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Neurodegenerative disease and adult neurogenesis

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Abstract

The generation and cell death of newly generated cells have critical roles in brain development and maintenance in the embryonic and adult brain. Alterations in these processes are also seen in neurodegenerative diseases. Genes that are key players in neurodegenerative diseases (α-synuclein, presenilin-1, tau, huntingtin) are also physiologically involved in modulating brain plasticity. Interestingly, in some neurodegenerative diseases, the specific alterations in neurogenic areas such as the dentate gyrus and subventricular zone/olfactory bulb system parallel the early or premotor symptoms that are seen in the early stages of these diseases, such as depression, anxiety or olfactory dysfunction. We will review the modulation of neurogenesis in animal models and human brains of Parkinson's disease, Huntington's disease and Alzheimer's disease.

Introduction

Why study neurogenesis in neurodegenerative diseases?

It might sound like a paradox to study an age-related disease in a newly generated young neuron. However, the elimination of axons, dendrites and synapses is a common theme during development of the nervous system and in response to acute or chronic injury (reviewed in Luo & O' Leary, 2005). Similarly, the generation and cell death of newly generated cells have critical roles in brain development and maintenance in the embryonic and adult brain, and alterations in these processes are seen in neurodegenerative diseases. Genes that are key players in neurodegenerative diseases [α-synuclein, presenilin (PSEN)1, tau, huntingtin] are also physiologically involved in modulating brain plasticity in the embryonic brain, specifically as membrane proteins and when concentrated in synapses. These proteins commonly show high conservation between species and are located close to membranes or are involved in microtubule transport. α-Synuclein is a protein that is physiologically enriched in presynaptic termini (Abeliovich *et al.*, 2000). Initially shown to be upregulated in a discrete population of presynaptic terminals of the song bird brain during a period of acquisition-related synaptic rearrangement (George *et al.*, 1995), α-synuclein can interact with tubulin (Alim *et al.*, 2002). In addition, it is involved in dopamine (DA) synthesis, metabolism and release, and slight changes in concentration can have vast effects on neurotransmitter release (Nemani *et al.*, 2010). α-Synuclein belongs to a highly conserved family of proteins; whereas α-synuclein knock-out mice and αβ-synuclein knock-out mice only present with subtle deficits, prominent age-dependent changes in synaptic protein composition and axonal structure lead to severe neuronal dysfunction in the central nervous system in αβγ-synuclein knock-out mice (Greten-Harrison *et al.*, 2010). PSENs are a family of transmembrane proteins that function as a part of the γ-secretase protease complex and have high conservation between species. Presenilin 1 (PSEN1) is not only prominently expressed in the embryonic brain but is also a key regulator in Notch and Wnt signaling. In this respect it has an important role in the developmental maturation of glia and neurons (Lee *et al.*, 1996). Tau is a highly soluble microtubule-associated protein that modulates the stability of axonal microtubules, but it is not present in dendrites and is mostly found in neurons rather than non-neuronal cells (Weingarten *et al.*, 1975). Huntingtin is a cytoplasmatic protein that has a role in vesicular trafficking but also functions in transcriptional regulation, and nucleo-cytoplasmatic shuttling and synaptic functions are proposed (Caviston & Holzbaur, 2009).

Interestingly, in Parkinson's disease (PD) and Huntington's disease (HD), the specific alterations in neurogenic areas such as the dentate gyrus (DG) and subventricular zone (SVZ)/olfactory bulb (OB) system parallel the early or premotor symptoms that are seen in the early stages of neurodegenerative disease, such as depression, anxiety or olfactory dysfunction (Simuni & Sethi, 2008). Therefore, it is intriguing that the mechanisms of neurodegenerative diseases are closely linked to brain plasticity.

Brain plasticity in the adult, originally conceived of as changes at the level of synaptic transmission, synaptic contacts and gene expression (reviewed in Buonomano & Merzenich, 1998), became a more complicated concept when the continuous generation of neural

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stem cells (NSCs) in the adult was first reported by Altman and colleagues. They reported a constitutive production of new neurons in the hippocampal DG (Altman & Das, 1965) and in the SVZ/OB system (Altman, 1969). These newly generated neurons had the electrophysiological properties of functional neurons, connected with neighboring cells, and integrated into existing neuronal circuits (van Praag *et al.*, 2002; Carleton *et al.*, 2003). These findings overturned the long-held belief that the mammalian brain is a postmitotic structure incapable of generating new neurons. Adult neurogenesis involves several crucial steps, including the asymmetric cell division of a stem cell, resulting in one daughter stem cell and one with the potential to develop into a neuron. Next, the newly generated neuroblast migrates to its final and appropriate destination in the brain, and the new neuron matures and integrates by forming efferent and afferent connections with neighboring cells (reviewed in Zhao *et al.*, 2008).

As described elsewhere in this issue (Lie, Kempermann, Kokaia and Hen), many layers of modulation and regulation of adult neurogenesis have been identified, including a variety of transcriptional and epigenetic regulation and signaling pathways but also environmental factors, age and diseases such as neurodegenerative diseases. The hippocampus- or OB-dependent functions in the formation of new memories, acquisition of new skills and olfactory learning may in part be attributable to adult neurogenesis at different stages (reviewed in Mu *et al.*, 2010; Aimone *et al.*, 2010; Ma *et al.*, 2010).

