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MINIREVIEW

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Molecular and cell biological aspects of Alzheimer disease

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Abstract Alzheimer disease (AD) is one of several types of chronic and very common dementing disorders, affecting individuals aged 65 years or older. During the last five years, an enormous growth in the field has enriched our understanding of this complex condition. Molecular genetic studies have identified at least three genes that, when mutated, cause the autosomal dominant, early-onset familial form of the disease. The late-onset, most common forms of the disease are likely to be associated with various genetic susceptibility factors. The application of cell biological techniques has given insight into basic aspects of the functions of important proteins involved in disease progression, and transgenic animal studies have further enriched our knowledge of the pathophysiological aspects of the disease. More efficient therapeutic drugs to retard its progression have been developed, as well as techniques to identify the preclinical phase of the disorder. Although we are still lacking the molecular basis and order of events involved in the disease process, the future for AD research, as well as for AD patients, is more promising than ever before.

Key words Alzheimer disease · Amyloid · Presenilins · Mutation · Gene · Oxidative stress

Introduction

In elderly people, dementia with Lewy body (DLB) is the most common cause of mild memory impairment (Perry et al. 1998). This memory impairment is caused by the Lewy bodies, which are composed of plaques and a few neurofibrillary tangles (NFT), in the cortical and brain stem structures. DLB also involves a disruption of the microcolumnar ensemble in the association cortex, but there is minimal neuronal loss. At the onset of illness, however, if DLB involves impaired cognition, it is difficult to distinguish it from another condition, Alzheimer disease (AD), which is the most common of all the dementias (St. George-Hyslop 2000; Selkoe 2001). In patients with AD and the Lewy body variant of AD, cholinergic function is reduced and there are fewer, neocortical synapses and a nearly complete loss of microcolumnar ensembles (Haroutunian et al. 2000; Buldyrev et al. 2000). There is also a population difference in the incidence rate and plaque density between AD and DLB (Hendrie et al. 2001; Lippa et al. 1999). This difference can be of potential use for differentiating the two disorders. Recently, more neuropsychological tests and neurochemical markers have also become available (Shimomura et al. 1998; Sabbagh et al. 1999; Tumani et al. 1999) to distinguish between the two disorders.

AD is the most feared cause of dementia and is an enormous public health burden. Although it is an age-related disease in the very old, not all aged people will develop AD (Ebly et al. 1994). In the past 5 years, an exponential growth in the field has enriched our understanding of this condition with respect to genetic susceptibility factors, clinical diagnoses, biology of mutant genes, and therapy. In this article, an attempt is made to highlight some of these advances. For a detailed account of the topic, readers are requested to consult the other comprehensive reviews cited.

Pathology

AD is a complex, chronic, and genetically heterogeneous neurodegenerative disorder affecting approximately four million people in the United States and 20 million individuals worldwide (Haass and De Strooper 1999). Neuropathologically, it is characterized by the presence of abundant intracellular NFT — mainly consisting of a hyperphosphorylated, microtubule-associated protein called tau — and extracellular senile plaques (SP) contain-

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ing a large amount of a highly fibrillogenic peptide termed β-amyloid peptide (Aβ), which aggregates into β-pleated sheets. These neuropathological changes have also been found in Alois Alzheimer's first patient's brain (Graeber et al. 1998). Clinically, this age-related disorder is characterized by impairment in cognition and memory. It selectively affects the neocortex, hippocampus, amygdala, basal forebrain, and anterior thalamus of the brain. A variability in impairment among cognitive domains has also been reported throughout the course of AD in some patients (Johnson et al. 1999), which suggests that not all cognitive domains are equally affected at a given time. Although the relationship between neuropathological changes and cognitive impairments in AD is not understood, the deposition of NFT (which are also found to be present in non-demented elderly individuals) and SP are considered to be contributing factors to the cognitive deficits (Haroutunian et al. 1999). In addition, cerebrovascular disease can also influence AD pathology and promote dementia (Esiri et al. 1999).

