Nuclear Ataxias

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Historically basic neuroscience research has made several important contributions to the cell biology of the nucleus, in particular the elucidation of nuclear structures and compartments. As research progressed towards elucidating the mechanism of neurological disease at the cellular and molecular levels, it is now providing insight into the importance and basis of coordination of nuclear pathways within the nucleus and with other cellular compartments. Ataxias, lethal neurodegenerative diseases that are distinguished by a progressive loss of motor coordination, stem from disruption of nuclear function.

It seems fitting to take note that Ramon y Cajal, often regarded as the father of cellular neuroscience, also made major contributions to delineating nuclear compartments through his studies of the neuronal nucleus (Lafarga et al. 2009). The importance of this work is highlighted by Cajal's discovery of the nuclear accessory body now designated as the Cajal body. This nuclear structure is at center stage given its role in the biogenesis of snRNPs and snoRNPs (Gall 2003). Spinal muscular atrophy (SMA) is a genetic neurodegenerative disorder caused by a deficiency in survival of motor neuron 1 gene (SMN1). The SMN protein targets to Cajal bodies by a direct interaction with the Cajal body signature protein colin (Herbert et al. 2001).

Ataxia, from Greek means literally a gross lack of coordination of movement, typically in

gait and limb. Although ataxia often results from degeneration in the cerebellum and associated connections, damage to any point along the neuroaxis controlling movement can lead to ataxia. This latter point provides the basis for the wide variety of genes that when mutated cause ataxia (Taroni and DiDonato 2004). There are three forms of ataxia for which evidence strongly supports a role of nuclear dysfunction in pathogenesis (Fig. 1). Among the dominantly inherited ataxias caused by expansions of glutamine tracts, are the spinocerebellar ataxia types 1 and 17. For each there is considerable evidence implicating misregulation of gene expression as being critical for disease. The third form of ataxia is the group of recessive ataxias caused by defects in DNA repair, most notably ataxia telangiectasia (AT).

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Figure 1. Overview of the Nuclear Ataxias. The different nuclear ataxias are positioned relative to the stage of gene regulation thought to be impacted by each disease. SCA1—spinocerebellar ataxia type 1; SCA17—spinocerebellar ataxia type 17; AT—ataxia telangiectasia; AOA1—ataxia with ocular apraxia type 1; SCAN1 spinocerebellar ataxia and neuropathy 1.

COORDINATION IN THE NUCLEUS— SPINOCEREBELLAR ATAXIA TYPE 1 (SCA1)

SCA1 typically presents in middle age and progresses over 10–20 year to cause premature death. Juvenile as well as late-onset cases owing to larger or smaller CAG repeat expansions, respectively, are observed. Ataxia, tremor, and dysarthria (difficulty in articulating words) are common to the SCA1 clinical picture. Purkinje cell loss from the cerebellar cortex is a prominent pathological feature of SCA1. Loss of several brain stem neurons, including the inferior olive, is also a common feature.

SCA1 is caused by expansion of a translated CAG repeat in a gene encoding the protein designated ataxin-1 (ATXN1) (Orr et al. 1993). Normal SCA1 alleles contain from six to 42 CAG repeats, encoding the amino acid glutamine, with those greater than 20 being interrupted with one to three CAT trinucleotides, encoding a histidine residue. Disease alleles, on the other hand, are pure CAG tracts ranging from 39 to 82 units. The length of the repeat tract is a major contributor to the age of disease onset.

The longer the repeat length on the mutant allele, the earlier is the age of onset. Individuals with 70 or more repeat units have a juvenile form of SCA1 whereas those containing mutant alleles with 40–50 repeats have an onset in the fourth or fifth decade of life. Mutant alleles also show germline instability such that in successive generations the repeat can expand further causing earlier onset of symptoms and increasing severity of disease in successive generations, a phenomenon known as anticipation.

Genetic evidence consistently indicates that a gain-of-function mechanism of pathogenesis is critical for induction of SCA1. Although polyglutamine pathogenesis was initially thought to center on the polyglutamine aggregates and large inclusions (Ross and Poier 2004), more recently this has come under considerable question (Cummings et al. 1999; Klement et al. 1998; Saudou et al. 1998; Slow et al. 2005). Particularly in the case of SCA1, it is becoming increasingly apparent that the disorder is defined by the actions of the expanded polyglutamine tract in the context of ATXN1 (Gatchel and Zoghbi 2005, Orr 2001). Central to this idea is the

concept that the normal function and interactions of ATXN1 are critical for defining the pathogenic pathway. It is further envisioned that expansion of the glutamine tract induces a change in protein conformation that in turn triggers alterations in its normal interactions with other cellular proteins. These altered interactions result in neuronal dysfunction, leading to neurodegeneration and neuronal loss.

An important step in understanding SCA1 pathogenesis is the observation that in order for mutant ATXN1 to cause disease it had to enter the nucleus of Purkinje cells (Klement et al. 1998). Later studies revealed that wild-type ATXN1 has biochemical properties consistent with a role in the nucleus, and in some instances the normal function of ATXN1 are linked to pathogenesis. These normal activities of ATXN1 include the ability to bind RNA (Yue et al. 2001), to shuttle between the nucleus and cytoplasm (Irwin et al. 2005), and to interact with a variety of other nuclear proteins including several transcription factors (Lam et al. 2006; Okazawa et al. 2002; Serra et al. 2006; Tsai et al. 2004; Tsuda et al. 2005; Lim et al. 2008).

