(1994) *Brodmann's Localization in the Cerebral Cortex*, Smith-Gordon]
29 **Luskin, M.B. and Price, J.L.** (1983) *J. Comp. Neurol.* 216, 264–291
30 **Hurley, K.M. *et al.*** (1991) *J. Comp. Neurol.* 308, 249–276
31 **McDonald, A.J., Mascagni, F. and Guo, L.** (1996) *Neuroscience* 71, 55–75
32 **Ottersen, O.P.** (1982) *J. Comp. Neurol.* 205, 30–48
33 **Canteras, N.S. and Swanson, L.W.** (1992) *J. Comp. Neurol.* 324, 180–194
34 **Canteras, N.S., Simerly, R.B. and Swanson, L.W.** (1992) *J. Comp. Neurol.* 324, 195–212
35 **Canteras, N.S., Simerly, R.B. and Swanson, L.W.** (1994) *J. Comp. Neurol.* 348, 41–79
36 **Krettek, J.E. and Price, J.L.** (1978) *J. Comp. Neurol.* 178, 225–254
37 **McDonald, A.J.** (1987) *J. Comp. Neurol.* 262, 46–58
38 **Ray, J.P. and Price, J.L.** (1992) *J. Comp. Neurol.* 323, 167–197
39 **Risold, P.Y., Thompson, R.H. and Swanson, L.W.** (1997) *Brain Res. Rev.* 24, 197–254
40 **Romanski, L.M. and LeDoux, J.E.** (1993) *Cereb. Cortex* 3, 515–532
41 **Van Groen, T. and Wyss, J.M.** (1990) *J. Comp. Neurol.* 302, 515–528
42 **Bernard, J.F., Alden, M. and Besson, J.M.** (1993) *J. Comp. Neurol.* 329, 201–229
43 **LeDoux, J.E., Farb, C. and Ruggiero, D.A.** (1990) *J. Neurosci.* 10, 1043–1054
44 **Yasui, Y., Saper, C.B. and Cechetto, D.F.** (1991) *J. Comp. Neurol.* 308, 293–310
45 **Krettek, J.E. and Price, J.L.** (1977) *J. Comp. Neurol.* 172, 687–722
46 **Krettek, J.E. and Price, J.L.** (1977) *J. Comp. Neurol.* 172, 723–752
47 **McDonald, A.J.** (1991) *Neuroscience* 44, 1–14
48 **McDonald, A.J.** (1991) *Neuroscience* 44, 15–33
49 **Krettek, J.E. and Price, J.L.** (1978) *J. Comp. Neurol.* 178, 255–280
50 **Hopkins, D.A. and Holstege, G.** (1978) *Exp. Brain Res.* 32, 529–547
51 **Bandler, R. and Shipley, M.T.** (1994) *Trends Neurosci.* 17, 379–388
52 **Rosen, J.B. *et al.*** (1991) *Behav. Neurosci.* 105, 817–825
53 **Whalen, P.J. and Kapp, B.S.** (1991) *Behav. Neurosci.* 105, 141–153
54 **Fallon, J.H. and Moore, R.Y.** (1978) *J. Comp. Neurol.* 180, 545–580
55 **Ricardo, J.A. and Koh, E.T.** (1978) *Brain Res.* 153, 1–26
56 **Moga, M.M., Weis, R.P. and Moore, R.Y.** (1995) *J. Comp. Neurol.* 359, 221–238
57 **Mascagni, F., McDonald, A.J. and Coleman, J.R.** (1993) *Neuroscience* 57, 697–715
58 **Sripanidkulchai, K., Sripanidkulchai, B. and Wyss, J.M.** (1984) *J. Comp. Neurol.* 229, 419–431
59 **Sesack, S.R. *et al.*** (1989) *J. Comp. Neurol.* 290, 213–242
60 **Kita, H. and Kitai, S.T.** (1990) *J. Comp. Neurol.* 298, 40–50
61 **Penfield, W.** (1958) *The Excitable Cortex in Conscious Man*, C.C. Thomas
62 **Simerly, R.B.** (1990) *Trends Neurosci.* 13, 104–110

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PERSPECTIVES ON DISEASE

Mutations in RNA: a first example of molecular misreading in Alzheimer's disease

Fred W. van Leeuwen, J. Peter H. Burbach and Elly M. Hol

In the past decade, considerable progress has been made in the understanding of the neurodegenerative changes that occur in Alzheimer's disease (AD). Knowledge about this disease is based mainly on studies of inherited forms of AD, although most cases of AD are of the non-familial type. Recently, a novel type of mutation in 'vulnerable' dinucleotide repeats in messenger RNA was discovered in AD patients: in this type of mutation a mutated transcript is produced from a correct DNA sequence, a process that we call 'molecular misreading'. The resulting mutated '+1 proteins' are prominent neuropathological hallmarks of AD and they are present in most elderly non-demented people also. This suggests that the dinucleotide deletions in transcripts could be one of the earliest events in the neuropathogenesis of AD and an important factor in normal aging.