Preclinical phase and diagnostic markers

The clinical feature of AD is chronic impairment of cognitive function. This is accompanied by massive neuronal loss in the hippocampus and frontal and temporal cortices due to the deposition of NFT and SP, although an exception to this has been reported (Poduslo et al. 1999). However, these histological studies have been conducted on postmortem brain tissue of AD patients, and they probably represent the end result of the disease. In order to understand AD and to develop strategies for its treatment and prevention, an earlier detection of its pathology or clinical changes is needed. For this purpose, persons with a mild cognitive impairment that is abnormal for his or her age and education is considered to have the initial preclinical sign of AD (Fox and Rossor 1999; Burns 2000; Small et al. 2000). By using this criterion, attempts have been made to identify the symptoms in individuals at early stages of the disease. A variety of methods, such as measuring the plasma concentration of the 42-residue β-amyloid (Mayeux et al. 1999), selective labeling of SP (Skovronsky et al. 2000), measurement of cerebrospinal fluid β-amyloid (Andreasen et al. 1999), magnetic resonance imaging (MRI, Fox and Rossor 1999), family history of AD, mutational analysis of genes involved in familial AD (Bookheimer et al. 2000), family history of Down syndrome, and use of positron-emission tomography (Rapoport 2000) have been developed. MRI measurement of AD brains has shown a loss of entorhinal cortex volume (Bobinski et al. 1999), and quantitative MRI has become useful to measure cerebral atrophy at the earliest stages of AD (Fox et al. 1999). However, it is not known whether such measurements are useful for correlating with the future development of neuropathological changes (Skoog 2000). In this regard, it is highly desirable to use a combination of molecular genetic markers along with other clinical methods (Growdon 1999).

Genetic factors: early-onset AD

AD is a polygenic and multifactorial disease that accounts for approximately two-thirds of the dementia of late life. Depending on its age of onset, it can be divided into early-onset (before age 60) and late-onset AD (after age 60). Early-onset AD is mostly an inherited dominant disorder. Although causes of sporadic AD, the most common form, are not yet understood, three genes have been found to play an important role in familial autosomal dominant early-onset AD, which is a relatively infrequent but devastating form of the disorder (Selkoe 2001; Emilien et al. 2000; Shastry and Giblin 1999; Shastry 1998; Hardy et al. 1998). Mutations in genes of amyloid precursor protein (*APP*) and presenilins 1 and 2 (*PS1* and *PS2*) have been shown to segregate in familial autosomal dominant early-onset cases of AD (Goate et al. 1991; Rogaeva et al. 1995; Sherrington et al. 1995; Murrell et al. 2000; Van Duijn et al. 1999; Yasuda et al. 1999; Dermaut et al. 1999). Mutations in *APP* (chromosome 21) and *PS2* (chromosome 1) are believed to account for less than 1% of all cases, whereas mutations in *PS1* (chromosome 14) may account for more than 40% of early-onset cases of familial AD (Lendon et al. 1997; Campion et al. 1999). Although the physiological roles of APP and PS are beginning to be understood, most familial AD mutations cause an increase in the production of the more amyloidogenic peptide (PS1 mutations affect the cleavage of APP at the amino-terminal end) that aggregates to form amyloid deposits (Lichtenthaler et al. 1999; Scheuner et al. 1996; Russo et al. 2000; Drouet et al. 2000). Since the above mutations account for less than 7% of AD cases and most AD cases are late-onset and sporadic, additional genes are likely to play roles in AD (Daw et al. 2000). In this respect, it is interesting to note that genetic polymorphism in the promoter region of the phenylethanolamine N-methyltransferase gene is associated with early-but not late-onset AD (Mann et al. 2001).

Late-onset AD

Because traditional genetic methods are difficult to apply to late-onset disorders (they exhibit more complex modes of inheritance, and only a limited number of affected individuals from a recent generation have been identified), most genetic susceptibility factors have been identified on the basis of their biological functions. In addition, other methods such as population-based linkage disequilibrium have been employed (Daw et al. 1999). These analyses have identified susceptible loci on chromosomes 1, 9, 10, 12, and 13 for late-onset AD (Kehoe et al. 1999; Hiltunen et al. 1999; Scott et al. 1999; Ertekin-Taner et al. 2000; Bertram et al. 2000; Myers et al. 2000). Additionally, late-onset AD is associated with genetic polymorphisms in genes for apolipoprotein E (APOE) (Saunders et al. 1993; Corder et al. 1993); presenilin-1; butyrylcholine esterase K, an enzyme that can hydrolyze choline esters including acetylcho-

