Glycosyltransferases represent a large family of enzymes that catalyse the biosynthesis of oligosaccharides, polysaccharides, and glycoconjugates. A number of studies have implicated glycosyltransferases in the pathogenesis of neurodegenerative diseases but differentiating cause from effect has been difficult. We have recently discovered that mutations proximal to the substrate binding site of glycosyltransferase 8 domain containing 1 (GLT8D1) are associated with familial amyotrophic lateral sclerosis (ALS). We demonstrated that ALS-associated mutations reduce activity of the enzyme suggesting a loss-of-function mechanism that is an attractive therapeutic target. Our work is the first evidence that isolated dysfunction of a glycosyltransferase is sufficient to cause a neurodegenerative disease, but connection between neurodegeneration and genetic variation within glycosyltransferases is not new. Previous studies have identified associations between mutations in UGT8 and sporadic ALS, and between ST6GAL1 mutations and conversion of mild cognitive impairment into clinical Alzheimer’s disease. In this review we consider potential mechanisms connecting glycosyltransferase dysfunction to neurodegeneration. The most prominent candidates are ganglioside synthesis and impaired addition of O-linked β-N-acetylglucosamine (O-GlcNAc) groups to proteins important for axonal and synaptic function. Special consideration is given to examples where genetic mutations within glycosyltransferases are associated with neurodegeneration in recognition of the fact that these changes are likely to be upstream causes present from birth.
Neurodegenerative diseases are increasing in frequency, in part due to an ageing population. Despite this, neurodegenerative diseases represent a significant unmet health need without effective treatments or clearly delineated pathogenic mechanisms. Changes in expression levels of glycosyltransferases have been strongly linked with neurodegeneration (Ludemann et al., 2005; Desplats et al., 2007; Schneider 2018), but determining whether these effects are upstream of neurotoxicity is difficult. Two distinct glycosyltransferase-associated mechanisms are prominent: ganglioside synthesis and addition of O-linked β-N-acetylglucosamine to proteins (O-GlcNAcylation). Major gangliosides are sialic acid-containing glycosphingolipids. Within the mammalian brain they are synthesized in the endoplasmic reticulum from a lactosylceramide precursor before remodelling during transit from the cis- to the trans-Golgi network by a series of glycosyltransferase enzymes (Fig. 1). Mature gangliosides are expressed on the plasma membrane of most vertebrate cells and within bodily fluids. They are particularly abundant on neuronal and glial cells within the CNS where they are thought to function prominently in cell signalling (Vajn et al., 2013). Altered levels of gangliosides have been reported in animal models of amyotrophic lateral sclerosis (ALS) and in post-mortem CNS tissue from ALS patients (Ariga, 2014; Dodge et al., 2015); similar findings have been reported in Parkinson’s disease (Wu et al., 2012) and Alzheimer’s disease (Gyllys et al., 2007). O-GlcNAcylation occurs predominantly in the brain and is regulated by the glycosyltransferases O-linked N-acetylgalcosamine transferase (OGT) and EGF domain-specific O-linked N-acetylgalcosamine transferase (EOGT), which attach the O-GlcNAc moiety to acceptor proteins at specific serine/threonine residues via an O-linked glycosidic bond. OGT acts intracellularly whereas EOGT acts extracellularly on secreted and membrane proteins (Fig. 2). O-GlcNAcylation of CNS proteins important for axonal and synaptic function is significantly reduced in animal models of neurodegenerative diseases and in patient tissue from diseases including Parkinson’s disease, Huntington’s...
disease, Alzheimer’s disease and ALS (Liu et al., 2004; Ludemann et al., 2005; Kumar et al., 2014; Frenkel-Pinter et al., 2017).

Neurodegenerative diseases exhibit late age of onset and it is therefore assumed that genetic mutations are upstream of disease pathogenesis. As a result, the discovery of neurodegenerative disease-associated DNA mutations is a significant step towards identification of upstream therapeutic targets. We have recently discovered that mutations proximal to the substrate-binding site of glycosyltransferase 8 domain-containing 1 (GLT8D1) disrupt enzyme activity and are associated with familial ALS (Cooper-Knock et al., 2019). Our work is the first evidence that dysfunction of a glycosyltransferase is sufficient to cause a neurodegenerative disease. Our data are consistent with an effect of GLT8D1 mutations on ganglioside synthesis. In support of this mechanism, we have demonstrated by immunocytochemistry that ALS-associated GLT8D1 mutations reduce membrane expression of glycosphingolipids, which include gangliosides, in human cells (unpublished data). Moreover, in this review we summarize previous literature linking genetic changes within glycosyltransferases to neurodegeneration, and provide new evidence that genetic mutations within EOGT are significantly associated with sporadic ALS making this another upstream therapeutic target.