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IN THE ADULT mammalian nervous system, the proliferation of neurons is rare, except in the olfactory epithelium[1] and the hippocampal dentate gyrus of rodents[2]. In primates, neuronal proliferation is even more limited, apart from mitosis-associated mutations and site-specific recombinations[3,4]. Consequently, mutation rates in the neuronal genome are very low[5], and the capacity of neurons to broaden the phenotypic repertoire as is seen in lymphocytes[3], is reduced. However, modification of expression is possible by alternative splicing and mRNA editing[6]. Indeed, in the nervous system, substitutional mRNA editing has been reported, in which specific nucleotides in RNA are modified post-transcriptionally[7].

Some years ago, when investigating the presence of vasopressin (VP) precursor products that theoretically could not exist[8,9], we discovered a novel type of transcript variability in homozygous Brattleboro rats[10]. These rats suffer from hypothalamic diabetes insipidus as a result of a single-base germ-line mutation in the *VP* gene that encodes an aberrant VP precursor. Surprisingly, we found that an additional mutation (ΔGA) in their VP transcripts results in restoration of the wild-type reading frame and the synthesis of a functional VP protein that can enter the secretory pathway and undergo axonal transport[10,11]. Two sites of the dinucleotide deletion (ΔGA) were found that occurred preferentially in GAGAG motifs of the VP mRNA. Moreover, the mutation rate

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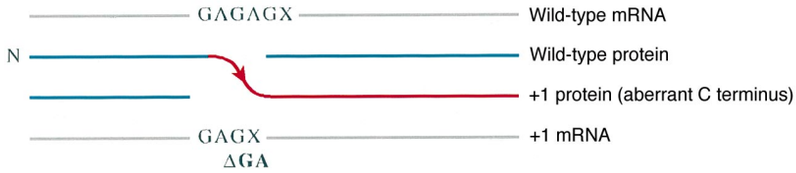

Fig. 1. ***Schematic representation of a frameshift mutation.*** *A +1 protein is formed as a result of a dinucleotide deletion (for example, ΔGA) and consists of a wild-type N terminus (blue). Downstream of the dinucleotide deletion, the transcript is translated in the +1 reading frame and gives rise to the aberrant (red) C terminus of the +1 protein.*

depended upon transcriptional activity[10]. Subsequently, it was shown that a similar mutation also occurs in wild-type rat and human gene transcripts, so that these mutations are not restricted to the VP cells of Brattleboro rats[10,12]. In wild-type VP transcripts, contrary to the restoration of the reading frame as seen in the Brattleboro rat, the outcome is a frameshift and the synthesis of a mutated protein. Dinucleotide deletions have since been shown to occur much more widely, both in other neuronal transcripts of postmitotic neurons and in proliferating tissues[13]. These findings suggest the existence of a novel mechanism, which we propose to call 'molecular misreading', by which correct genetic information can be misread during transcription.

What are '+1 proteins'?

In the VP system we showed previously that GAGAG motifs in RNA are 'hot spots' for mutations when transcriptional activity is very high[10,13]. A dinucleotide deletion (ΔGA) in the open reading frame of an mRNA molecule leads to its translation into a protein with a wild-type N terminus, but at the site of the mutation, the reading frame is shifted. As a result, the C terminus is translated in the '+1 reading frame', resulting in a +1 protein with a novel C terminus, denoted as β amyloid precursor protein^{+1} (βAPP^{+1}), for example (Fig. 1). Often, the +1 reading frame encodes a premature stop codon, resulting in a truncated protein. If the mutation occurs upstream or within a functional domain of the wild-type protein the resulting physico-chemically different +1 protein will, partially or completely, lose the functional domains of the wild-type protein. We anticipate that +1 proteins accumulate and eventually affect cellular functioning (see below). In addition to a loss of function, +1 proteins might gain undesirable properties, such as the ability to affect cellular metabolism and activity directly or the ability to interfere with the folding of other cellular proteins (as prions do). Thus, the dinucleotide deletion can initiate pathological processes and result in neuronal degeneration (for example, by apoptosis).