line (Tilly et al. 1999); very low-density lipoprotein receptor (McIlroy et al. 1999); lipoprotein lipase, which hydrolyzes triglycerides (Baum et al. 1999); choline acetyltransferase (Baskin et al. 1999); deficiency in aldehyde dehydrogenase-2, which metabolizes acetaldehyde produced from ethanol to acetate (Kamino et al. 2000); estrogen receptor α (Brandi et al. 1999); low-density lipoprotein receptor-related protein, which is a receptor for APOE; α-2-microglobulin, which is a serum protease inhibitor (Wavrant-DeVrieze et al. 1999; Alvarez et al. 1999); α-1-chymotrypsin inhibitor; bleomysin hydrolase (see review by Shastry and Giblin 1999); myeloperoxidase; dihydrolipoylsuccinyl transferase; N-acetyl transferase; angiotensin-converting enzyme; cathepsin D; transferrin; human leukocyte antigen (HLA) (A2 allele); seretonin receptor; interleukin-6 (Tanzi 1999); cystatin C (Finckh et al. 2000); and transcription factor LBP-1c/CP2/LSF (Lambert et al. 2000). It is possible that these genes act as risk factors for or a genetic modifier of the more common forms of late-onset AD. Although some of the above reports are controversial or refuted by others (Wang et al. 2001; Maruyama et al. 2000; Farrer et al. 2000; Small et al. 1999; Graeber 1999; Ki et al. 1999), these genes are still valuable because such variability in effect may be population specific and may increase the genetic susceptibility of the disease in certain populations.

Functions of APOE

Among the above susceptibility factors, the *APOE* gene has been widely accepted as a risk factor (Ganguli et al. 2000; Raber et al. 2000) and has been extensively studied. The *APOE* gene has three alleles called ε 2, ε 3 and ε 4, and the most common allele is the ε 3. The presence of the ε 4 allele of the *APOE* gene (chromosome 19) is found to accelerate the age of onset of familial AD (early-onset) and to increase the risk of developing the sporadic form of AD (late-onset). Those patients with two ε 4 alleles are at a higher risk, while ε 2 alleles have protective effect (the first Alzheimer patient of Alois Alzheimer had genotype ε 3/ε 3). APOE is involved in the transport of cholesterol (Porer 1994), and in the normal brain, it efficiently binds to β-amyloid protein (Aβ). This interaction may prevent the toxic aggregation of Aβ. In AD, this property is presumably lost, thus facilitating the accumulation of Aβ and the resulting plaque formation. APOE also binds to ciliary neurotrophic factor (CNTF) and potentiates its biological activity on hippocampal cells (Gutman et al. 1997). It has also been shown that isoform-specific APOE promotes deposition and fibrillization of Aβ and neuritic degeneration (Bales et al. 1999; Holtzman et al. 2000). Although APOE's association with AD is well recognized, its role in the pathogenesis of AD is not clear. It is neither required nor sufficient to cause AD, nor is it useful in improving diagnosis (Russo et al. 1998; Tsuang et al. 1999).

Biology of APP and the PSs

In the past 5 years, the most active area of research has been focused on the study of the biology of APP and the PSs (De Strooper and Annaert 2000; Sisodia 1999; Selkoe 1998; Thinakaran 1999; Checler 2001). These studies have helped to resolve the decade-long question as to whether the formation of plaques or tangles is the first or earliest event in the development of AD. It is now believed that the deposition and formation of plaques is the beginning of the clinical progression of AD because the Aβ level in the brain is increased in the frontal cortex before tau pathology is present (Naslund et al. 2000). This increase in the Aβ level is also correlated with cognitive decline.

The Aβ (a 40–42 residue peptide) is the major constituent of the extracellular SP and is generated by two successive proteolytic cleavages of β-APP. One enzyme, β-secretase, cleaves the N-terminus of APP, and the other, χ-secretase, generates the C-terminus. APP functions as a membrane receptor (Kang et al. 1987) and as a secreted derivative that acts upon other cells. It undergoes phosphorylation, N- and O-glycosylation, and sulfation. It is ubiquitously expressed, and the 695-residue isoform is more abundant in the nervous system, whereas the 751/770 amino acid spliced form is found in nonneuronal cells. APP is highly conserved, and it may mediate cell–cell adhesion (Breen et al. 1991) and stimulate neurite outgrowth (Kibbey et al. 1993).