**Impaired ganglioside synthesis is linked to neurodegeneration**

**Parkinson’s disease**

Reduced glycosyltransferase expression and lowered ganglioside synthesis has been implicated in the pathogenesis of Parkinson’s disease. A recent report described a reduction in gene expression of the glycosyltransferases B3GALT4 and ST3GAL2 in neuromelanin-containing neurons in the substantia nigra of patients with Parkinson’s disease compared to control subjects (Schneider, 2018). These genes are key players in the ganglioside biosynthesis pathway (Fig. 1). It is proposed that reduced B3GALT4 and ST3GAL2 expression leads to vulnerability of dopaminergic neurons via aberrant ganglioside synthesis. Consistent with this hypothesis, the number of GM1 ganglioside-expressing cells in the Parkinson’s disease substantia nigra are reduced (Wu et al., 2012), and levels of the major brain gangliosides—GM1, GD1a, GD1b and GT1b—are decreased in whole substantia nigra homogenates from patients with Parkinson’s disease (Seyfried et al., 2018). Model systems provide evidence that dysfunction of ganglioside synthesis is a cause and not just an association of typical Parkinson’s disease pathology: genetically engineered mice lacking major brain gangliosides display overt motor impairment with increasing age, which is accompanied by loss of dopaminergic neurons from the substantia nigra pars compacta and aggregation of α-synuclein (Wu et al., 2012).

**Huntington’s disease**

In a similar manner to Parkinson’s disease, reduced expression of glycosyltransferases involved in ganglioside synthesis has also been described in the R6/1 mouse model of Huntington’s disease and in human Huntington’s disease patients (Desplats et al., 2007). In this study >80% of gene expression changes observed in the striatum of R6/1 mice were also observed in the post-mortem caudate of human Huntington’s disease subjects. Overlapping genes were significantly enriched with glycosyltransferases involved in ganglioside synthesis including ST3GAL5, ST8SIA3, B4GALNT1 and ST3GAL2 (Fig. 1). Consistent with impaired ganglioside synthesis, the same study...
reported reduced ganglioside concentrations within both the diseased human caudate and the mouse striatum. It should be noted that despite significant homology to ST8SIA1, which has a well described role in ganglioside biosynthesis (Fig. 1), ST8SIA3 is traditionally associated with N-glycosylation of secreted/membrane proteins within the CNS (Lin et al., 2019). Like gangliosides, N-glycosylated proteins are important for cell signalling.

**Alzheimer’s disease**

There is good evidence for perturbed ganglioside metabolism in patients with Alzheimer’s disease, and in the development of amyloid-β pathology in particular (Barrier et al., 2007). In contrast to the findings in Parkinson’s disease and Huntington’s disease, the key observation appears to be increased ganglioside synthesis. Elevated GM1, GM2 and GM3 levels have been reported in the cerebral cortices of Alzheimer’s disease patients (Kracun et al., 1992; Gylys et al., 2007). Development of amyloid-β deposition is the defining pathology of Alzheimer’s disease and within brains exhibiting early Alzheimer’s disease pathology, a significant proportion of amyloid-β is bound to ganglioside species (Yanagisawa and Ihara, 1998). It has even been suggested that insoluble GM1-bound amyloid-β is the key toxin leading to neuronal death (Hayashi et al., 2004), as a result of high affinity binding between GM1 and amyloid-β, which facilitates formation of insoluble β-pleated sheets (Yamamoto et al., 2007). With increasing age GM1 is localized to presynaptic nerve terminals and this may have a role in directing amyloid-β deposition to the same locations (Yamamoto et al., 2008). Unlike evidence regarding gangliosides, reports of altered glycosyltransferase expression in Alzheimer’s disease are more limited. There is evidence that glycosyltransferase activity may modify Alzheimer’s disease pathology: overexpression of the glycosyltransferase B4GALNT1 leads to increased ganglioside expression but also increases APP cleavage to form amyloid-β pathology through suppression of lysosomal degradation of BACE1 (Yamaguchi et al., 2016). Currently, transgenic mouse models of Alzheimer’s disease do not mirror changes in ganglioside distribution seen in human post-mortem tissue (Barrier et al., 2007).