Dementia and Alzheimer's disease

Although most elderly demented patients suffer from Alzheimer's disease (AD) (Ref. 14), so far, it has only been possible to make a definite diagnosis of AD by postmortem assessment of neuropathological hallmarks (the presence of amyloid plaques, neurofibrillary tangles and kinky and curly neuropil threads) in autopsy brains[15,16]. How AD is initiated and which factors cause its neuropathology are not yet clear and these issues have been discussed in numerous reviews[17,18]. However, mutations in three different genes [βAPP, PS-1 and PS2 (Ref. 19)] can initiate AD and cause its neuropathology by increasing Aβ42 production as a result of mismetabolized βAPP. In such cases, the elevation of Aβ42 has been detected many years before symptoms occur, suggesting that it is not a secondary event in the course of degeneration seen in AD (Ref. 20). Other investigators have suggested that the hyperphosphorylated Tau seen in neurofibrillary tangles plays a primary role in the development of AD, although there is no published evidence to support this theory. In addition, other putative factors (such as decreased neuronal metabolism[21]) and several risk factors [such as apolipoprotein E_4 ($ApoE_4$)] might contribute to the pathogenesis of AD. For example, $ApoE_4$ increases Aβ40 deposition in plaques and blood vessels, both in AD brains and in the normal aging process[22,23].

However, the frequency of autosomal dominant forms of AD is very low (less than 5% of the total number of AD cases): there are far more cases with a positive family history of AD in first degree relatives, and even more cases without any familial history of AD, the so-called 'sporadic cases'. These sporadic cases are common, but it remains unclear how many of these cases actually have a genetic component and how many have no such component. Regardless of this, all sporadic AD patients display the same neuropathological hallmarks as the autosomally dominant forms of AD. Only a proportion of the sporadic cases are linked to risk factors such as $ApoE_4$ (Refs 17,24). Thus, a more general mechanism must exist that leads to neuronal degeneration in the sporadic cases. We suggest that the +1 proteins formed as a result of transcript mutations could play an important role in the pathogenesis of AD.

Frameshift mutations in gene transcripts associated with AD

Earlier studies in the Brattleboro rat indicated that GAGAG motifs in RNA are vulnerable sequences that can undergo dinucleotide deletions[10]. A search for these motifs in several genes associated with AD revealed that many of these genes do contain GAGAG motifs (Table 1; Fig. 1). We predicted that their mutant transcripts and +1 proteins should exist in brain tissue. To test this theory, we raised antibodies against the predicted novel C termini[13]. Several antibodies against βAPP^{+1} and ubiquitin-B^{+1} (Ubi-B^{+1}) obtained by this strategy stained the dystrophic neurites forming the neuritic plaques, neuropil threads and neurofibrillary tangles of AD patients and elderly controls (>72 years old) with initial neuropathology in 71% and 100%, respectively, of the 21 early or late onset AD patients tested (Fig. 2). No immunoreactivity for these +1 proteins was detected in non-demented controls <72 years old[13]. This suggests a direct relationship between +1 proteins and AD. The fact that tangles in elderly non-demented controls were also stained indicates that dinucleotide deletions might be an early event in AD neuropathogenesis. Subsequently, cloning experiments demonstrated that dinucleotide deletions in mRNA had occurred in or adjacent to the GAGAG motif (ΔGA in βAPP and ΔGU in Ubi-B). Deletions in βAPP and Ubi-B transcripts might be just two examples from a broad array of genes expressed in neurons [estimated to be about 65 000–80 000 (Ref. 25)] that are subject to a dinucleotide deletion. Because we also found a CU deletion in a CUCU motif

