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TDP-43: A New Player on the AD Field?

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Introduction

Alzheimer's disease accounts for an estimated 60–80% of dementia cases, and is the 5th leading cause of death for people aged 65 and older (Heron, 2008). The cognitive decline and amnesic dementia characteristic of the disease result from brain region-specific neuronal dysfunction and death, leading to memory loss, confusion, and changes in behavior, mood and personality. Ultimately, AD patients require help with daily tasks such as eating, bathing and communicating, primarily from unpaid caregivers including family members and friends. In 2009, the contribution of these unpaid caregivers to our nation was valued at \$144 billion. As a result of longer life expectancies and the aging baby boomer population, it is expected that by 2050 the number of people aged 65 and older with AD will be between 11–16 million (Hebert, et al., 2003). It is thus imperative that clinical trials toward potential therapeutic targets, which take many years and millions of dollars to reach completion, are initiated now.

The regulation of gene expression in the presence and absence of cellular stress is increasingly recognized to be dependent on post-transcriptional mRNA regulation (Liu-Yesucevitz, et al., 2011). In the absence of stress, mature mRNA is transported from the nucleus to the cytosol where it is translated into protein. However, under stress conditions mRNA may be reversibly bound by RNA binding proteins (RBPs) and converted to quiescent cytoplasmic RNA/protein complexes called stress granules (SGs). TAR DNA-binding protein 43 (TDP-43) is a nuclear protein expressed ubiquitously from the *Tardbp* gene on chromosome 1 (Liu-Yesucevitz, et al., 2010). It contains two highly conserved DNA/RNA recognition motifs, followed by a C-terminal glycine-rich domain and nuclear localization and export signals, which allow TDP-43 to be continuously shuttled between the nucleus and the cytoplasm. Under normal conditions, the predominant function for TDP-43 identified to date is regulation of nuclear transcription, splicing and stability of RNA transcripts (Kumar-Singh, 2011). However, during stress TDP-43 is sequestered in the cytoplasm as a component of insoluble protein aggregates. TDP-43 may also become cleaved by activated caspases, and the phosphorylated C-terminus has become a hallmark of TDP-43 proteinopathy (Liu-Yesucevitz, et al., 2010, Toh, et al., 2011). Although initially recognized for its role in repressing the human immunodeficiency virus type 1 (HIV-1) gene (Ou, et al., 1995), recent advances in molecular genetics have identified over 30 mutations in TDP-43 that are linked to amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD) (Lagier-Tourenne and Cleveland, 2009), suggesting a causative role for the protein in disease development. Indeed, TDP-43 inclusions occur primarily in degenerating motor neurons of the brain and spinal cord. Thus, RBPs have

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emerged as an important player in neurodegenerative processes, and are a potential targets for therapeutic development.

Pathology of ALS, FTLN and AD

AD is characterized by region-specific brain atrophy primarily in the frontal cortex and hippocampus; regions associated with learning, memory and behavior. Intraneuronal tangles of hyperphosphorylated tau protein and extracellular plaques composed of amyloid- β (A β) peptides are the two pathological hallmarks of AD and accumulate systematically throughout the brain. Interestingly, TDP-43 aggregates also appear in the AD brain, which suggests linkage between the pathophysiology of A β , tau and TDP-43. However, the nature of the relationship between TDP-43 and A β or tau, and indeed, the true physiologic functions of APP and A β are unknown, and the cellular processes underlying these pathological events remain poorly understood.

ALS is considered the most common adult-onset motor neuron disease (MND), and FTLN is the second most common form of young-onset cortical dementia (Seelaar, et al., 2011). ALS causes selective degeneration of both upper and lower motor neurons of the brain and spinal cord and culminates in muscle atrophy and death due to paralysis of the respiratory muscles (Ferraiuolo, et al., 2011, Janssens, et al., 2011), and most patients with FTLN also develop symptoms of MND such as ubiquitinated intraneuronal aggregates of TDP-43. In addition, 15–20% of ALS patients meet the criteria for FTLN (Strong and Yang, 2011), underscoring the significant clinical and pathological overlap between these two nervous system diseases.