**Amyotrophic lateral sclerosis**

ALS has been linked to abnormal lipid metabolism (Desport et al., 2005) and in particular, gangliosides and their ceramide precursors are thought to be modulators of disease progression (Saltzargueso et al., 1990; Stevens et al., 1993). Whether ganglioside production is increased or decreased is controversial. As early as 1985 a 10% reduction in b-series gangliosides was identified within the motor cortex of ALS brains compared to non-ALS controls (Rapport et al., 1985). More recently elevated levels of gangliosides GM1 and GM3 were reported within ALS post-mortem spinal cords compared to age-matched controls; findings were corroborated in the SOD1-G93A transgenic ALS mouse model (Dodge et al., 2015). Interestingly, autoantibodies against specific gangliosides produce an inflammatory disease of spinal motor neurons known as multifocal motor neuropathy with conduction block (Harschnitz et al., 2014), which is a frequent differential diagnosis of ALS.

ALS specifically inflicts pathology on the upper and lower motor neurons, the neuromuscular junction and muscle. The accessibility of this system in disease models facilitates the differentiation of up- and downstream disease associations. For example, increased expression of glycosphingolipids is observed in muscle tissue from end-stage mutant SOD1-ALS mice compared to controls, but similar changes were observed in response to surgically-induced muscle denervation suggesting a downstream effect (Henriques et al., 2015). Moreover, neurotransmission at the neuromuscular junction is unchanged in aged GM2 and GD3-deficient mice compared to controls (Zitman et al., 2011). However, our discovery that mutations in the glycosyltransferase GLT8D1 are a cause of familial ALS is a step forward, which places glycosyltransferase activity irrefutably upstream in the development of disease.

**Genetic mutations in glycosyltransferases cause neurodegeneration**

Genetic mutations in the development of an age-associated neurodegenerative disease are, by definition, upstream causes or risk factors rather than secondary to the disease process. Mutations discovered to date are included in Table 1 and described below.

**GLT8D1**

A recent study from our lab demonstrated that mutations within the glycosyltransferase domain of GLT8D1 are associated with familial ALS (Cooper-Knock et al., 2019). The function of GLT8D1 is unknown, but it is ubiquitously expressed and localized to the Golgi apparatus. Based on sequence homology, GLT8D1 is a member of glycosyltransferase family 8 and is expected to catalyse the transfer of a glycosyl group from a donor to an acceptor via a ‘retain-ing’ mechanism. Mutated GLT8D1 carrying ALS-associated amino acid changes is toxic to neuronal and non-neuronal cell lines, and induces motor deficits in zebrafish embryos; these observations are consistent with a role in motor neuron degeneration. Interestingly, relative toxicity of ALS-associated mutations in model systems mirrors the clinical severity. Glycosyltransferase enzyme activity is reduced in the mutated form of GLT8D1 commensurate with an increase in substrate affinity, which is predicted to impair cycling of substrate through the enzyme and thus reduce overall velocity (Cooper-Knock et al., 2019).
Table 1 Defects affecting specific glycosyltransferase enzymes observed in neurodegenerative disease

