial transport. Overexpression of the interacting region of DISC1 (to uncouple endogenous DISC1 from the mitochondrial trafficking complex) abrogates mitochondrial trafficking in neuronal culture (Norkett et al., 2016) and expression of a R37W mutant transcript abolishes the ability of DISC1 to promote anterograde mitochondrial transport, perhaps via increased association of DISC1 and TRAK1, preventing the TRAK1-Miro interaction (Ogawa et al., 2014). The interaction of DISC1 with this mitochondrially anchored protein confers specificity for mitochondrial trafficking over regulation of trafficking complexes in general, and highlights the ability of DISC1 to control mitochondrial motility locally at the trafficking complex (see figure 3a).

Of further interest, the roles of schizophrenia associated DISC1 mutations have been investigated with respect to mitochondrial trafficking. Upon knockdown of DISC1, expression of S704C was able to restore percentages of motile mitochondria to their

control levels. However, another variant, L607F, was unable to rescue this effect (Atkin et al., 2011). Overexpression of the DISC1 point mutation R37W appears to cause a decrease in anterograde (kinesin mediated) mitochondrial trafficking in comparison to overexpression of wildtype DISC1 (Ogawa et al., 2014). As well as point mutations, the DISC1-Boymaw fusion protein (a proposed outcome of the chromosomal translocation, see figure 1b) has been shown to decrease mitochondrial trafficking in axons and dendrites, consistent with a dominant negative activity of this aberrant transcript (Norkett et al., 2016). Thus, schizophrenia associated DISC1 mutations have differing abilities to regulate mitochondrial trafficking (see figure 3b). This not only serves to highlight the role of DISC1 in mitochondrial trafficking, but shows the potential for this regulation to be lost in certain cases of schizophrenia. Thus, decreased mitochondrial motility, and aberrant distribution, may be associated with the onset of schizophrenia like symptoms, perhaps via impaired ATP production and calcium buffering at synapses. This would lead to impaired synaptic communication (Li et al., 2004). Indeed, a loss of DISC1 dependent mitochondrial transport correlates with a decrease in dendrite outgrowth (Norkett et al., 2016), which could contribute to impairments in network connectivity leading to the onset of psychiatric disease (Kulkarni and Firestein, 2012).

In addition to mutations, DISC1 aggregation has been linked to mitochondrial trafficking defects. The ability of DISC1 to aggregate has been demonstrated by its presence in sarkosyl insoluble or resistant fractions of cell lysates and is increased in schizophrenic post mortem brain tissue (Leliveld et al., 2008). Certain DISC1 mutations may confer an increase in tendency to aggregate (Trossbach et al., 2016; Wen et al., 2014; Zhou et al., 2010), but, crucially, DISC1 can aggregate in response to cell stress. Therefore, aggregation may contribute to DISC1 dysfunction in sporadic cases of schizophrenia. Further, these aggregates have been identified as aggresomes – inclusions of misfolded protein to be degraded by proteasomal and autophagic pathways. This was shown by colocalisation of GFP DISC1 with aggresome markers such as ubiquitin and HSP70. GFP tagged DISC1 has a higher propensity to aggregate and has been shown by FRAP (fluorescence recovery after photobleaching) to be stable in these aggresomal structures. Importantly, cytosolic DISC1 can be recruited to these aggregates by misfolded DISC1. This corresponds with a decrease in mitochondrial trafficking, likely by decreasing the availability of

DISC1 as in the previously described knockdown experiments, and so contributing to the onset of psychiatric disease (Atkin et al., 2012).

Notably, the exact mechanisms by which DISC1 can regulate trafficking remain to be determined. DISC1 knockdown is known to impair mitochondrial function (Park et al., 2010), thus impaired bioenergetics could be responsible for the associated decrease in trafficking (Cai et al., 2012; Miller and Sheetz, 2004). Alternatively, DISC1 could be acting as a scaffold via interactions with molecular motors and adaptors at the outer mitochondrial membrane, for example, regulating cyclic AMP levels or GSK3beta activity to influence mitochondrial trafficking (Ogawa et al., 2016). In addition to regulating motor protein complexes, a recent study proposes that DISC1 could act as a coordinator of the interaction between Miro and the axonal mitochondrial static anchor syntaphilin (Park et al., 2016) – necessary for anchoring mitochondria at the presynapse for short term facilitation (Kang et al., 2008). In this model, DISC1 is shown to interact with the anchoring protein syntaphilin, preventing interaction between Miro and syntaphilin, thus increasing the fraction of motile mitochondria (Park et al., 2016).