Although distinct in many aspects, similarities between ALS, FTLN and AD are increasingly observed. These diseases primarily lead to neuronal loss and are classically diagnosed by the intraneuronal accumulation of misfolded or misaggregated proteins (ie: ubiquitin, TDP-43, A β and tau). Hyperactivation of kinases is another common factor, resulting in hyperphosphorylated tau filaments (in AD) or TDP-43 (in ALS and FTLN), possibly via common molecular mechanisms upstream in the disease process. TDP-43-positive inclusions are increasingly observed in combination with classic AD pathology, and are estimated to be present in up to 75% of brains from AD patients (Amador-Ortiz, et al., 2007, Wilson, et al., 2011). As we learn more about the convergence of these diseases, aligned treatment strategies may be developed to target the causative neuropathological insults prior to dementia, which appears only after pathology is pervasive.

TDP-43: Friend or Foe?

Homozygous disruption of *Tardbp* is embryonically lethal in mice, while disrupting only one copy of the gene leads to more subtle motor disturbances and muscle weakness (Kraemer, et al., 2010, Sephton, et al., 2010, Wu, et al., 2010). TDP-43 may therefore be linked to disease via loss-of-function mutations in which pathological TDP-43 fails to exercise its critical role in maintaining cellular homeostasis. This theory is supported by the 96% homology shared between the murine (m) and human (h) forms of TDP-43 (Feiguin, et al., 2009), perhaps resulting from an evolutionary conservation of gene function. Surprisingly, mice over-expressing wild type (WT) hTDP-43 develop ubiquitin-positive TDP-43 inclusions and ALS/FTLN-like neurodegeneration (Igaz, et al., 2011, Kumar-Singh, 2009, Swarup, et al., 2011, Xu, et al., 2010) yet mice over-expressing mTDP-43 have a very similar phenotype (Wils, et al., 2010), indicating that too much TDP-43 of either species may be just as detrimental as mutant TDP-43. Other groups have used cultured cells, *Drosophila*, zebrafish embryos and mouse models to confirm these results, with cumulative data demonstrating that over-expression of either mutant or WT hTDP-43 is neurotoxic, concomitant with cytoplasmic aggregation of TDP-43 and a motor phenotype (ie: shorter

motor neuron axons, premature and excessive neuronal branching, and movement deficits). Despite strong evidence indicating a toxic gain-of-function for TDP-43 *in vivo*, the presence of these pathologies even in the absence of any TDP-43 (Barmada and Finkbeiner, 2010, Feiguin, et al., 2009, Lu, et al., 2009, Tatom, et al., 2009) raises three alternate possibilities: 1) forced over-expression of TDP-43 in animal and cellular models might be deleterious and induce degeneration through a mechanism unrelated to ALS, 2) TDP-43 might cause neurodegeneration through a mechanism that does not require formation of insoluble protein aggregates, and 3) mutant TDP-43 may cause disease via a loss-of-positive-function phenotype (Kabashi, et al., 2010). While additional studies are certainly necessary to tease out the specialized role of TDP-43 in cellular viability, ultimately there may be truth to both.

Pathological inclusions of ubiquitin and TDP-43 have been observed in degenerating motor neurons of the brain and spinal cord of ALS and FTLN patients for decades. However, in the past 5 years a wave of attention has been paid to TDP-43 not only as it relates to ALS and FTLN, but also for its potential role in AD. Indeed, a consensus panel from the United States and Europe was recently convened to update the guidelines by which AD stages should be assessed (Hyman, et al., 2012). These guidelines were last updated in 1997, and have been revised not only to account for plaque and tangle staging criteria but also for nonconventional pathologies such as ubiquitin and TDP-43 accumulation (Montine, et al., 2012). A common factor among ALS, FTLN and AD neuropathology is the predominance of pathological misfolded protein aggregates that appear well before cognitive decline, and the nature of TDP-43 as a regulator of mRNA translation and SG formation suggests that it may effect much early aspects of disease than previously considered.