TABLE 1. Genes associated with Alzheimer's disease

Gene	Number of base pairs	GAGAG motifs		Exon from which +1 peptides are derived	+1 Peptide sequence
	Coding sequence, longest form	Expected number	Actual number		
βAPP	2234	2.2	7	9/10	RGRTSSKELA
Ubiquitin-B	687	0.7	2	2	DHHPGSGAQ
Tau	1056	1.1	–	13	HGRLAPARHAS[a]
Presenilin I	1392	1.4	3	9	SIQKFQV
Presenilin II	1346	1.3	3	3	VEKPGERGGR
Apolipoprotein E4	951	0.9	–	4	GAPRLPPAQAA[a]
MAP2b[b]	5595	5.6	13	18	KTRFQRKGPS
Neurofilament-light	1625	1.6	3	1	PGNRSMPGHE
Neurofilament-medium	2748	2.8	3	3	EAEGEGSPS
Neurofilament-heavy	3063	3.1	2	1	VGAARDSRAA
GFAP[c]	1299	1.3	6	6	EDRGDAGWRGH

[a]Based upon a GAGA motif. [b]Microtubule-associated protein 2B. [c]Glial fibrillary acidic protein.

of Ubi-B mRNA, other dinucleotide deletions seem to occur also, and the frameshift mutations that we have reported might be just the tip of the proverbial iceberg. Thus, a neuron could accumulate many of these aberrant proteins that increasingly impair neuronal function (for example, axonal transport). Whether the observed RNA mutations in βAPP and Ubi-B transcripts contribute to the etiology of AD, or are merely one of its results, is presently the focus of ongoing studies.

Are +1 proteins an early and specific event in AD and Down syndrome?

The presence of Ubi-B^{+1} proteins in the hippocampus and temporal cortex of elderly non-demented controls[13], all displaying the first signs of neuropathology, hints at their direct involvement in the initial steps of neuropathogenesis. In non-demented Down syndrome (DS) patients at the age of 17 days and nine years, who have no plaques or tangles whatsoever, nor any Aβ deposits, βAPP^{+1} immunoreactivity is found frequently in the neurites of apparently healthy looking neurons[26]. Additional evidence for the involvement of +1 proteins in the initiation of neuropathology has come from a non-demented DS patient who expressed the βAPP^{+1} and Ubi-B^{+1} proteins only in the cellular islands of the pre-α layers of the transenthorhinal cortex[15]. This area is an early target for neuropathological changes in AD (Ref. 15).

To investigate whether the transcript mutations in βAPP and Ubi-B are specific for AD, we studied the nigrostriatal system of 11 patients with Parkinson's disease for the presence of the βAPP^{+1} and Ubi-B^{+1} proteins and found a positive reaction in only one patient[13]; however, this patient also suffered from AD. In addition, in ten patients suffering from multiple sclerosis no reaction was found in or near the lesions. Therefore, these +1 proteins do not occur in all types of neuropathology, but appear to be specific for AD neuropathology[13].

Functional consequences of frameshift mutations in AD and DS

The cells displaying mutated mRNAs form a subpopulation of the total cell number in tissue samples[13]. However, at the single cell level this subpopulation has a high number of mutated Ubi-B transcripts, as has been shown by means of *in situ* hybridization[13]. As a result, the neurons of AD and DS patients demonstrate intense +1 immunoreactivy (Fig. 2). The extent to which a +1 protein loses or retains the function of the wild-type molecule is different for each type of transcript. For example, in the truncated βAPP^{+1} protein, the neurite extension-promoting domain (the RERMS sequence[27]) is mutated[13], whereas the complete C terminus, including the Aβ moiety, is probably not synthesized by an alternative internal translation initiation site[28]. An even better example is Ubi-B, which has an essential glycine moiety at the C terminus, and is tagged via an isopeptide bond to the ε-amino group of a lysine moiety in aberrant proteins. Subsequently, the lysine moiety at position 48 of Ubi-B is ubiquitylated. This process of multi-ubiquitylation is an essential signal for the proteasomal degradation of aberrant proteins[35]. This property of Ubi-B is lost because of the mutation (Fig. 3). As a result of the