| Glycosyltransferase | Functional consequence | Neurodegenerative disorder | Defect observed | Reference |
|---------------------|------------------------|-----------------------------|-----------------|-----------|
| ST6GAL1 | Disrupted cell surface signalling | Alzheimer’s disease | DNA mutations | Lee et al., 2017 |
| B3GALT4 | Reduced gangoside biosynthesis (GD1b) | Parkinson’s disease | Reduced gene expression | Schneider, 2018 |
| ST3GAL2 | Reduced gangoside biosynthesis (GT1b) | Parkinson’s disease | Reduced gene expression | Schneider, 2018 |
| B4GALNT1 | Reduced gangoside biosynthesis | Huntington’s disease | Reduced gene expression | Desplats et al., 2007 |
| ST8SIA3 | Implicated in gangloside biosynthesis | Huntington’s disease | Reduced gene expression | Desplats et al., 2007 |
| ST3GAL5 | Reduced gangoside biosynthesis | Huntington’s disease | DNA mutations | Desplats et al., 2007 |
| GLT8D1 | Reduced membrane expression of glycosphingolipids | ALS | DNA mutations | Cooper-Knock et al., 2019 |
| UGT8 | Disruption of myelin synthesis | ALS | DNA mutations | Pamphlett et al., 2011 |
| EO GT | Disruption of O-GlcNAcylation | ALS | DNA mutations | This article |
| OGT | Impaired O-GlcNAcylation | Alzheimer’s disease | Reduced concentration of O-GlcNAcylated proteins | Desplats et al., 2007 |
| OGT | Excessive O-GlcNAcylation | Parkinson’s disease | Increased concentration of O-GlcNAcylated proteins | Wani et al., 2017 |

Taken together, these data are consistent with loss-of-function toxicity. Our study is the first time inherited mutations that diminish glycosyltransferase enzyme activity have been associated with ALS. We have recently demonstrated by immunocytochemistry that ALS-associated mutations reduce membrane expression of glycosphingolipids in human cells (unpublished data). Glycosphingolipids include gangliosides and this would be consistent with disruption of ganglioside signalling within the CNS. GLT8D1 was recently identified as a risk gene for schizophrenia (Yang et al., 2018), and while schizophrenia is not a neurodegenerative disorder, it is noteworthy that ALS and schizophrenia share common genetic risk (McLaughlin et al., 2017).

UDP glycosyltransferase 8 (UGT8)

Like GLT8D1, UGT8 is a member of glycosyltransferase family 8. UGT8 functions in the biosynthesis of galactocerebroside, a sphingolipid that forms the myelin membrane in the central and peripheral nervous systems. Rare and potentially pathogenic copy number variants have been identified in the promoter region of UGT8 following in an unbiased genome-wide screen for de novo DNA mutations in 12 trios including sporadic ALS patients and unaffected parents (Pamphlett et al., 2011). Abnormal lipid biosynthesis and metabolism is a pathological hallmark of ALS (Dupuis et al., 2008; Dorst et al., 2011), therefore it is possible that UGT8 plays a role in the hypolipidaemia observed in ALS patients and the SOD1-G93A ALS mouse model (Kim et al., 2011; Yang et al., 2013). Mice lacking Ugt8a, the orthologue of UGT8, exhibit impaired locomotor activity and disruption in nerve conduction followed by degeneration of the myelin sheath (Bosio et al., 1996; Coetzee et al., 1996), which is rescued following transgenic expression of UGT8A (Zoller et al., 2005).

Interestingly the rescue occurred with expression of UGT8A under a promoter exclusively expressed within oligodendrocytes, which is consistent with other evidence implicating these cells in ALS-associated neurodegeneration (Morrison et al., 2013).

ST6 β-galactoside α-2,6-sialyltransferase 1 (ST6GAL1)

ST6GAL1 is an ‘inverting’ enzyme and a member of glycosyltransferase family 29. ST6GAL1 catalyses the transfer of sialic acid onto galactose-containing substrates including cell-surface signalling lipids and proteins (Garnham et al., 2019). A genome-wide association study implicated polymorphisms within ST6GAL1 in the conversion of mild cognitive impairment into clinical Alzheimer’s disease (Lee et al., 2017). Interestingly ST6GAL1 is cleaved and occurs in a soluble form; this cleavage is mediated by BACE1 (Kitazume et al., 2001), which is also involved in the cleavage of APP to form amyloid-β. Indeed, overexpression of ST6GAL1 increases APP secretion (Nakagawa et al., 2006) suggesting that the activity of ST6GAL1 can directly modify the central pathway in the development of Alzheimer’s pathology.

Glycosyltransferase O-GlcNAcylation: a key regulator of neurodegeneration?