5. Outlooks

We have described work elucidating involvement of DISC1 in aspects of mitochondrial function and distribution via interactions with components of the cristae organising complex and trafficking complex. We have also discussed how alterations in DISC1 contribute to defects in these processes either by knockdown or mutation. It remains to be confirmed if the mutations studied to date act as loss of function mutations, and thus contribute to the onset of psychiatric symptoms via a DISC1 haploinsufficiency, or if any of these mutations confer a toxic gain of function. An important aspect for future study is the connection between DISC1 involvement in mitochondrial function and involvement in trafficking. It has been shown that mitochondrial membrane potential, and so ATP production, is a positive regulator of anterograde mitochondrial trafficking (Cai et al., 2012; Miller and Sheetz, 2004). Further, calcium buffering capacity is linked both to mitochondrial trafficking and ATP production (Chang et al., 2011; McCormack et al., 1990). Calcium buffering is, in turn, facilitated by ER-mitochondria contacts (Rowland and Voeltz, 2012), another

aspect of mitochondrial biology in which DISC1 is implicated. Might DISC1 maintain mitochondrial calcium buffering capacity and ATP production so as to facilitate trafficking? Or indeed, might multiple isoforms of DISC1 be concerned with specific functions at the mitochondrion – for example a shorter isoform within the mitochondrion, perhaps at the IMM, to regulate cristae formation and a longer isoform at the outer mitochondrial membrane to coordinate the mitochondrial trafficking complex, as suggested by fractionation studies (James et al., 2004). Further, might DISC1 play a role in maintaining the health of the mitochondrial population – and thus the health of the neuron - via involvement in the mitophagic quality control pathway? This selective degradation of damaged mitochondria is essential for neuronal health (Birsa et al., 2013; Pickrell and Youle, 2015) and Miro is a key player in this process as a substrate for the E3 ubiquitin ligase Parkin (Birsa et al., 2014; Liu et al., 2012; Wang et al., 2011). DISC1 itself can be degraded by the autophagy pathway upon aggregation (Atkin et al., 2012) and so, might contribute to impairments in mitophagy and a deleterious build-up of damaged mitochondria in psychiatric disease.

Beyond function of neurons themselves, might impaired mitochondrial trafficking in astrocytes contribute to impaired network activity? DISC1 is known to be expressed in astrocytes and other glia (Seshadri et al., 2010), and Miro has been recently demonstrated to be essential for mitochondrial positioning opposing synapses in astrocytes (Jackson and Robinson, 2015; Stephen et al., 2015). These cells are a subset of glia crucial for shaping neuronal communication at the tripartite synapse (Stephen et al., 2014). Could DISC1 be regulating mitochondrial transport in these cells, and, thus, contributing to neuronal communication? Loss of ATP production and calcium buffering capacity, via damaged or incorrectly distributed mitochondria, would impair both neuronal development and synaptic activity (Kang et al., 2008; Li et al., 2004; Norkett et al., 2016; Sung et al., 2008). These conditions would impair network connectivity, contributing to the onset of psychiatric disease. Crucially, ongoing work must address the contributions of mitochondrial aspects of DISC1 to neuronal development and function in vivo in health and mental illness.