Human brain diseases are studied by analyzing neuropathological abnormalities in postmortem brain tissues. These brain tissues are not always well-preserved samples but rather often represent the end-stage of the disease. A significant difficulty in understanding adult neurogenesis in these diseases comes from restrictions in labeling methods of neuroblasts in the human adult brain. Some reports describe doublecortin (DCX) as a marker of neurogenesis in the adult human hippocampus; however, the morphology of these cells is somewhat different from rodent brains (Knoth *et al.*, 2010) and it remains questionable how well preserved the stained cells in human brains are and how they reflect the generation of new neurons. Moreover, DCX immunoreactivity appears to be rapidly reduced with increasing postmortem delay in rodent and human tissue (Boekhoorn *et al.*, 2006; Monje *et al.*, 2007). Improvements in imaging techniques, as previously described in neurogenesis reporter mice (Couillard-Despres *et al.*, 2008), will lead to the development of techniques that hopefully will permit labeling newly generated cells. Progress in spatially resolved spectroscopy *in vivo* is still limited, as the signals reported for NSCs in magnetic resonance spectroscopy (e.g. lipid signal at 1.28 ppm) (Manganas *et al.*, 2007) are not yet specific for reflecting NSCs, but may also indicate cell death (Ramm *et al.*, 2009).

Transgenic animal models mimic some aspects of a disease but, in rare cases, the transgene is expressed as observed in the human brain. The transgenic animals usually only present some, but rarely all, of the neuropathological findings in the respective brain regions. In contrast, the transgenes are in many cases strongly expressed in many brain regions, including regions of adult neurogenesis. Whether impaired adult neurogenesis contributes to deficits observed in neurodegenerative diseases is still not clear; however, impaired olfaction and hippocampus-related cognitive and emotional impairment are common findings in many different neurodegenerative diseases. The analysis of adult neurogenesis offers a unique chance to analyze the biology of NSCs in a pathological adult environment. Understanding how and at what level of development the generation of NSCs is impacted in brain diseases involving neurodegeneration will help to better understand these disease conditions at a cellular level. Understanding neurogenesis in neurodegenerative disease will lead to the identification of disease-relevant signaling pathways and compounds for disease modification; an additional goal might be to use stimulation of endogenous NSCs as a means to induce neuroregeneration.

Neurodegenerative diseases comprise a wide range of diseases that share the common characteristic of progressive loss of structure or function of neurons and glial cells in the brain and spinal cord. Many neurodegenerative diseases are a result of neuronal loss, although glial cells are also involved (Glass *et al.*, 2010). Although neuronal degeneration predominantly affects or starts with specific neuronal populations [including DAergic neurons in PD, striatal medium spiny neurons in HD, motor neurons in amyotrophic lateral sclerosis, and cortical and hippocampal neurons in Alzheimer's disease (AD)], there are many similarities between different neurodegenerative disorders. These include atypical protein assemblies and oligomerization as well as induced cell death. At a late disease stage, protein aggregation is no longer restricted to specific brain regions.

Although both endogenous NSCs and fetal cell transplantation have been tested up to clinical studies (extensively reviewed in Lindvall & Kokaia, 2010), we will limit our review to the aspects of endogenous generation of new neurons in the adult brain.

Adult neurogenesis increases after several acute pathologic stimuli, including stroke, seizure and acute trauma (Arvidsson *et al.*, 2002; Rice *et al.*, 2003; Parent, 2007). Neurodegenerative diseases present a chronic and slowly progressive process. Neurons in neurodegenerative diseases are affected by neuronal dysfunction at the level of synaptic transmission, synaptic contacts, and axonal and dendritic degeneration. In different neurodegenerative diseases, neurite degeneration and cell loss of neurons are present within specific neurotransmitter populations. In addition, numbers of functional neurons in neurogenic regions, and adult neurogenesis are altered or decreased. Brain regions differ in their vulnerability to aging; some regions that are very sensitive to age-related neurodegenerative changes are the DG of the hippocampus, subiculum (Small, 2003) and OB (Braak *et al.*, 2003).

Chronic neurodegeneration has different impacts on stem cell maintenance, proliferation, survival and functional integration. We will restrict our review to age-related neurodegenerative diseases and describe recent findings in AD, PD and HD.

Alterations in adult neurogenesis in different neurodegenerative diseases

When comparing studies of adult neurogenesis in animal models of neurodegenerative diseases, the results seem very diverse and variable. There are differences between different studies in transgenic animals. The models vary in promoters used, age of the animal and age of onset of the disease, transgene expression, neurotransmitter content and amount of overexpression/loss of the disease-causing protein. The amount of overexpression of the respective proteins is especially variable, depending on whether transgene knock-in is performed into knock-outs of the same gene, which would more closely model the disease situation. The gene encoding the mutant precursor protein remains in its normal chromosomal location. In many transgenic animal models, the transgene is added with the existing functional gene.

Alzheimer's disease

The pathology of AD includes neuronal and synaptic loss, neurofibrillary tangles due to hyperphosphorylated tau proteins and deposition of amyloid-β (Aβ) protein in senile plaques in the basal forebrain cholinergic neurons as well as in the cortex, hippocampus and amygdala (Hardy & Selkoe, 2002). Aβ is the product of proteolysis of

amyloid precursor protein (APP) by β- and γ-secretase enzymes (reviewed in Crews *et al.*, 2010b). Aβ accumulates intracellularly in the neuronal endoplasmic reticulum but also extracellularly (Trojanowski & Lee, 2000; Cuello, 2005). Although Aβ plaques are the neuropathological hallmarks of AD, the small Aβ oligomeric species rather than its amyloid counterpart is thought to be the toxic culprit in the disease. Evidence for this assumption includes a correlation between oligomerization and memory deficit in both transgenic mice and humans, the presence of oligomers in the brains of transgenic mice, the toxicity of Aβ dimer and trimer measured by long-term potentiation, and lack of a good correlation between plaque amount and AD (at least in the early phase of the disease) (Walsh *et al.*, 2002; Walsh & Selkoe, 2007). Patient deficits include olfactory deficits, memory impairment, cognitive and functional decline, and death. These symptoms can be partly related to regions and functions of adult neurogenesis.