Protein glycosylation and more specifically the addition of O-GlcNAc groups to CNS proteins important for axonal and synaptic function, is significantly reduced in animal models of neurodegenerative diseases and in patient tissue from diseases...
including Huntington’s disease, Alzheimer’s disease and ALS (Liu et al., 2004; Ludemann et al., 2005; Kumar et al., 2014; Frenkel-Pinter et al., 2017) (Table 1). O-GlcNAcylation is reported to negatively regulate tau phosphorylation (Liu et al., 2004), which is key in the pathogenesis of a number of neurodegenerative diseases, including Alzheimer’s disease. In contrast, an increase in O-GlcNAcylation is observed in the post-mortem temporal cortex of patients with Parkinson’s disease and is postulated to contribute to neurodegeneration through the inhibition of autophagy leading to an increase in α-synuclein accumulation (Wani et al., 2017). Neurofilaments are critical components of the neuronal cytoskeleton that can undergo O-GlcNAcylation (Yuan et al., 2012). Neurofilament levels are significantly higher in the serum and CSF of ALS patients compared to control subjects (Benatar et al., 2018). This increase is thought to be a consequence of axonal damage. However, there is evidence that neurofilament damage may be upstream in the pathogenesis of ALS including the observation that increased phosphorylation of neurofilaments is associated with neurotoxicity (Julien, 1997). It is thought that phosphorylation and O-GlcNAcylation are reciprocal, meaning that reduced O-GlcNAcylation could precipitate harmful phosphorylation; indeed this has been observed in a transgenic rat model of SOD1-ALS (Ludemann et al., 2005).

O-GlcNAcylation occurs predominantly in the brain and is regulated by the glycosyltransferases OGT and EOGT; the reverse reaction is catalysed by O-GlcNAcase (OGA). Together these reactions constitute a dynamic and reversible process (Fig. 2). OGT is an inverting enzyme and a member of glycosyltransferase family 41; OGT is highly enriched in the brain, where it is 10 times more active than in peripheral tissue (Okuyama and Marshall, 2003). OGT is localized to the nucleus, soma, dendrites and presynaptic terminals of neurons (Akimoto et al., 2003). Removal of postsynaptic OGT from primary neurons inhibits both synapse formation and the development of dendritic spines (Lagerlof et al., 2017). This highlights the importance of OGT in maintaining synaptic stability, and notably loss of synaptic stability is a unifying feature of neurodegenerative disease. EOGT is an inverting enzyme and a member of glycosyltransferase family 61. Despite distinct sites of action, OGT and EOGT are both regulated via the hexosamine biosynthetic pathway (Ogawa et al., 2015). EOGT activity is involved in Notch signalling, which is important for neurodevelopment. Indeed, homozygous loss-of-function mutations in EOGT produce Adams-Oliver syndrome, a congenital developmental disorder associated with actin cytoskeleton defects.

Conclusions

Overall there is substantial evidence for dysfunction of glycosyltransferases in neurodegenerative diseases including ALS, Alzheimer’s disease, Huntington’s disease and Parkinson’s disease. There are diverse functions associated with glycosyltransferase activity and for many of the enzymes the biological pathway associated with their activity is not yet clear. However, in our analysis, dysfunction associated with neurodegenerative disease can be seen to converge on the ganglioside synthesis pathway and altered O-GlcNAcylation. The exact nature of the defect appears to be variable in different diseases; for example ganglioside concentrations are reduced in Parkinson’s disease and Huntington’s disease, increased in Alzheimer’s disease and there is evidence for change in both directions in ALS. Similarly, increased O-GlcNAcylation is associated with the development of Parkinson’s disease pathology but reduced O-GlcNAcylation is associated with the development of tau pathology. We suggest that consensus will arise via efforts to position glycosyltransferase dysfunction within the cascade of pathogenesis leading to neuronal death—it is not glycosyltransferase dysfunction per se that is interesting, but rather upstream changes in glycosyltransferase function that initiate toxicity. With this in mind we have highlighted genetic associations between mutations in glycosyltransferases and neurodegenerative disease. Most prominently we have recently discovered autosomal dominant mutations in GLT8D1 to be a monogenic cause of ALS. Disease-associated mutations have also been discovered in UGT8 and ST6GAL1; and we have revealed a
new association between ALS and mutations in EOGT. Glycosyltransferases are likely to be an important therapeutic target in the effort of developing disease-modifying therapies for neurodegenerative disease.

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Competing interests
The authors report no competing interests.

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