As mentioned above, AD begins with the deposition of Aβ, and its neurotoxicity is attributed to its ability to form fibrils and to its aggregation (Lorenzo and Yankner 1994; Pike et al. 1991; Lorenzo et al. 2000). This Aβ toxicity may involve increased production of free radicals (Behl et al. 1994), Aβ-induced tau phosphorylation (Busciglio et al. 1995), interaction with the endoplasmic reticulum-associated binding protein (Yan et al. 1997), binding to the PSs (Dewji and Singer 1998) and binding to APP at the neuronal membrane (Lorenzo et al. 2000). The interaction between Aβ and APP is analogous to the pathogenic mechanism proposed for prion disease, in which the abnormal form (PrP-Sc) causes the normal form (PrP-C) of prion protein to form plaques (Lorenzo et al. 2000), which are believed to cause cell death. Additionally, a deficiency in neprilysin (Aβ-degrading protease) could contribute to AD by preventing the degradation of Aβ (Iwata et al. 2001), and the accumulation of Aβ aggregates may impair the function of the ubiquitin-proteasome system, thereby making it directly responsible for the neuronal degeneration (Bence et al. 2001).

Presenilins 1 and 2 are serpentine-like, membrane-bound, highly homologous and conserved proteins, mainly localized in the endoplasmic reticulum and Golgi apparatus (De Strooper et al. 1997, 1999; Haass and De Strooper 1999). PS1 is a 467-amino-acid polypeptide synthesized as a zymogen that undergoes endoproteolysis to give a 30-kDa N-terminal and a 20-kDa C-terminal fragment. Both fragments are needed for its activity, and both PS1 and PS2 are ubiquitously expressed in all tissues and cell lines (Haass

and De Strooper 1999). In detergent-solubilized, cultured human cells, PS1 has been shown to possess χ-secretase activity that can be inhibited by the transition-state-specific inhibitor pepstatin and that also can be precipitated by anti-PS1 antibody. The partially purified protein requires two conserved transmembrane (TM) aspartates (Asp 257 in TM 6 and Asp 385 in TM 7) for its catalytic activity. Substitution of either of these residues inactivates χ-secretase activity (Wolfe et al. 1999a, b; Selkoe and Wolfe 2000; Li et al. 2000; De Strooper and Annaert 2000; de Strooper 2000; Sisodia 2000; Octave et al. 2000; Wolfe 2001; Small 2001; Wolfe and Haass 2001; Zhang et al. 2001).

PS1 regulates APP processing (Palacino et al. 2000; Marambaud et al. 1998; Xia et al. 1998, 2000) and complexes with the C-terminal fragment of APP. It has a role in Notch signaling (Ye et al. 1999; Struhl and Greenwald 1999; De Strooper et al. 1999; Hardy and Israel 1999; Ray et al. 1999; Steiner et al. 1999), in neuronal differentiation during neurogenesis (Handler et al. 2000), and in nuclear accumulation of Ire-1 protein. Ire-1 is a bifunctional endoplasmic transmembrane protein that functions as a sensor that detects changes in the concentration of unfolded proteins (Niwa et al. 1999; Katayama et al. 1999). PS1 in association with various other proteins mediates cell survival and cell fate through signal transduction and vesicular trafficking, and a mutation in its gene causes defective trafficking of β-catenin, which is involved in Wnt signaling (Takashima et al. 1998; Zhang et al. 1998a, b; Smine et al. 1998; Buxbaum et al. 1998; Nishimura et al. 1999; Tanahashi and Tabira 2000). Thus, PS1 interaction with a variety of proteins shows that it potentially functions in signaling, apoptosis, intracellular calcium homeostasis, cytoskeleton stabilization, and cell–cell adhesion. All of these most likely play an important role in the development of AD (Boothwell and Giniger 2000).