Genetic studies have identified familial, early-onset and autosomal dominant mutations for AD. Expression of different mutant genes, among them those encoding APP, PSEN1 and presenilin 2 (PSEN2), causes familial AD.

These mutations provide insight into the molecular mechanisms underlying AD in both its familial and sporadic forms. They enhance the Aβ42 : Aβ40 ratio and result in toxic Aβ oligomers and deposition of the Aβ42 peptide in Aβ plaques (Selkoe, 1998; Walsh & Selkoe, 2007). A variety of mouse models expressing mutant forms of APP and combinations thereof have been generated (reviewed in Crews *et al.*, 2010b). APP mutations include mutations in the N- and C-terminal domains that result in the accumulation of intracellular and/or extracellular Aβ species (i.e. K670N/M671L, Swedish mutation; V717I, London mutation; V717F, Indiana mutation). Mutations in the central Aβ region lead to the development of amyloid angiopathy (i.e. D23N, Iowa mutation). Presenilin is the catalytic component of γ-secretase, which is responsible for the intramembranous proteolysis of membrane proteins, including APP (De Strooper, 2003). At the same time, presenilin plays a role in regulating the Notch and Wnt signaling mechanisms and is responsible for developmental maturation of glia and neurons (Gaiano & Fishell, 2002). γ-Secretases sequentially cleave the notch receptor to generate a notch intracellular domain (Kojro & Fahrenholz, 2005). The notch intracellular domain activates nuclear genes such as hairy and enhancer of split 1 (HES1) and hairy and enhancer of split 5 (HES5) to facilitate neurogenesis during development and damage repair (reviewed in Kopan *et al.*, 2009).

For AD research, a model of great interest is the triple transgenic model [overexpression of Swedish mutant APP, mutant P301L Tau in a homozygous mutant of presenilin 1 (M146V)] knock-in mouse. These mice develop hippocampal tangle-like pathology, neurological deficits and Aβ deposition (Crews *et al.*, 2010b).

In different transgenic models, adult neurogenesis is compromised in AD and precedes neuronal loss; dysfunctional neurogenesis, both decreased and increased, has been reported for AD transgenic models in both regions of adult neurogenesis (reviewed in Lazarov & Marr, 2010; Marlatt & Lucassen, 2010). Experimental conditions largely differ, depending on the use of PSEN1, PSEN2 or different APP single mutations, knock-ins or combinations thereof. In addition, bromodeoxyuridine (BrdU) regimens, doses, time points analyzed after BrdU treatment, genetic backgrounds of the mice, and regions investigated vary considerably in all of the studies and have been extensively reviewed elsewhere (Lazarov & Marr, 2010; Marlatt & Lucassen, 2010), as summarized in Tables 1 and 2. Promoters determine specific neuronal populations and topographical distribution of the transgene. For example, the use of the platelet-derived growth factor (PDGF) promoter results in the production of diffuse plaques (Mucke *et al.*, 2000), whereas prion protein and mouse THYmocyte differentiation antigen 1 (mThy1) promoters favor plaque formation in the hippocampus and neocortex. In human AD, Aβ42 is broadly distributed. It can be found intracellularly and extracellularly and in and around vessels, specifically in a condition known as cerebral amyloid angiopathy, where amyloid is found to cause vascular fragility and hemorrhages (reviewed in Pezzini *et al.*, 2009). One difficulty in characterizing adult neurogenesis in AD is that it is difficult to delineate autonomous and non-autonomous effects of AD pathology on NSCs in the stem cell niche. In an aged APP23 transgenic mouse model of cerebral amyloidosis with strong Aβ deposits, Ermini *et al.* (2008) reported a decrease of quiescent astrocyte type 1-like cells, in conjunction with strong attraction of granule cell layer-derived new neurons by Aβ deposits.

Under many conditions, adult neurogenesis is impaired in transgenic AD models (reviewed in Lazarov & Marr, 2010), specifically when a single mutation of PSEN1 (Wang *et al.*, 2004; Wen *et al.*, 2004; Choi *et al.*, 2008) was studied. Although a single APP transgene mutation (Indiana mutation) has only negative effects on adult neurogenesis at an aged and symptomatic stage after amyloid deposition (Donovan *et al.*, 2006), double and triple mutations of APP (APP Swedish and Indiana) under many circumstances result in increased proliferation and, in some cases, survival of new neurons (Haughey *et al.*, 2002a,b; Mirochnic *et al.*, 2009). BrdU injection paradigms differ between the different experiments as well as the BrdU cell numbers reported. Another possible explanation of these divergent results of increased or decreased proliferation in AD transgenic models might be other responses to damage due to protein overexpression, such as glia activation or aberrant cell cycle changes, as described in other brain regions (Yang *et al.*, 2001; Varvel *et al.*, 2009). These might in turn trigger either neurogenesis or pathology.

An important study in adult neurogenesis was performed in a commonly used AD model, the triple transgenic mice (3× Tg-AD) harboring three mutant genes (APP, PSEN1 and tau). Decreased proliferation was found in male 3× transgenic-AD mice. This reduction in proliferation was directly associated with the presence of Aβ plaques and an increase in the number of Aβ-containing neurons in the hippocampus, which, in the case of 3× gTg females, was directly correlated (Rodriguez *et al.*, 2008).