The recent work, by two groups based at Georgetown University who have made significant contributions to the understanding of AD and PD, confirms TDP-43 pathology present in brain tissue from AD patients. Previously, Herman et al. used gene-manipulation techniques for the targeted accumulation of intracellular A β 42 and found that it induced pathological changes in endogenous TDP-43, including increased expression, cleavage, and cytosolic aggregation (Herman, et al., 2011). In the current manuscript, the same group has used these techniques to express WT hTDP-43 specifically in the motor cortex of rats in the presence and absence of intracellular A β 42 and found that, in addition to its role in RNA regulation, TDP-43 may modify the expression and activity of the BACE1 enzyme; a necessary initiating enzyme in the AD amyloid cascade.

The ABC's of APP Processing

A β is a 39–43 amino acid, 4 kDa peptide resulting from the sequential proteolysis of APP, and autosomal dominant mutations in APP that increase A β are causal factors for early-onset familial AD (FAD) (Selkoe and Podlisny, 2002). APP is a type I transmembrane protein expressed by neurons in the CNS, with a large extracellular N-terminal domain and a smaller intracellular C-terminal domain (Figure 1). During maturation, APP becomes N- and O-glycosylated, giving rise to the mature form of APP that undergoes cleavage by β -, α - and γ -secretases (Buoso, et al., 2010). For the release of A β , APP must first be cleaved by β -secretase, a transmembrane aspartic protease commonly known as BACE1 (Lin, et al., 2000, Vassar, et al., 1999, Yan, et al., 1999), followed by the intramembrane γ -secretase complex consisting of nicastrin, anterior pharynx defective 1, presenilin enhancer 2 (PEN2) and presenilin 1 (PSEN1) (Edbauer, et al., 2003). Amyloidogenic cleavage of APP thus results in the release of soluble N-terminal APP (sAPP β) or A β peptide from the plasma membrane, and the remaining membrane-bound C-terminal APP fragment (CTF- β). Non-amyloidogenic processing of APP is initiated primarily by A Disintegrin and Metalloproteinase Domain-Containing Protein 10 (ADAM10; α -secretase) cleavage within the A β domain, resulting in sAPP α . The C-terminal cytoplasmic tail of APP is further processed into the APP

intracellular domain (AICD), which binds intracellular adapter proteins for complex roles in transcription and modulation of cytoskeletal dynamics (Chang and Suh, 2010). Because AD, ALS and FTLT share similar pathologies, Herman et al. ambitiously tried to find a common underlying molecular mechanism. They found that over-expressing hTDP-43 increased the levels of endogenous CTF- β via increased BACE1 activation while sparing the non-amyloidogenic pathway. This result is intriguing as recent therapeutic strategies for AD have centered around selectively modulating or inhibiting BACE1 activity (for review, see (Evin, et al., 2011, Mancini, et al., 2011)). A primary challenge in this respect has been creating a small molecule inhibitor with appropriate bioavailability in the brain (i.e.: the ability to cross the blood brain barrier in an active form). Additional challenges have been the efficacy with which these compounds actually enhance cognitive function (or prevent cognitive decline) rather than merely decreasing the A β burden. Unfortunately, the BACE1-inhibiting compounds created to-date have not withstood the rigors of clinical trials, either due to lack of efficacious or the pervasiveness of unwanted side effects. However, gene-based strategies rather than pharmacological intervention may be a new method to specifically target BACE1 expression without compromising other sensitive signaling cascades within the CNS, and selective genetic modification prior to the onset of clinical symptoms are crucial because memory and behavioral changes appear at the end-stages of disease progression.