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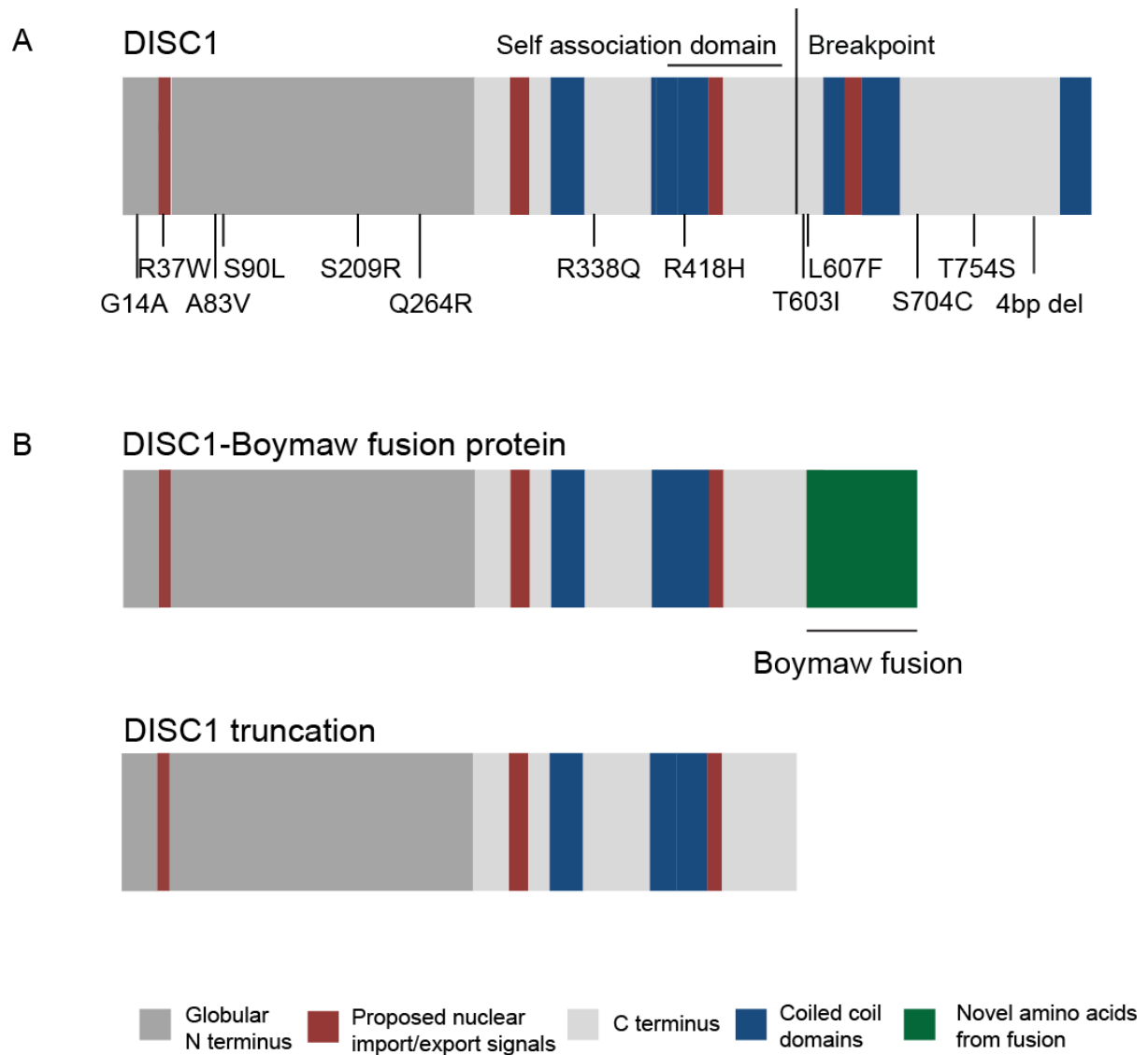
Figure 1: Schematic of the DISC1 protein. A Structure of the DISC1 protein showing globular N terminus, Coiled coil rich C terminus and sites of psychiatric disease associated mutations. B Possible outcomes of the balanced chromosomal translocation at the protein level. The translocation may give rise to a fusion protein between DISC1 and Boymaw/DISC1 fusion partner 1, or a truncated DISC1.
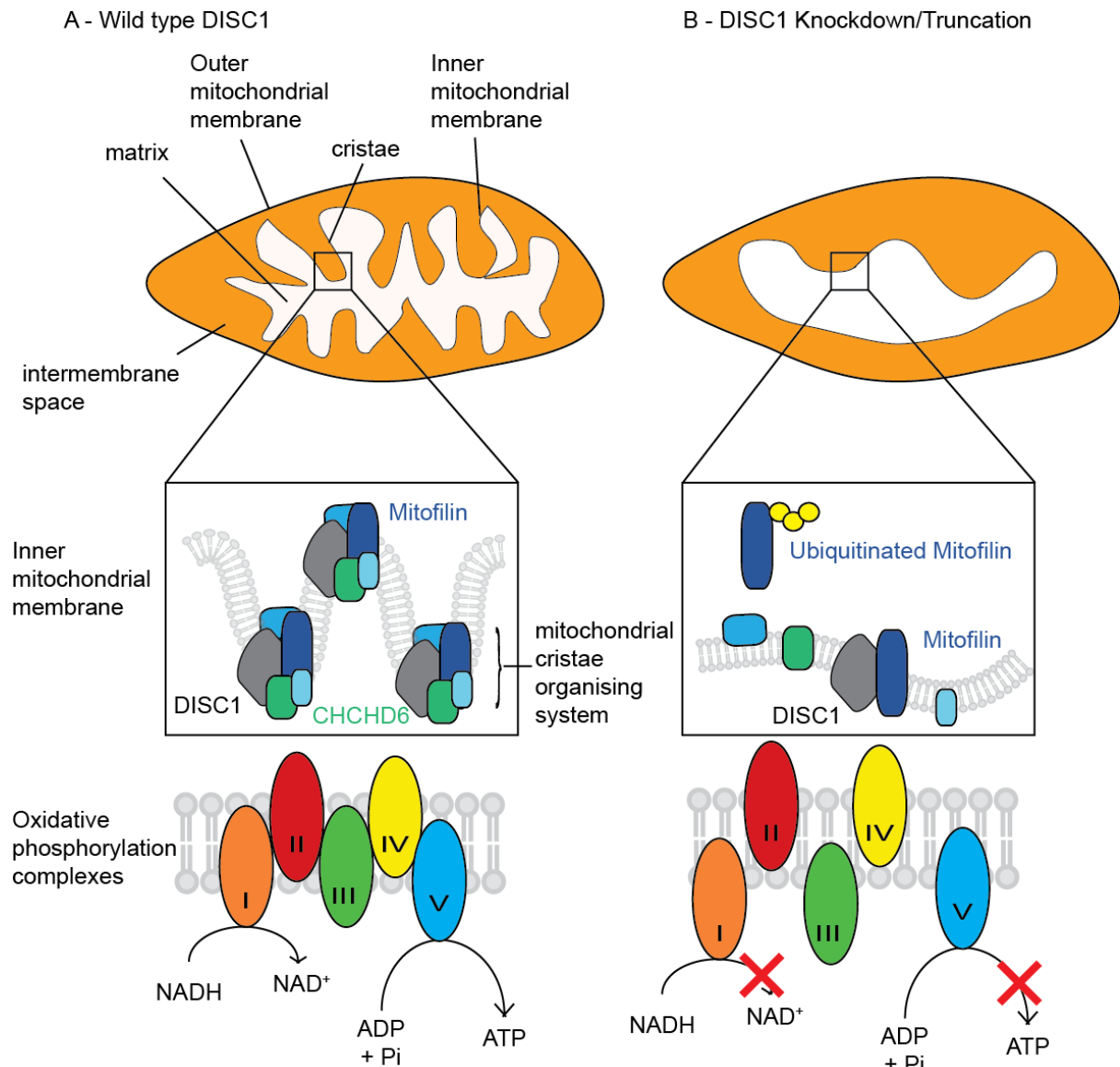
Figure 2: DISC1 as a regulator of mitochondrial function. A DISC1 interacts with mitofilin and other components of mitochondrial cristae organising complexes to correctly fold the inner mitochondrial membrane. Under these conditions oxidative phosphorylation for ATP