Longer dendrites, increased spine density and functional responses in early-stage, newly generated neurons in APP transgenic mice have recently been reported (Sun *et al.*, 2009), possibly as compensatory mechanisms. During later maturation, the morphology and functionality of these newly generated neurons were impaired, suggesting that an imbalance in GABAergic and glutamatergic neurotransmission was present in APP models. Longer time periods after BrdU injection and more retroviral labeling studies will therefore be necessary for future studies of adult neurogenesis. Detailed studies of the dendrites and spines of the newly generated neurons and their functional integration in different animal models will add important information.

How the slow neurodegenerative process may also induce NSC proliferation is still a matter of debate. An important experiment would be to dissect out the impacts of intracellular vs. extracellular effects of Aβ on newly generated neurons. Neural differentiation was increased *in vitro* when Aβ peptide was added to striatal and hippocampal NSCs (Lopez-Toledano & Shelanski, 2004). Sisodia and colleagues studied the NSC autonomous vs. non-autonomous effect by performing coculture experiments of NSCs and microglia derived from PSEN mutants or controls. They reported a strong decrease in proliferation and neuronal lineage commitment when wild-type NSCs were cocultured with PSEN1 mutated microglia (Choi *et al.*, 2008). These

TABLE 1. Exemplary results for analysis of adult neurogenesis in neurodegenerative diseases in the hippocampal DG

Animal model	Citation	Promoter/lesion	Age/species	Stem cells	Proliferation (SGZ)	Neuroblasts	Survival	Cell death
AD								
Transgenics/genotype								
APP_{Ind}	Donovan *et al.* (2006)	PDGF	2 M presymptomatic		↔BrdU+ cells	↔DCX+ cells	↔BrdU+ cells	
APP_{Ind}	Donovan *et al.* (2006)	PDGF	12 M symptomatic		↓BrdU+ cells	↓DCX+ cells (SGZ) ↔BrdU/DCX+ cells	↓BrdU+ cells	↓aCasp3+ cells (SGZ) ↔aCasp3+ cells (GCL)
APP_{Swe} KM670/671NL	Ermini *et al.* (2008)	Thy-1	5 M presymptomatic B6D2/C57Bl/6J			↓DCX+ cells	↔BrdU+ cells ↔BrdU/NeuN+ neurons	
APP_{Swe} KM670/671NL	Ermini *et al.* (2008)	Thy-1	25 M symptomatic B6D2/C57Bl/6J			↑BrdU+ cells ↑BrdU/NeuN+ neurons		
APP_{Swe} × L166P PSEN1	Ermini *et al.* (2008)	Thy-1	8 M presymptomatic B6D2/C57Bl/6J	↓astrocyte-like ↔transit amplifying		↓DCX+ cells	↔BrdU+ cells ↔BrdU/NeuN+ neurons	
$APP_{Swe,Ind}$	Jin *et al.* (2004a)	PDGF	3 M presymptomatic				↑BrdU+ cells (1 week BrdU paradigm)	
$APP_{Swe,Ind}$	Jin *et al.* (2004a)	PDGF	12 M symptomatic				↑BrdU+ cells(1 week BrdU paradigm)	
APP_{Swe}	Haughey *et al.* (2002b)	PrP	12-14 M		↓BrdU+ cells		↓BrdU+ cells	
PS1P117L	Wen *et al.* (2004)	NSE	3–4 M		↔BrdU+ cells		↓BrdU+ cells ↓BrdU/βIIItub+ cells ↓ BrdU/calbindin+ cells ↓BrdU/GFAP+ cells	
PS1ΔE9 and PS1M146L	Choi *et al.* (2008)	PrP	3 M		↔BrdU+ cells	↔BrdU/DCX+ cells	↔BrdU/NeuN+ cells	
APP_{Swe} × tauP301L × PS1M146VK I (3× Tg-AD)	Rodriguez *et al.* (2008) Rodriguez *et al.* (2008)	Thy-1	Male 2, 3, 4, 6, 9, 12 M Female 2, 3, 4, 6, 9, 12 M		↓HH3+ cells (9, 12) dorsal hipp ↓HH3+ cells (6, 9, 12) dorsal hipp			
Lesion	Cooper-Kuhn *et al.* (2004)	Cholinergic forebrain lesion: stereotactic 192IgG-saporin injection	Male Fischer-344 albino rats				↔BrdU+ cells ↓BrdU/NeuN+ neurons	↑TUNEL
Human AD/patients								
14 probable AD 11 controls	Jin *et al.* (2004b)					↑AD hippocampus (western blot) for DCX, PSA-NCAM, NeuroD, calbindin		
9 AD (Braak 5-6) 10 controls	Boekhoorn *et al.* (2006)				↔Ki67 (DG) ↑Ki67 (CA1/2/3) increase in Ki67 in glial and vasculature-rich areas in GCL	↔DCX (semiquantitative)		
7 early AD 7 severe AD 5 controls	Crews *et al.* (2010a,b)			↓Sox2		↓DCX		