Structurally, the carboxyl terminus of ATXN1 shares a 120-residue stretch with the HMG box transcription factor HBP1 (HMG box-containing protein-1) (Mushegian et al. 1997; de Chiara et al. 2003), designated as the AXH (ataxin-1/HBP1) domain. The genomes of *Caenorhabditis elegans* and *Drosophila melanogaster* encode small proteins consisting of essentially just an AXH domain, indicating that perhaps this region has the ability to fold independently (de Chiara et al. 2003). Analysis of the crystal structure of the AXH domain from ATXN1 showed it exists as a dimer in an OB (oligomer-binding)-fold (Chen et al. 2004). Proteins with an OB-fold are known to bind nucleic acids, particularly RNA. Thus, the AXH domain of ATXN1 is likely responsible for its RNA-binding property (Yue et al. 2001; de Chiara et al. 2003). It is worth noting that ATXN1 is SUMOylated on at least five lysine residues, two of which are in the AXH domain (Riley et al. 2005). SUMOylation of ATXN1 is inversely affected by the length of the polyglutamine tract and dependent on the ability of ATXN1 to be

localized to the nucleus. Most targets of SUMOylation are nuclear proteins, and many play a role in gene transcription (Seeler and Dejean 2003).

In neurodegenerative diseases, understanding why specific sets of neurons are affected in spite of widespread expression of the disease protein remains one of the unresolved seminal issues. Interaction of ATXN1 with ROR α , and the ROR α coactivator Tip60 provides some insight into the enhanced susceptibility of Purkinje cells to SCA1. This work also challenges the concept that neurodegenerative diseases are unrelated to developmental abnormalities. Serra et al. (2006), using a conditional transgenic mouse model of SCA1 to delay the postnatal expression of mutant ATXN1 until after completion of cerebellar development, found that delayed postnatal expression of mutant ATXN1 led to a substantial reduction in disease severity in adults in comparison with early postnatal mutant ATXN1 expression. This result seems to be linked to a destabilization of ROR α , a transcription factor critical for cerebellar development (Hamilton et al. 1996). In SCA1 mice, ROR α was depleted and expression of genes controlled by ROR α reduced. Furthermore, partial loss of ROR α enhanced mutant ATXN1 pathogenicity. These studies suggest a basis for the Purkinje cell specificity of SCA1 because in the cerebellum these neurons are the only ones that express both ATXN1 and ROR α .

Another important step in dissecting ATXN1's function in the nucleus was the realization that a major portion of wild type as well as mutant ATXN1 is located within large, soluble and relatively stable complexes (Lam et al. 2006). Moreover, substituting an Ala for the Ser at position 776 in ATXN1 decreases considerably the amount of ATXN1 in certain of these large complexes. The importance of this latter observation is linked to the previous demonstration that the S776 is a site where ATXN1 is phosphorylated and an A776 replacement abolishes Purkinje cell toxicity of mutant ATXN1 in vivo (Emamian et al. 2003). These data lead to the idea that mutant ATXN1 induced neuropathology stems from its assembly into native complexes with other nuclear

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proteins and that this assembly might be regulated by the phosphorylation of ATXN1 at S776.

More recently it was shown that glutamine expansion has opposing affects on different complexes (Lim et al. 2008). In complexes containing mutant ATXN1 and the RNA-binding motif protein 17, RBM17, glutamine expansion increased complex formation. Interestingly, SPF45 (the *Drosophila* homolog of RBM17) is a splicing factor that functions to regulate the second step of splicing by virtue of it having a role in defining the site of exon ligation (Lallena et al. 2002). In contrast to the situation with RBM17, the amount of mutant ATXN1 in complexes with the transcription repressor Capicua is decreased with glutamine expansion. Additional data suggest that the ATXN1-Capicua complex is protective while its complex with RBM17 is neurotoxic. Thus, shifting the balance of cellular protein complexes contributes to neurodegeneration induced by mutant ATXN1.

The data suggest a model with ATXN1 as a multifunctional regulatory protein in neurons where it acts to regulate and couple events along the multistep pathway of gene expression (Fig. 2). In the nucleus it is becoming increasingly apparent that transcription is coupled to the steps of RNA processing and transport including splicing, 3'-end formation and mRNA export from the nucleus (Wilkinson and Shyu 2001; Maniatis and Reed 2002; Reed 2003; Pandit et al. 2008). Functional coupling is facilitated by physical contacts between transcription and RNA processing molecular complexes such that the various steps in regulating are tethered to each other. Thus, ATXN1, which interacts with various regulators of transcription (e.g., Capicua and ROR α /Tip60), RNA, as well as RNA-processing proteins (e.g., RBM17), is well positioned to function in the integration of transcription and RNA processing. Because the interaction of ATXN1 with RBM17 is modified by phosphorylation at S776 (Lim et al. 2008), it is reasonable to suggest that such a function under normal conditions would be dynamic and tightly regulated. Any disturbance in either the dynamics or regulation as a result of a mutation in ATXN1

would likely alter at several steps the expression of many critical genes.