Rather than plaques, recent research has focused on soluble oligomeric assemblies of A β as the proximate cause of neuronal injury, synaptic deterioration and the eventual dementia characteristic of AD (Haass and Steiner, 2001, Klein, et al., 2001, Terry, 2001, Youmans, et al., 2012). Indeed, stable A β 42 oligomers isolated from brain, plasma and CSF correlate with the severity of neurodegeneration in AD (Lue, et al., 1999, McLean, et al., 1999, Roher, et al., 2000, Wang, et al., 1999). Previous research has demonstrated that A β 42 oligomers are neurotoxic *in vitro*, directly disrupt cognitive function and inhibit neuroplasticity that may be necessary for the formation and maintenance of memory (Cleary, et al., 2005, Dahlgren, et al., 2002, Gotz, et al., 2001, Hartley, et al., 1999, Walsh, et al., 1999, Walsh, et al., 2002, Wang, et al., 2002, Wang, et al., 1999, Westerman, et al., 2002). Evidence also indicates that soluble A β 42 is taken up by axons, and that it may accumulate in axons or synapses leading to impaired axonal transport processes (Pigino, et al., 2009, Takahashi, et al., 2002). Interestingly, increased soluble A β correlates with cognitive decline in both AD patients and A β -transgenic mouse models (Aoki, et al., 2008, Christensen, et al., 2010, Thal, et al., 2006, Tomiyama, et al., 2010, Yu, et al., 2010). In the 3xTg mouse model of AD, increased pathological TDP-43 correlates with increased soluble A β oligomers, and removal of oligomeric A β restores TDP-43 to normal levels (Caccamo, et al., 2010). In addition, intraneuronal A β 42 accumulates prior to extracellular amyloid deposits in humans and mice (Cataldo, et al., 2004, Christensen, et al., 2010, Gouras, et al., 2010, Langui, et al., 2004, Oakley, et al., 2006, Oddo, et al., 2006). These intraneuronal accumulations increase with age, particularly in disease-relevant brain regions, and may correlate with cognitive and behavioral deficits (Billings, et al., 2005, Busciglio, et al., 2002, Oddo, et al., 2003, Oddo, et al., 2006). To determine whether intraneuronal A β 42 might also play a role in TDP-43 pathology, Herman et al. produced a virus that targeted A β 42 to the endoplasmic reticulum such that A β 42 produced by cells is not secreted but accumulates intracellularly. Thus, their model recapitulates several physiologically-relevant aspects of disease. Intraneuronal A β aggregates may seed further A β assembly, as has been proposed (Kayed, et al., 2010, Wu, et al., 2010), creating an important route for preventative intervention. Targeted delivery of pH-activated compounds to the H⁺ rich lysosomes or late endosomes may be a method for manipulating TDP-43-positive intraneuronal A β inclusions, and may provide a novel means of toxic A β removal.

Inflammation

Chronic inflammatory processes within the central nervous system (CNS) involve prolonged astrocytic and microglial activation and increased cytokine expression, and have been highlighted as a key contributor to AD pathogenesis. Activated microglia are initially beneficial by actively clearing A β from the brain (Lee and Landreth, 2010, Mandrekar, et al., 2009), yet chronic stimulation leads to release of pro-inflammatory cytokines such as TNF α , IL-6 or IL-1 β (Hickman, et al., 2008, Holmes, et al., 2009, White, et al., 2005), initiating a self-propagating feedback mechanism that eventually decreases A β phagocytosis and increases neuronal damage (White, et al., 2005). In AD, amyloid plaques are often surrounded by microglia, likely due to initial attempts at A β clearance followed by an ultimate inability to overcome substantial A β burden. A concomitant breakdown of the blood-brain barrier (BBB) in advanced stages of AD also results in the infiltration of peripheral macrophages to the CNS to help decrease amyloid, yet removing plaques at such a late stage does little to benefit dementia. Therefore, inflammation due to neurodegeneration, as well as autoimmune disorders such as multiple sclerosis (MS), is an expanding area for clinical intervention.