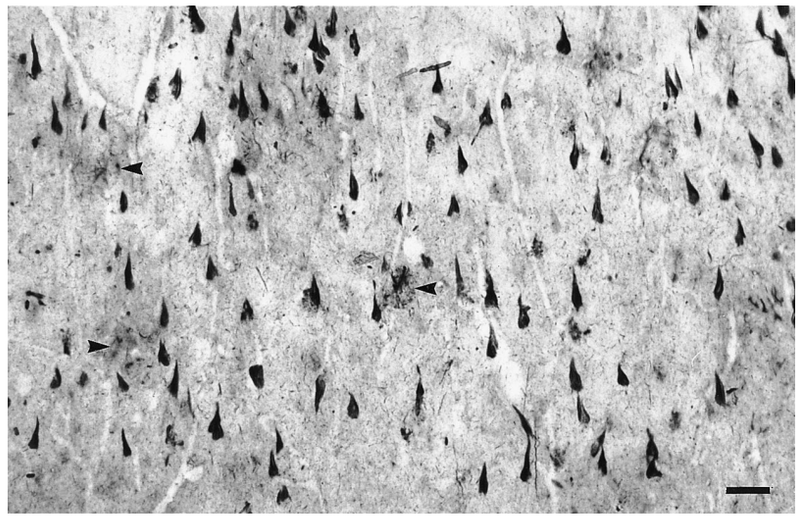

Fig. 2. ***Ubiquitin-B^{+1} immunoreactivity in a 50-μm-thick vibratome section of the hippocampus (CA1 and subiculum) of a 92-year-old patient with Alzheimer's disease.*** *Intense immunoreactivity was present in the neurofibrillary tangles (flame-shaped), neuropil threads and the dystrophic neurites surrounding the neuritic plaques (arrowheads). Scale bar, 50 μm.*

dinucleotide deletion, degradation of aberrant proteins by the 26S proteasome could be very inefficient. Mono-ubiquitylation of hyperphosphorylated Tau is indeed prominent in AD, which indicates that the multi-ubiquitylation process is affected[29] (Fig. 3). In this way, accumulation of different aberrant proteins might add to increased dysfunctioning of neurons, in accord with the fact that AD progresses slowly with a mean duration of approximately eight years.

DNA or RNA mutations

In the homozygous Brattleboro rat, an age-dependent increase in the number of cells with a revertant VP phenotype was found, which we interpreted as due to somatic mutations occurring in the genes at an exceptionally high frequency[9,30]. However, we were unable to show a mutation at the genomic level whereas, in transcripts, the mutation (ΔGA) could be determined readily (D.A.P. Evans *et al.*, unpublished observations). Similar results were obtained for βAPP and Ubi-B using even more sensitive approaches[13]. Using the most sensitive approach, as a positive control, we were able to amplify ten copies of mutant plasma DNA out of a background of 500 ng genomic DNA. However, when we analyzed a total of 5 μg DNA for each control, Alzheimer patient and Down syndrome patient no mutations were found[13]. Consequently, it is very unlikely that these dinucleotide deletions take place in the genome. Therefore, we favor the theory that transcript mutation occurs, especially as different mutant proteins co-exist in the same neurons[13].

Enhanced gene transcription: DS

The high transcriptional activity of the *VP* gene in homozygous Brattleboro rats promotes the generation of solitary VP cells expressing +1 proteins[10]. A comparable situation exists in DS patients in whom, as a result of trisomy 21, transcription of the *βAPP* gene is higher than would be predicted on the basis of gene dosage alone[31,32]. Therefore, we expected to find a high frequency of mutations in βAPP transcripts (ΔGA) and a very intense βAPP^{+1} protein immunoreactivity in neuritic plaques, neuropil threads and neurofibrillary tangles, which was indeed the case[13]. It is puzzling why trisomy 21 results in elevated levels of a +1 protein other than βAPP (for example, $Ubi\text{-}B^{+1}$). As a result of the overproduction of a number of proteins in DS (Refs 33,34), the expression of the Ubi-B protein involved in proteasomal protein degradation[35] is enhanced[36] and, consequently, $Ubi\text{-}B^{+1}$ proteins were detected in all of the demented DS patients studied[13]. The mutation in Ubi-B might result in an inefficient degradation of aberrant proteins (Fig. 3), which then feeds forward to result in progressively increasing dysfunction. Indeed, many DS patients develop Alzheimer neuropathology in their fourth decade[37].