BASAL TRANSCRIPTION— SPINOCEREBELLAR ATAXIA TYPE 17

Perhaps no other neurodegenerative disorder exemplifies the paradox of selective neuropathology caused by mutations in a widely expressed protein more than does spinocerebellar ataxia type 17 (SCA17), which is caused by expansion of a glutamine tract located in the TATA-binding protein, TBP (Nakamura et al. 2001). TBP, also known as TFIID, is a well-studied universal transcription factor essential for the function of all three nuclear RNA polymerases. Assembly of the transcription pre-initiation complex, sufficient to drive a basal level of transcription, typically begins with TBP/TFIID binding to the TATA box found in the core promoter of many genes (Thomas and Chiang 2006). Yet, SCA17 is characterized by late onset of neurological symptoms that consists of progressive dementia, ataxia, and seizures. SCA17 pathology includes marked cerebellar atrophy and loss of Purkinje cells as well as less pronounced degeneration in other regions of the brain (Rolfs et al. 2003; Bruni et al. 2004).

Another interesting question highlighted by TBP/TFIID is whether the polyglutamine tract has a normal function to regulate activity of the protein. It has been recognized for some time that polyglutamine or glutamine-rich stretches are present in many eukaryotic transcription factors, perhaps functioning as a transcription activation domain (Courey and Tjian 1988). The glutamine tract in wild-type alleles of human TBP/TFIID, like the glutamine stretch in other human polyglutamine proteins (Hardy and Orr 2006), is typically longer and much more polymorphic than in other species including nonhuman primates. This raises the interesting possibility that perhaps the glutamine tract of some proteins has evolved to assume an additional regulatory function. Evidence that this might be the case for TBP/TFIID was reported recently (Friedman et al. 2007). Previous work showed that dimerization of

Figure 2. (A) ATXN1, a nuclear protein. A confocal image of Purkinje cells from a SCA1 transgenic mouse expressing an expanded allele of the *SCA1* gene. The ATXN1 protein (yellow) is within Purkinje cell nuclei. (B) A model depicting ataxin1 nuclear function. In this model coupling of transcription and RNA splicing is mediated by the interactions of ATXN1 with Capicua (CIC), ROR α /Tip60, and RBM17. **P** Denotes ATXN1 interactions regulated by phosphorylation at Ser776.

TBP/TFIID functions to prevent the up-regulation of gene expression (Jackson-Fisher et al. 1999). Friedman and colleagues went on to show that the formation of inactive dimers of TBP/TFIID, driven by the carboxy-terminal dimerization domain, was inversely related to the length of the glutamine tract at the amino terminus. These investigators further show that

the length of the glutamine stretch in TBP/TFIID affects the extent to which it interacts with the general transcription factor TFIIB, with expanded glutamines enhancing interaction. They also examined the occupancy of TATA-containing promoters in the cerebellum of SCA17 transgenic mice expressing TBP with an expanded glutamine tract and found

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selectively decreased occupancy at some but not all TATA-containing promoters. Notably, they found a decrease in the amount of both TBP/TFIID and TFIIB at the promoter of the gene encoding the small heat shock protein HSPB1. *Hspb1* expression is down-regulated in affected SCA17 mice and its overexpression reduces the toxic effects of mutant TBP. The recent demonstration that the polyglutamine region from huntingtin adopts multiple conformations (Kim et al. 2009), suggests that this region imparts considerable conformational flexibility to the native protein that likely has important functional consequences.

DNA REPAIR—ATAXIA TELANGIECTASIA (AT), ATAXIA WITH OCULAR APREXIA TYPE 1 (AOA1), AND SPINOCEREBELLAR ATAXIA AND NEUROPATHY (SCAN1)

In dividing cells, the link between defective DNA repair and unregulated cell division, i.e., cancer, dates back to studies on xeroderma pigmentosum published in 1968 by James E. Cleaver (Cleaver 1968). Postmitotic neurons, in contrast, respond to deficits in DNA repair with the induction of neuronal cell death that often presents clinically with ataxia (Rass et al. 2007). Among the ataxias associated with defects in DNA repair (Paulson and Miller 2005), recent studies on ataxia telangiectasia (AT), ataxia with ocular apraxia Type 1 (AOA1), and spinocerebellar ataxia and neuropathy-1 (SCAN1) suggest specific repair pathways and how their disruption may lead to neurodegeneration (Table 1).

AT is an autosomal recessive childhood disease characterized by progressive ataxia with cerebellar atrophy and loss of Purkinje cells as well as an increased instance of lymphoid cancer (Lavin 2008). The gene mutated in AT (Savitsky et al. 1995), AT mutated (*ATM*) encodes a Ser/Thr kinase that associates with the Mre11/Rad50/Nbs1 (MRN) complex that acts as a sensor of double strand breaks (DSBs) in DNA. *ATM* is critical for proper activation of the broad cellular response to DSBs. The recognition of DSBs by the MRN complex does not require *ATM* (Mirzoeva and Petrini 2003). Yet it is involved in the activation of *ATM* and as an adaptor for *ATM*-mediated phosphorylation of some of its substrates. Although numerous phosphorylation substrates for *ATM* are reported, perhaps the most notable substrate is p53 given its well characterized role in genome instability (Banin et al. 1998; Canman et al. 1998; Khanna et al. 1998).