Table 1. Continued

Animal model	Citation	Promoter/lesion	Age/species	Stem cells	Proliferation (SGZ)	Neuroblasts	Survival	Cell death
30 early AD 30 controls	Laske *et al.* (2008)	↓stem cell factor in plasma and CSF						
HD								
Transgenics/genotype								
51 CAG repeats rat	Kandasamy *et al.* (2010)		8 M	↑ BrdU+/Sox2+/ PCNA-cells	↔BrdU+ cells ↔PCNA+ cells	↑BrdU/DCX+ cells ↑DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	
51 CAG repeats rat	Kandasamy *et al.* (2010)		12 M	↑ BrdU/Sox2+/ PCNA-cells	↓BrdU+ cells ↓PCNA+ cells	↓DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	
R6/1	Gil *et al.* (2004) Gil *et al.* (2005)							
R6/1	Lazic *et al.* (2004)		1 M 5 M		↔BrdU+ cells ↓BrdU+ cells			
R6/2	Phillips *et al.* (2005)				↓BrdU+ cells	↔DCX+ cells		
R6/2	Kohl *et al.* (2007)				↓PCNA+ cells	↓DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	
Lesion								
Human HD								
PD								
Transgenics/genotype								
α-Synuclein hWT	Crews *et al.* (2008), Winner *et al.* (2004)	PDGF	4 M		↔PCNA+ cells	↓DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	↑TUNEL
α-Synuclein mutant A53P	Crews *et al.* (2008)	PDGF	4 M		↓PCNA+ cells ↓BrdU+ cells	↓DCX+ cells		↑TUNEL
α-Synuclein hWT inducible	Nuber *et al.* (2008)	CaMK	4 M		↔PCNA+ cells	↓DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	↑TUNEL
Human PD								
3 PD 3 PDD 3 controls	Hoglinger *et al.* (2004)			↓Nestin+ cells PD and PDD		↓β3 tub+ cells PD and PDD		

AD, Alzheimer's disease; APP, amyloid precursor protein; CaMK, calcium/calmodulin-dependent protein kinase II alpha; M, months; NeuN, neuronal nuclear antigen; PDGF, platelet-derived growth factor; PSA-NCAM, polysialylated-neural cell adhesion molecule; Thy-1, THYmocyte differentiation antigen 1; TUNEL, Tdt-mediated dUTP-biotin nick end labeling.

TABLE 2. Exemplary results for adult neurogenesis in neurodegenerative diseases in the SVZ/OB system

Animal model	Citation	Promoter/lesion	Age/ species	Stem cells	Proliferation	Neuroblasts	Survival GCL	Survival GLOM	Cell death
AD									
APPSwe,Ind	Jin *et al.* (2004a)	PDGF	3 M presymptomatic				↔BrdU+ cells (1 week BrdU paradigm)		
APPSwe,Ind	Jin *et al.* (2004a)	PDGF	12 M symptomatic				↑BrdU+ cells (1 week BrdU paradigm)		
APPSwe	Haughey *et al.* (2002a)	PrP	11–12 presymptomatic		↓BrdU+ cells		↓BrdU+ cells		
Lesion	Cooper-Kuhn *et al.* (2004)	Cholinergic forebrain lesion: stereotactic 192IgG-saporin injection	Male Fisher-344 albino rats				↓BrdU+ cells ↓BrdU/NeuN+ neurons	↑BrdU+ cells ↔BrdU/NeuN+ neurons	↔TUNEL (GLOM) ↑TUNEL (GLOM)
HD									
Tg R6/2 130-150 CAG repeats	Kohl *et al.* (2010)				↔PCNA+ cells		↓BrdU+ cells ↓BrdU/NeuN+ neurons	↓BrdU+ cells ↓BrdU/NeuN+ neurons ↔BrdU/TH+ neurons	↑TUNEL
R6/2	Phillips *et al.* (2005)				↔BrdU+ cells				
Lesion Quinolonic acid (striatum)	Tattersfield *et al.* (2004)	Wistar rats (300–350 g)			↑BrdU+ cells (7 days)	Striatal migration of neuroblasts (DCX)	Striatal migration of new neurons (BrdU/NeuN+ cells)		
Human HD 3 HD 3 control 9 HD 6 controls	Curtis *et al.* (2003, 2005)				↑PCNA+ cells ↑ PCNA/ GFAP+ cells				
PD									
Transgenic α-Synuclein WT	Winner *et al.* (2004)	PDGF	5 M		↔PCNA+ cells	↓DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	↓BrdU+ cells ↓BrdU/TH+ cells	↑TUNEL
α-Synuclein WT	Winner *et al.* (2008a,b)	PDGF	15 M		↔PCNA+ cells	↓DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	↓BrdU+ cells ↓BrdU/TH+ cells	↑TUNEL
α-Synuclein A53T	Winner *et al.* (2008a,b)	PGDF	15 M		↓PCNA+ cells	↓DCX+ cells	↓BrdU+ cells ↓BrdU/NeuN+ cells	↓BrdU+ cells ↓BrdU/TH+ cells	↑TUNEL
α-Synuclein A30P mutant	Marxreiter *et al.* (2009)	CaMK	4 M		↔PCNA+ cells		↓BrdU+ cells ↓BrdU/NeuN+ cells	↓BrdU+ cells ↓BrdU/TH+ cells	↑TUNEL

TABLE 2. Continued

Animal model	Citation	Promoter/lesion	Age/ species	Stem cells	Proliferation	Neuroblasts	Survival GCL	Survival GLOM	Cell death
Lesion									
6-OHDA	Hoglinger *et al.* (2004)				↓PCNA+ cells				
6-OHDA	Baker *et al.* (2004)				↓BrdU+ cells ↓Ki67+ cells				
6-OHDA	Winner *et al.* (2006)				↓PCNA+ cells		↓BrdU+ cells ↓BrdU/NeuN+ neurons	↓BrdU+ cells ↑BrdU/TH+ neurons	
MPTP	Hoglinger *et al.* (2004)				↓PCNA+ cells		↓BrdU+ cells ↓BrdU/NeuN+ neurons		
Human PD									
4 PD 4 controls	Hoglinger *et al.* (2004)				↓PCNA+ cells		↓PSA-NCAM+ cells		
6 PD 6 controls	O' Keeffe *et al.* (2009)				↓(EGF-R)				