The mechanism of RNA mutations and RNA quality control

RNA mutations might occur either co- or post-transcriptionally. Substitutional RNA editing has been described in the nervous system[6]. Knowledge of the mechanisms by which RNA polymerases produce errors in repeats, such as GAGAG or CUCU (for example, slippage or stuttering[38,39]) in the brain tissue of mammals is lacking. From our experiments, it appears that the generation of dinucleotide deletions by molecular misreading of correct DNA is promoted by their enhanced transcription, as has been shown both in VP cells of homozygous Brattleboro rats[10] and in βAPP and Ubi-B transcripts of the cerebral cortex of DS patients[13]. The finding that two different +1 proteins, arising from two different transcripts, co-exist in neurons of AD patients points to a general controlling mechanism (the 'common denominator'[13]) that shows a failure to detect mutated mRNA in AD patients[13]. It is well-known that such a proof-reading mechanism for DNA acts during DNA replication[40,41]. In the case of RNA, mRNA surveillance was described as a mechanism that checks for premature stop codons in mRNA (Refs 42,43). This system increases the fidelity of gene expression by eliminating RNAs that have been translated incompletely and could act as the common denominator. Indeed, recently a human homologue of a yeast gene with potential 'mRNA surveillance' activity (human upstream frameshift mutation, HUPF1) has been cloned[44,45]. The declining accuracy of such an mRNA surveillance system later in

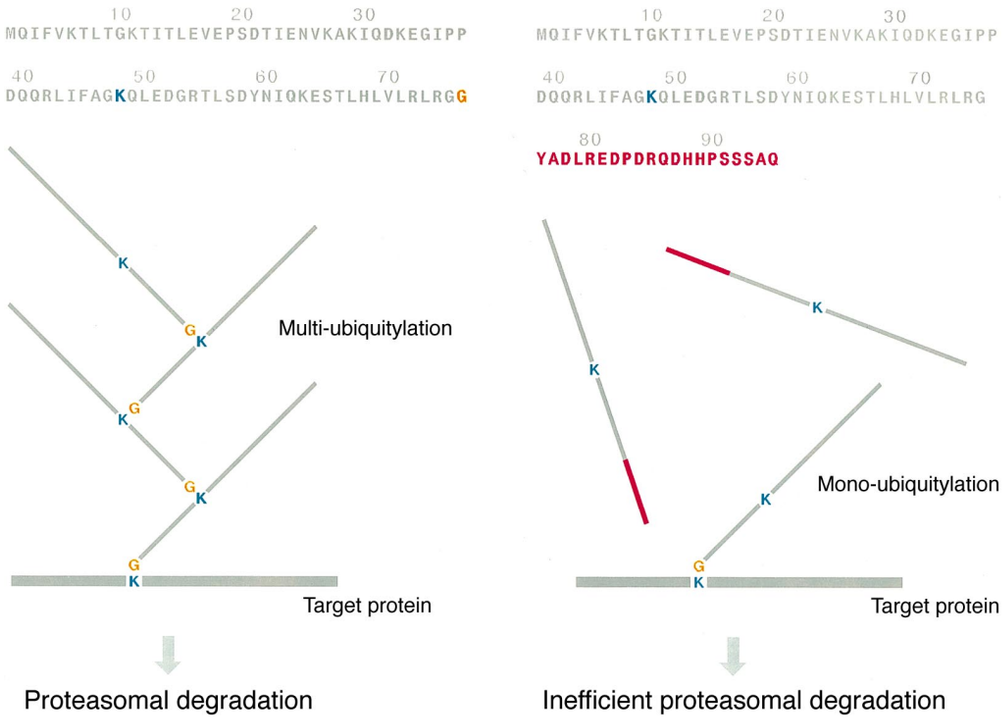

Fig. 3. ***The ubiquitin-proteosomal pathway to degrade aberrant proteins.*** *Under normal circumstances (left side), a lysine (K) residue of the target protein (thick line, for example, hyperphosphorylated Tau or any other protein that is degraded via the proteosomal pathway) is recognized by the C-terminal glycine (G, yellow) residue of ubiquitin-B (Ubi-B). In turn, a lysine residue of Ubi-B at position 48 is recognized by another Ubi-B molecule. If this process is repeated, multi-ubiquitylation occurs, the proteasomal pathway is triggered and the protein is degraded. The right panel shows that a GU deletion in the Ubi-B transcript results in the loss of the G residue and the formation of an aberrant C terminus (red), which blocks the process of multi-ubiquitylation. Only the wild-type transcripts are still able to ubiquitylate. In Alzheimer's disease, however, the Tau protein is mainly mono-ubiquitylated[36]. It is hypothesized that in time (Alzheimer's disease lasts for approximately eight years) the proteasomal degradation becomes increasingly inefficient, resulting in a piling up of aberrant proteins in the neuron whose function is increasingly disturbed.*

life could be an important aging factor, in addition to those already known (such as oxidative stress and DNA damage[46]).