In addition to inflammation, mitochondria are a primary source of reactive oxygen species (ROS) that can oxidize DNA, protein or lipids (Nunomura, et al., 2007, Orrenius, et al., 2007, Sultana, et al., 2009). Healthy mitochondria also express enzymes to detoxify ROS, such as superoxide dismutase (SOD), to remove oxidative stressors that might otherwise induce cellular apoptosis. The importance of mitochondria in the removal of O $_2^-$ cannot be overstated, particularly in motor neuron degeneration. Mutations in the SOD1 gene targets mutant SOD1 protein to mitochondria, making them dysfunctional (Shi, et al., 2010), and for reasons that are not entirely understood SOD1 mutations cause familial ALS by selectively affecting motor neurons (Brotherton, et al., 2012, Kawamata and Manfredi, 2010). Oxidative stress also increases BACE1 expression (Tamagno, et al., 2005) which facilitates A β production, and A β itself generates free radicals during oligomerization (Tabner, et al., 2005). Thus, another feedback loop of mitochondrial impairment is created. Intraneuronal A β accumulates early in disease in humans and AD mouse models (Youmans, et al., 2012), and is consequently stationed perfectly (both spatially and temporally) to wreak havoc on already-overburdened mitochondria.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been administered for years as symptomatic drugs that inhibit cyclooxygenase (COX) enzymes, thereby decreasing the conversion from arachidonic acid to prostaglandins. COX2 is increased in AD brain and it has been shown to increase A β pathology *in vitro* and *in vivo*, possibly via modulation of the γ -secretase complex (Qin, et al., 2006, Xiang, et al., 2002). Unfortunately, no COX2 inhibitors that have been brought to AD clinical trials (such as ibuprofen, tarenflurbil, naproxen, or celecoxib) have succeeded in slowing AD progression (for review, see (Dumont and Beal, 2011)). The Herman et al. group looked at inflammation using both immunohistochemical and biochemical methods (Figure 2 of their manuscript) and determined that hTDP-43 enhanced inflammatory processes even in the absence of exogenous A β 42, suggesting that TDP-43 itself may regulate aspects of inflammation in the CNS. Interestingly, their data suggests that TDP-43 and TNF α may have overlapping pathways while A β 42 increase IL-6 above that of TDP-43, indicative of two separate methods for IL-6 stimulation. If the overlapping mechanism for TNF α induction can be determined, innovative intervention strategies may be revealed.

As an alternative to traditional pharmacological modulation, some research groups have focused on natural compounds to reduce inflammation or free radical production. Curcumen appears to be at the forefront of this movement. Curcumen is a polyphenol derived from the

spice turmeric that acts as a free radical scavenger. It is capable of crossing the BBB from the bloodstream, and can reduce A β fibrillogenesis and plaque deposition *in vitro* and *in vivo*, respectively (Frautschy, et al., 2001, Garcia-Alloza, et al., 2007, Lim, et al., 2001, Yang, et al., 2005). Unfortunately, curcumen has very little bioactivity when ingested (Anand, et al., 2007, Yang, et al., 2008), limiting its practical at-home use by AD patients or caregivers. However, alterations to its chemical structure may generate analogous compounds that are not broken down during digestion and maintain the ability to inhibit A β aggregation. Development of such compounds seems imminent and would make a huge impact on diseases of amyloidosis, making this a very exciting time in the field of drug development.

What Remains to be Studied

Some research suggests that A β 40 peptide alone is insufficient to form dense-core A β deposits in the absence of A β 42, and that the longer more hydrophobic A β 42 peptide is necessary for plaque formation *in vivo* (McGowan, et al., 2005). In the current manuscript, Herman et al. reveal that over-expression of hTDP-43 alone increases murine A β 40 (Figure 4 of their manuscript). This would be expected based on its general BACE1 up-regulation. However, it is interesting that hTDP-43 increases A β 40 in the formic acid (FA)-soluble fraction. FA is commonly used as a terminal extraction buffer during serial protein extractions, as it effectively breaks up dense-cored amyloid (Youmans, et al., 2011). The current data suggests that A β 40 is an essential component of plaques, as viral expression of A β 42 in the absence of hTDP43 does not induce presumable plaque deposition (ie: A β 42 alone does not increase FA-soluble A β 40). However, viral A β 42 expression combined with hTDP-43 seemingly flips the ratio of soluble:insoluble A β 40 compared to hTDP-43 alone, which suggests that altering the A β 40:A β 42 ratio may determine the aggregation properties of murine A β 40 (Tai, et al., 2011). Nixon and colleagues have provided overwhelming evidence for lysosomal A β accumulation that is supported by recent work from the LaDu lab (Youmans, et al., 2012), which they predict leads to lysosomal membrane destabilization followed by neuronal death (Cataldo, et al., 1997, Nixon, 2007, Nixon and Cataldo, 2006). It has been proposed that death of A β -containing neurons and the subsequent release of lysosomal content may seed dense-cored neuritic plaques. Cellular TDP-43 has not been reported to accumulate in lysosomal compartments, but it remains a possibility that intracellular A β may merge with cytosolic TDP-43 aggregates and that neuronal death releases these “seeds” upon which A β 40 peptides can deposit. Although hTDP-43 alone does not increase A β 42 levels in this study (Figure 1 of their work), APP is endogenous from rat in this model and therefore does not harbor the familial AD mutations that favor γ -secretase-based A β 42 production in humans. The authors also overexposed Western blots of rat brain tissue to depict high molecular weight A β aggregates (see their 4th figure), providing further evidence for TDP-43 modulation of A β assembly state. Several critical next steps toward understanding the link between TDP-43 and A β include the use of Thioflavin-S to monitor fibrillogenesis, and oligomer-specific antibodies to reveal toxic oligomer production specifically in transgenic mice expressing mutant forms of human APP.