Functions of tau

The microtubule-associated phosphoprotein tau is the major constituent of intraneuronal NTF, and its unusual phosphorylation followed by aggregation has been suggested to be a cause of neuronal degeneration (Mandelkow and Mandelkow 1998; Billingsley and Kincaid 1997). It is a highly soluble protein that occurs mainly in axons. It is necessary for the outgrowth of neurites, and it stabilizes neuronal microtubules, which are reported to protect neuronal cells against Aβ-induced toxicity (Michaelis et al. 1998), implying that neurodegeneration may involve damage to the cytoskeleton. Surprisingly, however, mice lacking tau have few defects (Harada et al. 1994). The tau protein contains an acidic N-terminal, a basic proline-rich middle, and a C-terminal domain. There are six isoforms of tau (352–441 amino acids) in the human brain. They are rich in serine and threonine, and can be phosphorylated at more than 20 residues (in AD) by many kinases, including cyclin-dependent kinase 5 (Cdk-5) and cell-cycle kinase (cdc-2). When tau is phosphorylated at serine 262 or at serine 214 (in an AD brain), it detaches from the microtubules, causing their breakdown.

Tau hyperphosphorylation is believed to occur before aggregation, and, hence, it is considered to be the earliest sign of neurodegeneration in AD. Dimerization and nucleation are necessary for the formation of paired helical filaments, and this process depends on a ligand mechanism, so tau hyperphosphorylation is not considered responsible for its aggregation (Friedhoff et al. 1998; King et al. 1999; Schneider et al. 1999). The hyperphosphorylated tau from an AD brain binds to a prolyl isomerase, pin 1, which is also a component of paired helical fragments and is localized in the neuronal cells (Lu et al. 1999; Goeredt 1999). The significance of this interaction in causing AD is not clear at present. However, aggregation followed by breakdown of intracellular transport appears to be a reasonable explanation for the neuronal degeneration in AD.

Neuroinflammation, oxyradicals, and oxidative stress

There are other factors that are also thought to contribute to the neurodegenerative process of AD, and these include neuroinflammation, oxyradicals, and oxidative stress. There is some evidence that the immune system plays a role in the brain inflammatory process. Deposition of Aβ may activate microglial cells (which aggregate along the plaques and tangles), which may be involved in the inflammatory process. Consistent with this is the observation that inflammatory cytokines are linked to the clinical progression of AD dementia, and anti-inflammatory drugs can enhance cognitive performance. Region-specific imbalance of neurotrophin, which supports the survival, differentiation, and maintenance of neurons, is likely to be another factor contributing to the degeneration of specific neurons in the hippocampal and cortical area (Tan et al. 1999; McGeer and McGeer 2000; Halliday et al. 2000; Shepherd et al. 2000; Leturman et al. 2000; Hock et al. 2000).

Metal-mediated oxyradical and peroxide formation and aggregation of Aβ; the increase in the frequency of mitochondrial DNA mutation in the hippocampus and cerebellum of an AD brain; an increase in the oxidation of lipids, carbohydrates, proteins, and DNA (Markesbery 1999); an increased level of oxidative stress-related enzymes (superoxide dismutase, hemeoxygenase-1, glucose-6-phosphate dehydrogenase); and decreased activity of glutathione transferase support the notion that oxidative stress may cause neuronal and ischemic brain injury in AD (Gabbita et al. 1998; Behl 1999; Huang et al. 1999; Liu et al. 1999; Chang et al. 2000). It is conceivable that brain tissue is particularly sensitive to free radicals because it lacks large amounts of antioxidants when compared to many other tissues. Cell culture and transgenic animal studies also demonstrate an increased production of free radicals in neurons (Mattson 1997). However, it is not known whether free radicals are the primary cause or the end result of AD. Long-term antioxidant therapy before the preclinical phase of the disease

may shed some light on the efficacy of antioxidants as drugs to retard the progression of AD.