Somewhat paradoxically, although less than 20% of AT patients are reported to develop cancer, AT is a paradigm for linking DNA damage, cell signaling and cancer (Lavin 2008). On the other hand, efforts to understand the loss of Purkinje cells from the cerebellum, a hallmark of AT such that patients typically are wheelchair-bound early in life, have proven to be much more intractable. One impediment to understanding the neurodegeneration seen in AT is the lack of a similar phenotype in *Atm* knockout mice. Although mice homozygous for a null allele of *Atm* show many signs of AT including extreme sensitivity to γ -irradiation and lymphomas, the neurological deficits are relatively mild

Table 1. Ataxias associated with defects in DNA repair

Disease	Gene	DNA damage repaired	Neurological SYMPTOMS	Nonneurological symptoms
Ataxia telangiectasis (AT)	ATM	DSBs	Ataxia	Predisposition to cancer, immunodeficiency, telangiectasia
Ataxia with oculomotor apraxia one1 (AOA1)	APTX	SSBs	Ataxia, OA, neuropathy	None
Spinocerebellar ataxia with axonal neuropathy (SCAN1)	TDP1	SSBs	Ataxia, neuropathy	None

and, importantly, are not associated with cerebellar pathology (Barlow et al. 1996; Xu et al. 1996). Histological examination of *Atm*^{-/-} mice show normal Purkinje cells and no evidence of any other brain abnormalities. These data suggest there is a missing link in the mouse.

A physiological function of the MRN complex in the brain, with which ATM interacts in response to DNA damage, was demonstrated using a conditional knockout approach. The mouse homologue of human NBS1, a component of the MRN complex and the gene mutated in the AT-related disorder Nijmegen breakage syndrome (D'Amours and Jackson 2002), was selectively deleted in the CNS (Frappart et al. 2005). Loss of *Nbn* results in an ataxia similar to that in AT and the induction of apoptosis of postmitotic neurons of the cerebellum, including Purkinje cells. These results argue that the ATM-associated MRN complex has a role in maintaining neuronal integrity and suggest that loss of *Nbn* in CNS of the mouse may provide a model for the neurodegeneration seen in AT.

Unlike AT, AOA1 has no symptoms outside of the nervous system, i.e. cancer. The autosomal recessive disorder AOA1 consists of early onset cerebellar ataxia. In addition AOA1 is characterized by sensorimotor neuropathy. The mutation causing AOA1 is in the gene encoding Aprataxin (Date et al. 2001). Aprataxin is a 342 amino acid nuclear/nucleolar protein that has three domains, an amino-terminal forkhead-associated domain, a central histidine triad (HIT) domain, and a carboxy-terminal zinc-finger domain. Aprataxin interacts with XRCC1 and XRCC4, subunits of the DNA ligase complexes involved in single-strand break (SSB) and DSB repair, respectively. These interactions plus the presence of a DNA-binding zinc-finger domain in Aprataxin hinted at an involvement in DNA repair. Importantly, most of the AOA1 mutations are found within or near the HIT domain of Aprataxin (Rass et al. 2007). Typically HIT domains are associated with nucleotide hydrolase and transferase activities (Brenner 2002). However, the nucleotide hydrolase activity of Aprataxin is two orders of magnitude lower than that seen for other hydrolases. More recent biochemical studies show that Aprataxin is a

DNA-specific adenylase with this activity being several orders of magnitude greater than its hydrolase activity (Ahel et al. 2006), indicating that it has the ability to scan the genome for adenylated DNA lesions.

Like AOA1, SCAN1 symptoms are largely restricted to the nervous system. SCAN1 patients are affected with cerebellar ataxia and axonal sensorimotor neuropathy. In addition, they have mild hypercholesterolemia and hypoalbuminemia. The gene affected in SCAN1, TDP1, encodes tyrosyl-DNA-hosphodiesterase 1 (Takashima et al. 2002). TDP1 is known to repair covalent topoisomerase I-DNA adducts created by aborted topoisomerase I reactions. Removal of these adducts by TDP1 generates SSBs that are subsequently repaired by polynucleotide kinase 3' phosphatase (PNKP). Besides interacting with PNKP, TDP1 was recently reported to be in a complex with XRCC1 and DNA-ligase III that repair SSBs (El-Khamisy et al. 2005). Accordingly, SCAN1 cells are unable to repair SSBs induced by the drug camptothecin. Thus, TDP1 likely functions as a critical component of a complex involved in the repair of SSBs.

AT, AOA1, and SCAN1 provide compelling evidence that neurons are especially sensitive to the presence of DNA lesions, in particular SSBs. Clearly, this sensitivity resides in some aspect or combination of features unique to neurons—with cerebellar Purkinje cells being particularly distinctive. The first point that typically comes to mind is that neurons are terminally differentiated postmitotic cells. Not being cycling cells neurons would not have the ability to repair lesions using replication-based mechanisms. Over the years, as one argument goes, unrepaired lesions accumulate in absence of ATM, Aprataxin, or TDP1. This accumulation might be enhanced because of the high metabolic rate of neurons and an exposure to oxidative DNA damage. Accumulated damage would in turn impede transcription eventually hitting functions critical for neuronal integrity. Although such factors likely contribute to toxicity, this scenario differs little from that proposed linking DNA repair defects to cancer where eventually the regulation of oncogene

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and/or tumor suppressor gene expression is circumvented. Except in cycling cells the result is uncontrolled growth and in neurons it is death.