The *apoE* gene is the sole genetic risk factor modulating both FAD and sporadic AD. The majority of apoE in the CNS is produced locally by glial cells (DeMattos, et al., 2001), and a major role for apoE in the CNS is neuronal uptake of cholesterol for growth, repair and synaptogenesis (Hayashi, et al., 2004, Mahley, 1988, Mauch, et al., 2001). Indeed, following nervous system injury, glial apoE synthesis increases by up to 150-fold, and post-mortem apolipoprotein E (apoE) immunoreactivity is localized to extracellular amyloid plaques (Huang, et al., 2001, Zhang, et al., 2001). Additionally, intraneuronal A β forms cytoplasmic complexes with apoE in AD brains, and these complexes localize to neurons undergoing cell death (LaFerla, et al., 1997). *In vitro*, apoE enhances the uptake of soluble A β at nerve

terminals (Gyls, et al., 2003), indicating that internalization may be a prerequisite for intraneuronal A β accumulation. This uptake is blocked by the addition of apoE receptor associated protein (RAP; an antagonist for apoE receptors), implicating a role for apoE in the uptake of soluble A β species (Gyls, et al., 2003). Further, the presence of RAP abolishes A β 42-induced neurotoxicity *in vitro* (Manelli, et al., 2007). It is therefore surprising that TDP-43 pathology does not appear to correlate with apoE genotype (Nelson, et al., 2011). Single nucleotide polymorphisms (SNPs) in the *Tardbp* gene do not significantly correlate with apoE status (Shibata, et al., 2009), although a comprehensive evaluation of apoE as it relates to TDP-43 has not been reported. Accordingly, apoE genotyping of brains containing TDP-43 inclusions or the presence/absence of apoE receptors may provide essential missing information that would allow us to integrate our understanding of AD pathology with that of other neurodegenerative diseases of aging.

Conclusions

Over the past 5 years TDP-43 has been increasingly linked to neurodegenerative pathology, with an emphasis on TDP-43-positive inclusions in AD brains. In 2008, V. Lee's group wrote a comprehensive review describing TDP-43 proteinopathies as insoluble cytoplasmic aggregates in which TDP-43 moves out of the nucleus and into the cytoplasm, and how these inclusions may be linked to AD (Kwong, et al., 2008). Although the nature of scientific research often necessitates focusing on one or two disease-related proteins, converging evidence suggests that multiple pathways may overlap in ALS, FTLN and AD, including signaling cascades, axonal transport and feedback loops for regulation of cell cycling, growth or regulated cell death. Although the specifics of RBP-based regulation are beyond the scope of this review, RBPs are emerging as crucial chaperones for many such pathways, and their dysregulation apparently moves beyond cellular death to overall systemic failure. The next 5 years will undoubtedly reveal distinct fundamental roles for RBPs in neurodegenerative disease progression. Results from Herman et al. have established the groundwork for uncovering the synergistic effects of TDP-43 and intraneuronal A β 42, which hopefully will reveal upstream molecular targets that can be modulated toward the ultimate goal of disease prevention.

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Figure 1. Simplified diagram of APP structure and processing

APP undergoes sequential proteolysis by b-secretase (b), a-secretase (a) and g-secretase (g) for the release of Ab from the neuronal plasma membrane. TDP-43 has been shown to increase intraneuronal Ab accumulation via increased b-secretase activation.