Animal models

Various lines of transgenic mice have been developed by overexpressing APP, mutant APP and the PSs, the C-terminal fragment of APP, and the APOE ε 4 allele. These mice produced a variety of phenotypes, among which some features are similar to human AD. For instance, mice overexpressing human mutant APP exhibited memory deficits and amyloid plaque deposition (Games et al. 1995; Hsiao et al. 1996; Sturchler-Pierrat et al. 1997; Lamb et al. 1999; Chen et al. 2000), while mice harboring PS mutations exhibited increased production of amyloid β peptide 42/43, increased neurodegeneration, mild pulmonary fibrosis and hemorrhage, and disturbance of calcium homeostasis (Duff et al. 1996; Holcomb et al. 1998; Herreman et al. 1999; Guo et al. 1999a, b; Chui et al. 1999; Schneider et al. 2001). Additionally, mice carrying human the APOE ε 4 allele but not the ε 3 allele showed impaired cognitive performance (Raber et al. 2000). Interestingly, mice lacking the high affinity nicotine receptor (β 2 subunit of the nicotinicacetylcholine receptor) exhibited loss of hippocampal neurons and alterations in the cortical region during aging (Zoli et al. 1999). Although these mice have provided some valuable information on human AD and can be used as an assay system, none of them are considered to be a fully equivalent model for human AD. This is supported by the fact that the chemical structure and morphology of transgenic mouse plaques are not equivalent to those of human AD. If such differences are found to be widespread between animal systems and human AD, then the development of therapeutic drugs using animal models may be hampered (Kuo et al. 2001).

Treatment

At present, it is a strongly held view that AD begins with the deposition of large numbers of SPs (this is known as the amyloid hypothesis), which then induce NFTs. These then lead to neuronal dysfunction, resulting in the clinical appearance of symptoms, and death (Morris 1999). Alternatively, NFTs initiate the cascades of events that ultimately result in recognizable symptoms of AD. If either of these hypotheses is correct, then, theoretically at least, it is possible to interfere with the progression of the disorder by reducing or inhibiting the formation of SPs or NFTs (Wagner and Munoz 1999) in the brain. For instance, development of specific inhibitors of β- and χ-secretase should help by reducing the production of SPs and NFTs in the AD brain. A hopeful approach will be to begin antidementia treatment before the disease strikes. Regenerating the damaged nervous system is an alternative approach, although it is not readily applicable at present (Horner and Gage 2000; Selkoe 1999).

Drugs that inhibit acetylcholine esterase (e.g., tacrine and donepezil) are the most recent development in the treatment of AD, but side effects such as nausea, hepatotoxicity, vomiting, and abdominal pain, as well as their marginal benefit for the patients, have severely limited their use (Flicker 1999). Additionally, many companies are developing more specific and powerful inhibitors, but whether these drugs will make a difference for patients with respect to their daily living activities and cognitive functions without any unacceptable side effects remains to be determined (Mayeux and Sano 1999; De Strooper and Konig 1999). An equally efficient method to reduce the production and deposition of Aβ is Aβ peptide immunization. Recently, some success has been reported in animal models with this approach (Schenk et al. 1999; Janus et al. 2000; Morgan et al. 2000). Because several molecular targets and animal models are now available, it is hoped that an effective therapy for this devastating disorder will be developed in the near future.

Concluding remarks

A voluminous body of literature in the field suggests that gene mutations cause genetically inherited, early-onset AD, while the most common form, late-onset AD, is likely due to genetic risk factors (Tanzi 1999). Although research has grown exponentially during past 5 years and cell biological functions of APP, PSs, and APOE are beginning to be understood, we are still lacking the molecular basis and order of events involved in the disease process. The currently held view (amyloid hypothesis) is that AD begins with the deposition of large numbers of SPs. This then sets up a series of events, including alteration of tau, which in turn lead to neuronal dysfunction and dementia. Although there is a wealth of information suggesting that Aβ deposition occurs before NFT formation, there is no compelling evidence for the toxicity of Aβ in AD pathogenesis. Amyloid deposits have also been found in normal brains as well as in nondemented elderly individuals (Wujek et al. 1996; Neve and Robakis 1998). There is also no correlation between the density of SPs and the degree of dementia. However, NFTs are correlated with dementia. Additionally, the existence of neuronal cell death prior to Aβ deposition brings into question the primary role of Aβ in AD pathogenesis (LaFerla et al. 1997). Thus, the amyloid hypothesis cannot explain all of the molecular and cellular events in AD. It remains to be seen whether clumps of Aβ are toxic and give rise to dementia and what happens to these deposits in the later stage of the disease. Another interesting approach is to investigate whether nondemented but aged families contain any additional protective factors similar to APOE (Silverman et al. 1999). The future for AD research is more promising than ever before.

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