Maybe the response of neurons to defects in DNA repair does reside in their being postmitotic and like cycling cells the eventual target of DNA lesions is regulation of the cell cycle. However, as highlighted recently by Herrup and Yang (2007), the fact that once a neuron leaves the region of neurogenesis it will never divide again could place strong pressure to constantly keep its cell cycle in check. Experimental evidence shows that if a neuron is induced to re-enter the cell cycle it dies. In mice null for the retinoblastoma protein, Rb, postmitotic neurons undergo cell death that is coupled with DNA synthesis and dependent on transcription factors E2F1 and p53 (Clarke et al. 1992; Jacks et al. 1992; Lee et al. 1992; Macleod et al. 1996; Tsai et al. 1998). Likewise, inactivation of Rb in neurons using a SV40 T antigen transgene induces rapid cell death associated with DNA synthesis and E2F1 (al-Ubaidi et al. 1992; Feddersen et al. 1992; 1995; 1997; Athanasiou et al. 1998). It is intriguing that AT, AOA1, and SCA1 are neurodegenerative diseases of childhood with a relatively rapid progression. These features of AT, AOA1, and SCAN1 are quite distinct from the late age of onset and slower progression typical of the dominant polyglutamine-based ataxias (Orr and Zoghbi 2007). Possibly these features are related mechanistically to the rapid course of cell death as seen in the mice with inactivation Rb in their Purkinje cells, i.e., reflecting misregulation of the cell cycle in a postmitotic neuron.

CONCLUDING REMARKS

An unrelenting question concerning the nuclear ataxias (as well as for many other forms of ataxia and neurodegenerative disease) is why is there a very specific set of symptoms with a mutation in a gene that encodes a protein that is widely expressed in the brain and has what is considered to be a housekeeping function. In the case of SCA1, there is increasing evidence that mutant ATXN1 affects the expression and function of proteins more selectively expressed by

Purkinje cells, e.g., ROR α , thereby altering pathways uniquely critical for their function (Serra et al. 2006).

What about the other nuclear ataxias? Why does a polyglutamine expansion in the TATA binding protein, which has a role in regulating basal transcription of many genes in many cell types, cause late onset SCA17 that is highlighted by a prominent loss of cerebellar Purkinje cells? How does one explain a disruption in DNA repair leading to the loss of specific nondividing neurons, i.e., cerebellar Purkinje cells, in AT, AOA1, and SCAN1? Perhaps the answer lies in neuronal chromatin.

TBP, mutated in SCA17, as well as components of the DNA repair machinery, affected in AT, AOA1, and SCAN1, all function upon interacting with DNA. Chromatin structure is emerging as an essential aspect in regulating access of proteins to DNA. Concurrent with their mitotic exit, neurons have a switch in the subunit composition in their chromatin-remodeling complexes. This switch in subunit composition is critical for the proper regulation of dendritic development (Wu et al. 2007). Moreover, a distinct feature of cerebellar Purkinje cells is their large and euchromatic nuclei. Other neurons, such as cerebellar granule cells, manifest a more typical distribution of more densely packed heterochromatin.

Epigenetic modification, e.g., DNA methylation, is another means by which chromatin structure is regulated. In light of the recent identification of a methylated nucleotide, 5-hydroxymethylcytosine, unique to the brain and enriched in Purkinje cells this kind of regulation could provide another avenue for marking chromatin in these neurons (Kriaucionis and Heintz 2009). Thus, there are aspects of chromatin structure and remodeling unique to neurons as well as to specific populations of neurons that might very well affect the access pattern of DNA-binding proteins that could underlie the cellular specificity of pathology in SCA17, AT, AOA1, and SCAN1. Regardless, as the pathogenesis of these nuclear ataxias is elucidated a better understanding of how critical nuclear functions are regulated will be forthcoming.