6-OHDA, 6-hydroxydopamine; aCasp3, activated Caspase 3; AD, Alzheimer's disease; APP, amyloid precursor protein; b3tub, beta 3 tubulin; CA, Cornu amonis; CaMK, calcium/calmodulin-dependent protein kinase II alpha; CSF, cerebro spinal fluid; GCL, granule cell layer; GFAP, glial fibrillary acidic protein;GLOM, glomerular layer; HH3, phosphorylated Histone H3; M, months;MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NeuN, neuronal nuclear antigen; NeuroD, neurogenic differentiation; NSE, neuron specific enolase; PDD, Parkinson disease dementia; PDGF, platelet-derived growth factor; PrP, prion protein; PSA-NCAM, polysialylated-neural cell adhesion molecule; Sox2, sex determining region Y-box 2; tg, transgenic; TH, tyrosine hydroxylase; Thy1, THYmocyte differentiation antigen 1; TUNEL, TdT-mediated dUTP-biotin nick end labeling; WT, wild-type.

data indicate that the non-NSC autonomous mechanisms might be the key to understanding the divergent findings of how AD-related proteins act on newly generated neurons. A detailed summary of the divergent reports on adult neurogenesis in PSEN models (reviewed in van Tijn *et al.*, 2010) recently indicated the difficulty that most of these studies were performed in young mice, and only one report investigated old PS1-P264L/KI mice and found a reduction of adult neurogenesis up to 18 months of age (Zhang *et al.*, 2007). Interestingly, a recent study investigating global gene expression levels in human AD brains at different Braak stages indicated that the appearance of AD neuropathology in the prefrontal cortex is preceded by changes in gene expression that point to increased synaptic activity and plasticity (Bossers *et al.*, 2010).

It is also important to note that, under certain circumstances, an enriched environment in APP and PSEN1 transgenic mice not only improves memory function but also reduces Aβ deposition in the central nervous system (Lazarov *et al.*, 2005). However, depending on the mouse models and ages used, the results were variable. The APP/PS1KI mouse model failed to show significant improvement after 4 months of continuous enrichment (physical activity plus social enrichment), possibly because the mice were not exposed to the enriched environment until after disease onset (Cotel *et al.*, 2010).

The investigation of adult neurogenesis in AD is involved in a larger picture of alterations in synaptic plasticity, spine morphology and axonal pathology. In summary, altered proliferation and survival are observed in many studies using APP transgenic models of familial AD with advanced progression of the disease (reviewed in Lazarov & Marr, 2010). Understanding the role of amyloid formation vs. oligomerization in adult NSCs will probably be a crucial next step in understanding the different effects. Similar to the analysis of mouse genetic backgrounds and their impact on neurogenesis (Kempermann *et al.*, 2006), a systematic comparison of different AD transgenic models under the same promoter with a similar labeling paradigm, sex, age and background would be necessary to compare adult neurogenesis in these different models and draw relevant conclusions. An additional crucial component of these studies would be the functional implication of alterations in neurogenesis in these models.

Studies of human AD have led to seemingly variable results; one study reported that hippocampal neurogenesis was increased in patients with AD, as shown by an increase in protein expression of DCX and polysialylated-neural cell adhesion molecule (PSA-NCAM), TOAD-64/Ulip/CRMP (TUC-4), and neurogenic differentiation (NeuroD) in Western blots from AD hippocampus (Jin *et al.*, 2004b). This study suggested that the increase might be a compensatory mechanism in the neurodegenerative process. Recent reports indicate an increase in gliosis and vascular-associated changes in presenile AD human hippocampus (Boekhoorn *et al.*, 2006). Masliah and colleagues performed cell counts and reported a decrease in DCX- and sex determining region Y-box 2 (Sox2)-positive cells in human AD (Crews *et al.*, 2010a). Bone morphogenetic protein 6 (BMP6) levels are increased in these human brains and in APP transgenic mice and are speculated to be crucial for the defective neurogenesis in AD (Crews *et al.*, 2010a). More detailed studies during different disease stages will be necessary to understand the effects of AD on hippocampal neurogenesis.

Huntington's disease

Huntington's disease is a devastating autosomal dominant neurodegenerative disease that results from a CAG trinucleotide repeat expansion within the disease-causing huntingtin/IT15 gene. This gene encodes an extended polyglutamine tract in the huntingtin protein

(The Huntington's Disease Collaborative Research Group, 1993). The clinical symptoms of HD are progressive involuntary choreatic movements, bradykinesia, cognitive decline and psychiatric syndromes (reviewed in Walker, 2007). Impaired olfactory function was noticed in patients and presymptomatic gene carriers (Mochel *et al.*, 2007). Aggregation of the mutant huntingtin results in neuronal damage in the medium spiny neurons of the neostriatum and other neurons such as in the cortex (reviewed in Li & Li, 2004). Among several mechanisms, a recently suspected toxic mechanism is due to the presence of toxic oligomers (Sathasivam *et al.*, 2010).

Among the most widely used animal models for HD are transgenic mice (R6/1 and R6/2 lines) with the introduction of exon 1 of the human HD gene carrying highly expanded CAG repeats into the mouse germ line. They differ in their number of CAG repeats, age of onset and survival (Mangiarini *et al.*, 1996), and they develop a progressive neurological phenotype that exhibits many of the features of HD, including involuntary stereotypic movements, tremor and epileptic seizures, as well as non-movement disorder components. Promising models for HD research that are considered closer to the human disease have also been a full-length human mutant huntingtin mouse with 97 glutamine repeats on a bacterial artificial chromosome (Gray *et al.*, 2008) and yeast artificial chromosome mice expressing normal yeast artificial chromosome (YAC) 18 and mutant (yeast artificial chromosome 46 and yeast artificial chromosome 72) huntingtin (Hodgson *et al.*, 1999). These mice exhibit progressive motor deficits, neuronal synaptic dysfunction and late-onset cortical and striatal neuropathology.