GAGAG motifs and other age-related neurodegenerative diseases

The chance that a GAGAG motif occurs in an mRNA sequence is one in every 1024 (1:4[5]) bases. The human haploid genome consists of 3×10^9 bases, 9×10^7 (3%) of which code for transcripts. This implies that there are 9×10^4 GAGAG motifs within coding sequences. In addition, the human genome consists of 65 000–80 000 genes, with a mean length of 2.2 kb, so that an average of 2.1 GAGAG motifs per gene can be expected[25]. Thus, it is possible that molecular misreading plays a role in other neurodegenerative diseases.

Several genes thought to be involved in other age-related neurodegenerative diseases do contain vulnerable sequences such as GAGAG motifs (Table 1). Candidates are diseases with inclusion bodies such as frontal lobe dementia, amyotrophic lateral sclerosis (ALS) and Lewy body disease, all of which contain Ubi-B, and possibly also Ubi-B^{+1}. The resulting differential pathology might be determined by various other factors (such as other +1 proteins, cell type and risk factors[24]). If no Ubi-B^{+1} and APP^{+1} proteins are present in all these diseases, this would imply that these +1 proteins are specific for AD. However, it is possible that other transcripts are mutated in these diseases.

Future studies

Our major challenge in the next few years will be to find out whether molecular misreading of correct DNA is a primary event in AD. It will be necessary to address the question of whether +1 proteins play a causal role in AD neuropathology in transgenic mice. Whether overexpression of one or two +1 proteins is sufficient to initiate neuropathology will soon be clear. However, it may turn out that multiple +1 proteins are required for a full-blown neuropathology. Therefore, we are undertaking a search for transcripts other than βAPP and Ubi-B that also undergo dinucleotide deletions.

Another important question involves the actual mechanism whereby dinucleotide deletions occur in simple repeats such as GAGAG or CUCU. At present, all that is known is that it is promoted by enhanced transcriptional activity[10,13]. *In vitro* systems (such as cell lines), where transcription can be modulated and cells can be transfected with gene reporter constructs, will be instrumental in elucidating the mechanism involved.

We speculate that the phenomenon of dinucleotide deletion in transcripts is associated with a loss of function of the cellular machinery. The presence of various +1 proteins in one neuron[13] points to such a common denominator. The process of mRNA surveillance[43–45] might be involved in molecular misreading: its activity might be decreased during AD. Recently, a similar mechanism has been suggested to play a role in sporadic ALS where, as a result of RNA processing errors, aberrant mRNA molecules of a glutamate transporter excitatory amino acid transporter can produce a dominant negative effect and interfere with wild-type protein function[47]. If molecular misreading occurs in proliferating cells and can be shown in other age-related diseases, this novel mechanism could explain why age is the greatest risk factor for developing a variety of neural and non-neural pathologies[48].