REFERENCES

- Ahel I, Rass U, El-Khamisy SF, Katyal S, Clements PM, McKinnon PJ, Caldecott KW, West SC. 2006. The neurodegenerative diseases protein aprataxin resolves abortive DNA ligation intermediates. *Nature* **443**: 713–716.
- Al-Ubaidi MR, Hollyfield JG, Overbeek PA, Baehr W. 1992. Photoreceptor degeneration induced by the expression of simian virus 40 large tumor antigen in the retina of transgenic mice. *Proc Natl Acad Sci* **89**: 1194–1198.
- Athanasiou MC, Yunis W, Coleman N, Ehlenfeldt R, Clark HB, Orr HT, Feddersen RM. 1998. The transcription factor E2F-1 in SV40 T antigen-induced cerebellar Purkinje cell degeneration. *Mol Cell Neurosci* **12**: 16–28.
- Banin S, Moyal L, Shieh S, Taya Y, Anderson CW, Chessa L, Smorodinsky NI, Prives C, Reiss Y, Shiloh Y, et al. 1998. Enhanced phosphorylation of p53 by ATM in response to DNA damage. *Science* **281**: 1674–1677.
- Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, Shiloh Y, Crawley JN, Ried T, Tagle D, et al. 1996. *Atm*-deficient mice: a paradigm of ataxia telangiectasia. *Cell* **86**: 159–171.
- Brenner C. 2002. Hint, Fhit, and GalT: function, structure, evolution and mechanism of three branches of the histidine triad superfamily of nucleotide hydrolases and transferases. *Biochem* **41**: 9003–9014.
- Bruni AC, Takahashi-Fujigasaki J, Maltecca F, Foncin JE, Servadio A, Casari G, D'Adamo P, Maletta R, Curcio SA, De Michele G, et al. 2004. Behavioral disorder, dementia, ataxia, and rigidity in a large family with TATA-box binding protein mutation. *Arch Neurol* **61**: 1314–1320.
- Canman CE, Lim DS, Cimprich KA, Taya Y, Tamai K, Sakaguchi K, Appella E, Kastan MB, Siliciano JD. 1998. Activation of the ATM kinase by ionizing radiation and phosphorylation of p53. *Science* **281**: 1677–1679.
- Chen YW, Allen MD, Veprintsev DB, Lšwe J, Bycroft M. 2004. The structure of the AXH domain of spinocerebellar ataxin-1. *J Biol Chem* **278**: 3758–3765.
- Clarke AR, Maandag ER, van Roon M, van der Lugt NM, van der Valk M, Hooper ML, Berns A, te Riele H. 1992. Requirement for a functional *Rb-1* gene in murine development. *Nature* **359**: 328–330.
- Cleaver JE. 1968. Defective DNA repair replication in xeroderma pigmentosum. *Nature* **218**: 652–656.
- Courey AJ, Tjian R. 1988. Analysis of Sp1 in vivo reveals multiple transcriptional domains, including a novel glutamine-rich activation motif. *Cell* **55**: 887–898.
- Cummings CJ, Reinstein E, Sun Y, Antalffy B, Jiang Y-H, Ciechanover A, Orr HT, Beaudet AL, Zoghbi HY. 1999. Mutation of the E6-AP ubiquitin ligase reduces nuclear inclusion frequency while accelerating polyglutamine-induced pathology in SCA1 transgenic mice. *Neuron* **24**: 879–892.
- D'Amours D, Jackson SP. 2002. The Mre11 complex: at the crossroads of DNA repair and checkpoint signaling. *Nat Rev Mol Cell Biol* **3**: 317–327.
- Date H, Onodera O, Tanaka H, Iwabuchi K, Uekawa K, Igarashi S, Koike R, Hiroi T, Yuasa T, Awaya Y, et al. 2001. Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. *Nat Genet* **29**: 184–188.
- de Chiara C, Giannini C, Adinolfi S, de Boer J, Guida S, Ramos A, et al. 2003. The AXH module: an independently folded domain common to ataxin-1 and HBP1. *FEBS Letters* **551**: 107–112.
- El-Khamisy SF, Saifi GM, Weinfeld M, Johansson E, Helleday T, Lupski JR, Caldecott KW. 2005. Defective DNA single-strand break repair in spinocerebellar ataxia with axonal neuropathy-1. *Nature* **434**: 108–113.
- Emamian ES, Kaytor MD, Duvick LA, Zu T, Tousey SK, Zoghbi HY, Clark HB, Orr HT. 2003. Serine 776 of ataxin-1 is critical for polyglutamine-induced disease in SCA1 transgenic mice. *Neuron* **38**: 375–387.
- Feddersen RM, Ehlenfeldt R, Yunis WS, Clark HB, Orr HT. 1992. Disrupted cerebellar development and progressive degeneration of Purkinje cells in SV40 T antigen transgenic mice. *Neuron* **9**: 955–966.
- Feddersen RM, Clark HB, Yunis WS, Orr HT. 1995. In vivo viability of postmitotic Purkinje neurons requires pRb family member function. *Mol Cell Neurosci* **6**: 153–167.
- Feddersen RM, Yunis WS, O'Donnell MA, Ebner TJ, Shen L, Iadecola C, Orr HT, Clark HB. 1997. Susceptibility to cell death induced by mutant SV40 T-antigen correlates with Purkinje neuron functional development. *Mol Cell Neurosci* **9**: 42–62.
- Frappart P-O, Tong W-M, Demuth I, Radovanovic I, Herceg Z, Aguzzi A, Digweed M, Wang Z-Q. 2005. An essential function for NBS1 in the prevention of ataxia and cerebellar defects. *Nat Med* **11**: 538–544.
- Friedman MJ, Shah AG, Fang Z-H, Ward EG, Warren ST, Li S, Li X-J. 2007. Polyglutamine domain modulates TBP-TFIIB interaction: Implications for its normal function and neurodegeneration. *Nat Neurosci* **10**: 1519–1528.
- Gall JG. 2003. The centennial of the Cajal body. *Nat Rev Mol Cell Bio* **4**: 975–980.
- Gatchel JR, Zoghbi HY. 2005. Diseases of unstable repeat expansion: Mechanisms and common principals. *Nat Rev Genet* **6**: 743–755.
- Hamilton BA, Frankel WN, Kerrebrock AW, Hawkins TL, Fitz-Hugh W, Kusumi K, Russell LB, Mueller KL, van Berkel V, Birren B, et al. 1996. Disruption of the nuclear hormone receptor ROR α in *staggerer* mice. *Nature* **379**: 736–739.
- Hardy J, Orr HT. 2006 The genetics of neurodegenerative diseases. *J Neurochem* **97**: 1690–1699.
- Herbert MD, Szymczyk PW, Shpargel KB, Matera AG. 2001. Colin forms the bridge between Cajal bodies and SMN, the spinal muscular atrophy protein. *Genes Dev* **15**: 2720–2729.
- Herrup K, Yang Y. 2007. Cell cycle regulation in the postmitotic neuron: Oxymoron or new biology? *Nat Rev Neurosci* **8**: 368–378.
- Irwin S, Vandelft M, Howell JL, Graczyk J, Orr HT, Truant R. 2005. RNA association and nucleocytoplasmic shuttling by ataxin-1. *J Cell Sci* **118**: 233–242.
- Jacks T, Fazeli A, Schmitt EM, Bronson RT, Goodell MA, Weinberg RA. 1992. Effects of an Rb mutation in the mouse. *Nature* **359**: 295–300.
- Jackson-Fisher AJ, Chitikila C, Mitra M, Pugh BF. 1999. A role for TBP dimerization in preventing unregulated gene expression. *Mol Cell* **3**: 717–727.