In addition, a rat model of huntingtin (von Horsten *et al.*, 2003) has been established that carries a truncated huntingtin cDNA fragment encoding for 51 CAG repeats under the control of the rat huntingtin promoter (von Horsten *et al.*, 2003). These rats exhibit adult onset of reduced anxiety, cognitive impairment and slowly progressive motor dysfunction.

Adult neurogenesis in transgenic animal models of Huntington's disease

Both the DG and SVZ have been studied for adult neurogenesis, mostly in R6/1 and R6/2 mice and the rat HD model. Several studies have reported reduced progenitor proliferation rates in both mouse models of HD in the DG. In the DG, a decline in proliferation was documented in the R6/1 (Lazic *et al.*, 2004, 2006) and R6/2 (Gil *et al.*, 2004, 2005; Phillips *et al.*, 2005; Kohl *et al.*, 2007) HD mouse models, which resulted in a reduction in newly generated neurons, although in most reports neuronal differentiation was not compromised. Different stimuli known to increase adult neurogenesis were tested. Physical activity and environmental enrichment (van Dellen *et al.*, 2000; Spires *et al.*, 2004) had positive effects on survival, cognitive performance and striatal brain-derived neurotrophic factor (BDNF) levels (Pang *et al.*, 2006), as well as the reduction of the neuronal intranuclear inclusion load (Benn *et al.*, 2010). Neither asialoerythropoietin (Gil *et al.*, 2004), running (Kohl *et al.*, 2007) nor seizures (Phillips *et al.*, 2005) were able to reverse the reduction of adult neurogenesis in these HD models; only environmental enrichment could increase the levels of hippocampal neurogenesis to some extent (Lazic *et al.*, 2006). In a transgenic rat model of HD (von Horsten *et al.*, 2003), important molecular cues were found. This is an interesting model for translational research, as 51 CAG repeats more closely reflect the human disease, and the longer survival of these animals allows age-related studies. Adult neurogenesis was analyzed in 8- and 12-month-old HD rats. The decrease in hippocampal progenitor cells was accompanied by an expansion of the quiescent stem cell pool (characterized by BrdU and Sox2 coexpression) and diminished cAMP-responsive element-binding protein signaling (Kandasamy *et al.*, 2010). Phospho-Smad 2, which is involved in transforming growth factor beta (TGF-β) signaling that is normally not present in subgranular stem cells, is increased in neural quiescent stem cells in these HD transgenic rats, indicating that TGF-b signaling is involved in modulating adult neurogenesis in HD (Kandasamy *et al.*, 2010).

In contrast to decreased proliferation in the DG, SVZ proliferation was reported to be unchanged in R6/2 mice (Phillips *et al.*, 2005; Kohl *et al.*, 2010). A reduction in newly generated neurons was present in the OB, which affected GABAergic more severely than DAergic newly generated neurons (Kohl *et al.*, 2010). In the OB, huntingtin aggregates were described in mature neurons in the granule cell layer and glomerular layer, but not in glial fibrillary acidic protein (GFAP)-positive B cells or epidermal-growth-factor (EGF) receptor-positive C cells in the SVZ or DCX-positive newly generated neuroblasts in the SVZ or OB. This finding suggests a non-cell-autonomous mechanism of aggregated huntingtin on newly generated neurons (Kohl *et al.*, 2010). Curtis and colleagues reported an increase in cell proliferation in the human SVZ (as determined by increased numbers of proliferating cell nuclear antigen (PCNA)-positive cells in the SVZ of human HD). Increased PCNA numbers correlated with the severity of disease and the number of CAG repeats. In the human ventricle wall, the PCNA/GFAP-colabeled cells were found in the most superficial regions close to the ventricular edge (Curtis *et al.*, 2003, 2005). The key to a better understanding of these processes might come from further investigation of the quiescent stem cell population in these brains, specifically NSCs that express Sox2 and GFAP.

The PCNA/β-III tubulin-positive cells were reported to be close to the human caudate nucleus (Curtis *et al.*, 2005), which suggests potential migration of neural precursors to the degenerating striatum. This phenomenon of neuroblasts migrating towards the striatum was also reported for R6/2 mice (Phillips *et al.*, 2005; Kohl *et al.*, 2010). However, these neuroblasts were not able to survive and form mature, functional neurons in the striatum, indicating that the striatal microenvironment provided a stimulus for abnormal migration of the newly generated cells but did not allow functional integration. This phenomenon of ectopic migration from the SVZ following changed microenvironmental cues has some similarities to what is observed after stroke (Arvidsson *et al.*, 2002).

An important observation in regard to striatal plasticity was that adenoviral overexpression of BDNF and Noggin in the ventricular wall increased the number of new neurons in the striatum of R6/2 huntingtin mutant mice. Under these conditions, newly recruited striatal neurons expressed striatal neuronal markers such as dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) and glutamate decarboxylase (GAD) 67. In addition, extended neuronal fibers to the ipsilateral globus pallidus were noted, indicating that these new striopallidal projection neurons survived and integrated as GABAergic striatal neurons. This integration was accompanied by substantial motor improvement and longer survival (Cho *et al.*, 2007) and indicates that changing the striatal microenvironment will be crucial for survival of new neurons in HD.

A next crucial step for this area of research will be a detailed analysis of stem-cell autonomous vs. non-autonomous actions in HD, as well as figuring out the impact of different size aggregates for adult neurogenesis and testing compounds that have been shown to be protective to HD in rodent models, e.g. matrix metalloproteases, to determine whether they have an impact in modulating adult neurogenesis (Miller *et al.*, 2010).