production proceeds normally. B Loss of wild type DISC1 leads to collapse of cristae via mitofilin degradation and disassembly of cristae organising complexes. Under these conditions, mitochondrial membrane potential is decreased and so, ATP production is impaired.
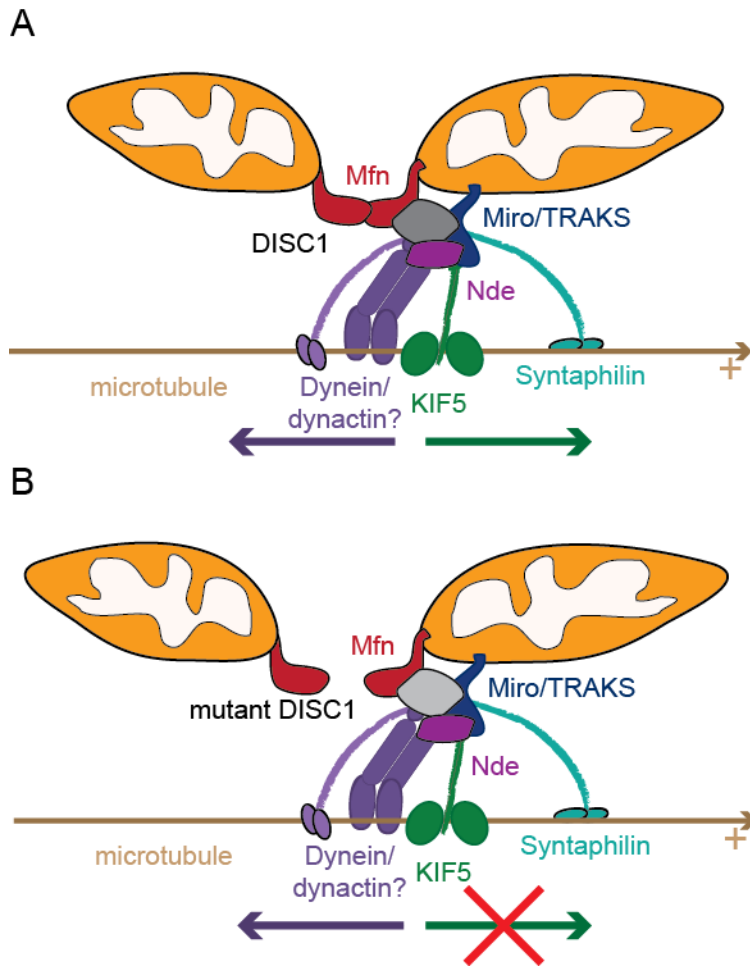
Figure 3: DISC1 as a regulator of mitochondrial trafficking. A DISC1 interacts with molecular motor complexes (kinesin and dynein) known to be essential for microtubule based transport of mitochondria. DISC1 also interacts with Miro, TRAK and syntaphilin proteins to specifically regulate mitochondrial transport, and mitofusins to regulate mitochondrial fusion. B Mutant DISC1 impairs microtubule based transport of mitochondria with kinesin mediated anterograde transport more affected.