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- Khanna KK, Keating KE, Kozlov S, Scott S, Gatei M, Hobson K, Taya Y, Gabrielli B, Chan D, Lees-Miller SP, et al. 1998. ATM associates with and phosphorylates p53: mapping the region of interaction. *Nat Genet* **20**: 398–400.
- Kim MW, Yagarany C, Kim SW, Otwinowski Z, Bezprozvanny I. 2009. Secondary structure of Huntingtin amino-terminal region. *Structure*, **17**: 1205–1212.
- Klement IA, Skinner PJ, Kaytor MD, Yi H, Hersch SM, Clark HB, Zoghbi HY, Orr HT. 1998. Ataxin-1 nuclear localization and aggregation: Role in polyglutamine-induced disease in *SCA1* transgenic mice. *Cell* **95**: 41–53.
- Kriaucionis S, Heintz N. 2009. The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain. *Science* **324**: 929–930.
- Lafarga M, Casafont I, Bengoechea R, Tapia O, Berciano MT. 2009. Cajal's contribution to the knowledge of the neuronal cell nucleus. *Cromosoma* **118**: 437–443.
- Lallena MJ, Chalmers KJ, Llamazares S, Lamond AI, Valcárcel J. 2002. Splicing regulation at the second catalytic step by sex-lethal involves 3' splice site recognition by SPF45. *Cell* **109**: 285–296.
- Lam YC, Bowman AB, Jafar-Nejad P, Lim J, Richman R, Fryer JD, Hyun E, Duvick LA, Orr HT, Botas J, et al. 2006. Mutant ATAXIN-1 interacts with the repressor Capicua in its native complex to cause *SCA1* neuropathology. *Cell* **127**: 1335–1347.
- Lavin ME. 2008. Ataxia-telangiectasia; from a rare disorder to a paradigm for cell signaling and cancer. *Nat Rev Mol Cell Bio* **9**: 759–769.
- Lee EY, Chang CY, Hu N, Wang YC, Lai CC, Herrup K, Lee WH, Bradley A. 1992. Mice deficient for *Rb* are nonviable and show defects in neurogenesis and hematopoiesis. *Nature* **329**: 288–294.
- Lim J, Crespo-Barreto J, Jafar-Nejad P, Bowman AB, Richman R, Hill DE, Orr HT, Zoghbi HY. 2008. Opposing effects of polyglutamine expansion on native protein complexes contribute to *SCA1*. *Nature* **452**: 713–719.
- Macleod KE, Hu Y, Jacks T. 1996. Loss of *Rb* activates both p53-dependent and independent cell death pathways in the developing mouse nervous system. *EMBO J* **15**: 6178–6188.
- Maniatis T, Reed R. 2002. An extensive network of coupling among gene expression machines. *Nature* **416**: 499–506.
- Matera AG, Frey MR. 1998. Nuclear structure '98. Coiled bodies and gems: Janus or Gemini? *Am J Hum Genet* **63**: 317–321.
- Mirzoeva OK, Petrini JH. 2003. DNA replication-dependent nuclear dynamics of the Mre 11 complex. *Mol Can Res* **1**: 207–218.
- Mushegian AR, Bassett DE Jr, Boguski MS, Bork P, Koonin EV. 1997. Positionally cloned human disease genes: patterns of evolutionary conservation and functional motifs. *Proc Natl Acad Sci* **94**: 5831–5836.
- Nakamura K, Jeong SY, Uchihara T, Anno M, Nagashima K, Nagashima T, Ikeda S, Tsuji S, Kanazawa I. 2001. *SCA17*, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein. *Hum Mol Genet* **10**: 1441–1448.
- Okazawa H, Rich T, Chang A, Lin X, waragai M, Kajikawa M, Enokido Y, Komuro A, Kato S, Shibata M, et al. 2002. Interaction between mutant ataxin-1 and PQBP-1 affects transcription and cell death. *Neuron* **34**: 701–713.
- Orr HT, Chung MY, Banfi S, Kwiatkowski TJJr, Servadio A, Beaudet AL, McCall AE, Duvick LA, Ranum LPW, Zoghbi HY. 1993. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nat Genet* **4**: 221–226.
- Orr HT. 2001. Beyond the Qs in the polyglutamine diseases? *Genes Dev* **15**: 925–932.
- Orr HT, Zoghbi HY. 2007. Trinucleotide repeat disorders. *Ann Rev Neurosci* **30**: 575–621.
- Pandit S, Wang D, Fu X-D. 2008. Functional integration of transcriptional and RNA processing machines. *Curr Opin Cell Bio* **20**: 260–265.
- Paulson HL, Miller VM. 2005. Breaks in coordination: DNA repair in inherited ataxia. *Neuron* **46**: 845–848.
- Rass U, Ahel I, West SC. 2007. Defective DNA repair and neurodegenerative disease. *Cell* **130**: 991–1004.
- Reed R. 2003. Coupling transcription, splicing and mRNA export. *Curr Opin Cell Bio* **15**: 326–331.
- Riley BE, Zoghbi HY, Orr HT. 2005. SUMOylation of the polyglutamine protein, ataxin-1 is dependent on a functional nuclear localization signal. *J Biol Chem* **280**: 21942–21948.
- Rolfs A, Koeppen AH, Bauer I, Bauer P, Buhlmann S, Topka H, Schöls L, Riess O. 2003. Clinical features and neuropathology of autosomal dominant spinocerebellar ataxia (*SCA17*). *Ann Neurol* **54**: 367–375.
- Ross CA, Poier MA. 2004. Protein aggregation and neurodegenerative disease. *Nat Med* **10**: S10.
- Saudou F, Finkbeiner S, Devys D, Greenberg ME. 1998. Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell* **95**: 55–66.
- Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S, et al. 1995. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* **268**: 1749–1753.
- Seeler J-S, Dejean A. 2003. Nuclear and unclear functions of SUMO. *Nat Rev Cell Bio* **4**: 690–699.
- Serra HG, Duvick L, Zu T, Carlson K, Stevens S, Jorgensen N, Lysholm A, Burright E, Zoghbi HY, Clark HB, et al. 2006. ROR α -mediated Purkinje cell development determines disease severity in adult *SCA1* mice. *Cell* **127**: 697–708.
- Slow EJ, Graham RK, Osmand AP, Devon RS, Lu G, Deng Y, Pearson J, Vaid K, Bissada N, Wetzel R, et al. 2005. Absence of behavioral abnormalities and neurodegeneration in vivo despite widespread neuronal huntingtin inclusions. *Proc Natl Acad Sci USA* **102**: 11402–11407.
- Taroni F, DiDonato S. 2004. Pathways to motor incoordination: the inherited ataxias. *Nat Rev Neurosci* **5**: 641–656.
- Thomas MC, Chiang CM. 2006. The general transcription machinery and general cofactors. *Crit Rev Biochem Mol Biol* **41**: 105–178.