Selected references

1 **Farbman, A.I.** (1990) *Trends Neurosci.* 13, 362–365
2 **Cameron, H.A., McEwen, B.S. and Gould, E.** (1995) *J. Neurosci.* 15, 4687–4692
3 **Rakic, P.** (1985) *Science* 227, 1054–1056
4 **Schatz, D.G., Oettinger, M.A. and Schlisser, M.S.T.I.** (1992) *Annu. Rev. Immunol.* 19, 359–383
5 **Dollé, M.E.T. *et al.*** (1997) *Nat. Genet.* 17, 431–434
6 **Newman, A.J.** (1994) *Curr. Opin. Genet. Dev.* 4, 298–304
7 **Simpson, L. and Emeson, R.B.** (1996) *Annu. Rev. Neurosci.* 19, 27–52
8 **van Leeuwen, F.W. *et al.*** (1989) *Proc. Natl. Acad. Sci. U. S. A.* 86, 6417–6420
9 **Finch, C.E. and Goodman, M.F.** (1997) *Trends Neurosci.* 20, 501–507
10 **Evans, D.A.P. *et al.*** (1994) *Proc. Natl. Acad. Sci. U. S. A.* 91, 6059–6063
11 **Sonnemans, M.A.F. *et al.*** (1996) *Neuroscience* 72, 225–231
12 **Evans, D.A.P. *et al.*** (1996) *Neuroscience* 71, 1025–1030
13 **van Leeuwen, F.W. *et al.*** (1998) *Science* 279, 242–247
14 **Ott, A. *et al.*** (1995) *Br. Med. J.* 310, 970–973
15 **Braak, H. *et al.*** (1996) *J. Neural Transm.* 103, 455–490
16 **Terry, R.D. *et al.*** (1994) in *Alzheimer Disease*, pp. 179–196, Raven Press
17 **Neve, R.L. and Robakis, N.K.** (1998) *Trends Neurosci.* 21, 15–19
18 **Terry, R.D.** (1996) *J. Neuropathol. Exp. Neurol.* 55, 1023–1025
19 **Blacker, D. and Tanzi, R.E.** (1998) *Arch. Neurol.* 55, 294–296
20 **Scheuner, D. *et al.*** (1996) *Nat. Med.* 2, 864–870
21 **Swaab, D.F. and Salehi, A.** (1997) *J. Neuropathol. Exp. Neurol.* 56, 216
22 **Greenberg, S.M. *et al.*** (1995) *Ann. Neurol.* 38, 254–259
23 **Polvikowski, T. *et al.*** (1995) *New Engl. J. Med.* 333, 1242–1247
24 **Mann, D.M.A. *et al.*** (1997) *Br. Med. J.* 315, 1078–1081
25 **Strachan, T. and Read, A.P.** (1997) in *Human Molecular Genetics*, pp. 147–182, Bios Scientific Publishers
26 **Van Leeuwen, F.W. *et al.*** *Soc. Neurosci. Abstr.* 24 (in press)
27 **Jin, L.W. *et al.*** (1994) *J. Neurosci.* 14, 5461–5470
28 **Citron, M., Haass, C. and Selkoe, D.J.** (1993) *Neurobiol. Aging* 14, 571–573
29 **Morishima-Kawashima, M. *et al.*** (1993) *Neuron* 6, 1151–1160
30 **Evans, D.A.P., Burbach, J.P.H. and van Leeuwen, F.W.** (1995) *Mutat. Res.* 338, 173–182
31 **Neve, R.L., Finch, E.A. and Dawes, L.R.** (1988) *Neuron* 1, 669–677
32 **Rumble, B. *et al.*** (1989) *New Engl. J. Med.* 320, 1446–1452
33 **Kola, I. and Hertzog, Q.J.** (1997) *Hum. Mol. Genet.* 6, 1713–1727
34 **Oyama, F. *et al.*** (1994) *J. Neurochem.* 62, 1062–1066
35 **Varshavsky, A.** (1977) *Trends Biochem. Sci.* 20, 383–387
36 **Ali-Khan, Z. *et al.*** (1992) *Neurosci. Lett.* 139, 24–28
37 **Mann, D.M.A. *et al.*** (1989) *J. Neurol. Sci.* 92, 247–260
38 **Jacques, J.P. and Kolakovsky, D.** (1991) *Gene Dev.* 5, 707–713
39 **Kolakovsky, D. and Hausmann, S.** (1998) in *Modification and Editing of RNA* (Grosjean, H. and Benne, R., eds), pp. 413–420, ASM Press
40 **Radman, M. and Wagner, R.** (1988) *Sci. Am.* 259, 24–30
41 **Kunkel, T.A.** (1995) *Curr. Biol.* 5, 1091–1094
42 **Pulak, R. and Anderson, P.** (1993) *Genes Dev.* 7, 1885–1897
43 **Ruiz-Echevarria, M.J. *et al.*** (1996) *Trends Biochem. Sci.* 21, 433–438
44 **Applequist, S.E. *et al.*** (1997) *Nucleic Acids Res.* 25, 814–821
45 **Perlick, H.A. *et al.*** (1993) *Proc. Natl. Acad. Sci. U. S. A.* 93, 10928–10932
46 **Finch, C.E.** (1990) *Longevity, Senescence and the Genome*, University of Chicago Press
47 **Lin, C-L.G.** (1998) *Neuron* 20, 589–602
48 **Vogel, G.** (1998) *Science* 279, 174

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Erratum

In the Perspectives article entitled "Rembrandt's 'The Anatomy Lesson of Dr. Joan Deijman" by Charles G. Gross, which was published in the June issue of *TINS* (Vol. 21, 237–240), an error was not corrected before publication.

The final sentence should be as follows:
'Today, the original functions of anatomy-lesson paintings are fulfilled by group photographs, usually posed in front of the organization's building or meeting place. The lay functions of the public dissection, namely entertainment, voyeurism and education, are largely carried out by television.'

We apologize to the author and readers.

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