- Tsai KY, Hu Y, Macleod KF, Crowley D, Yamasaki L, Jacks T. 1998. Mutation of E2f-1 suppresses apoptosis and inappropriate S phase entry and extends survival of Rb-deficient mouse embryos. *Mol Cell* **2**: 293–304.
- Tsai CC, Kao HY, Mitzutani A, Banayo E, Rajan H, McKeown M, Evans RM. 2004. Ataxin 1, a SCA1 neurodegenerative disorder protein, is functionally linked to the silencing mediator of retinoid and thyroid hormone receptors. *Proc Natl Acad Sci USA* **101**: 4047–4052.
- Tsuda H, Jafar-Nejad H, Patel AJ, Sun Y, Chen H-K, Rose MF, Venken KJT, Botas J, Orr HT, Bellen HJ, et al. 2005. The AXH domain in mammalian/*Drosophila* Ataxin-1 mediates neurodegeneration in spinocerebellar ataxia 1 through its interaction with Gfi-1/Senseless proteins. *Cell* **122**: 633–644.
- Wilkinson MF, Shyu AB. 2001. Multifunctional regulatory proteins that control gene expression in both the nucleus and the cytoplasm. *Bioessays* **23**: 775–787.
- Wu JI, Lessard J, Olave IA, Qiu Z, Ghosh A, Graef IA, Crabtree GR. 2007. Regulation of dendritic development by neuron-specific chromatin remodeling complexes. *Neuron* **56**: 94–108.
- Xu Y, Ashley T, Brainerd EE, Bronson RT, Meyn MS, Baltimore D. 1996. Targeted disruption of ATM leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma. *Genes Dev* **10**: 2411–2422.
- Yue S, Serra H, Zoghbi HY, Orr HT. 2001. The SCA1 protein, ataxin-1, has RNA-binding activity that is inversely affected by the length of its polyglutamine tract. *Hum Mol Genet* **10**: 25–30.

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