In a quinolonic lesion model, migration of neuroblasts from the SVZ to the lesion site was reported (Tattersfield, 2010). In this lesion

model, even expression of neuronal markers was reported [neuronal nuclear antigen (NeuN) and microtuble-associated protein 2 (MAP2)] in the newly generated neurons between day 13 and 37 after lesioning (Tattersfield *et al*., 2004).

Parkinson's disease

Loss of DAergic neurons in the substantia nigra of the midbrain and loss of other neurotransmitter phenotype neurons in other brain regions are characteristic neuropathological hallmarks (reviewed in Goedert, 2001). Prominent clinical features of PD are motor symptoms (bradykinesia, tremor, rigidity and postural instability) and non-motor-related PD symptoms (olfactory deficits, autonomic dysfunction, depression, cognitive deficits and sleep disorders).

Non-DA brain regions that are affected in PD have recently attracted increasing interest because the onsets of the non-motor symptoms linked to these neuropathological alterations are observed early in the course of the disease. They include rapid eye movement (REM) sleep behavior disorder, subtle cognitive deficits, depression, olfactory dysfunction and constipation (for review see Tolosa & Poewe, 2009). As described above, a subset of these functions is connected to the stem and progenitor cell populations in the hippocampus and SVZ/OB system. Interestingly, several monogenetic forms of PD show a decreased gray matter volume in the hippocampal region (Reetz *et al.*, 2010).

α-Synuclein animal models

Multiple genetic mutations can cause PD; the first gene identified, and still one of the most important, was α-synuclein. α-Synuclein, a 140-amino-acid protein physiologically found in presynaptic terminals of neurons, is the major fibrillar protein in Lewy bodies and Lewy neurites in sporadic and inherited PD. Moreover, point mutations (A53T, A30P, E46K) and gene multiplications of human wild-type (hWT) α-synuclein are related to rare familial autosomal dominant forms of early-onset PD (Polymeropoulos *et al.*, 1996; Kruger *et al.*, 1998; Singleton *et al.*, 2003; Zarranz *et al.*, 2004). PD is a synucleinopathy, with accumulation of misfolded α-synuclein that forms intracellular inclusions in neurons: Lewy bodies and Lewy neurites. Overexpression of mutant α-synuclein in transgenic mice can lead to neurodegeneration, although these models cannot reflect all aspects of PD (reviewed in Sulzer, 2010). Although α-synuclein knock-out mice do not show severe neuropathological alterations, different α-synuclein-overexpressing and mutant mice under various promoters present certain aspects of PD and Lewy body dementia; however, they do not show Lewy bodies. The models studied for adult neurogenesis are mice under a platelet-derived growth factor (PDGF) promoter (Masliah *et al.*, 2000; Hashimoto *et al.*, 2003) and a conditional model under a calcium/calmodulin-dependent protein kinase II alpha promoter (Nuber *et al.*, 2008).

Adult neurogenesis in transgenic mouse models of Parkinson's disease

The overexpression of hWT α-synuclein in transgenic mice has a negative impact on adult neurogenesis. Reduced levels of adult neurogenesis have been reported in both the DG (Winner *et al.*, 2004; Crews *et al.*, 2008; Nuber *et al.*, 2008) and SVZ/OB systems (Winner *et al.*, 2004, 2008b). Under the platelet-derived growth factor (PDGF) promoter, coexpression of hWT α-synuclein and neural progenitor cell markers in regions of neurogenesis is found as early as Sox2 expression. There is strong expression of α-synuclein in DCX-positive neuroblasts in both regions of adult neurogenesis (Winner *et al.*, 2004). Although proliferation is not changed in hWT α-synuclein-overexpressing mice, a decrease in neuroblasts and newly generated neurons is present. This decrease is paralleled by an increase in cell death in regions of neurogenesis, indicative of reduced survival of newly generated neurons. Decreased adult neurogenesis in the DG and in both areas of the OB, the glomerular layer and granule cell layer, was found in transgenic mice (Winner *et al.*, 2004).

The promoter used determines the stage of expression of α-synuclein in newly generated neurons. The decrease in new neurons is present in hWT α-synuclein mice not only under a platelet-derived growth factor (PDGF) promoter but also under a calcium/calmodulin-dependent protein kinase II alpha promoter (Nuber *et al.*, 2008). As the calcium/calmodulin-dependent protein kinase II alpha model is regulatable, we were able to show that adult hippocampal neurogenesis can be modulated by transiently switching off α-synuclein expression of a conditional mouse model of synucleinopathies. In this model, a correlation between decreased hippocampal neurogenesis and memory retention was present (Nuber *et al.*, 2008).

A decrease in adult neurogenesis was also present in the A53T mutant transgenic model. Here, a decrease in proliferation was present in the DG and OB (Crews *et al.*, 2008; Winner *et al.*, 2008a). Decreased adult neurogenesis was present in the OB of a mouse model with conditional expression of A30P α-synuclein. Suppression of the transgene was able to completely restore the negative influence of α-synuclein on OB neurogenesis (Marxreiter *et al.*, 2009). The effect of decreased adult neurogenesis in α-synuclein models was still present in aging mice. Decreased neurogenesis was present in the OB in hWT α-synuclein and A53T mice (Winner *et al.*, 2008b).

Lesion

Dopamine interacts with different receptors (D1-like receptors D1 and D5, D2-like receptors D2, D3 and D4) and specific intracellular signaling pathways and has a dual role in embryonic development and adult neurogenesis. D2-like receptors are involved in promoting the proliferative effect of DA, whereas D1-like receptors decrease proliferation at the level of cell cycle entry (Diaz *et al.*, 1997; Ohtani *et al.*, 2003). During brain development, DA receptors (mostly D3) are abundantly expressed in proliferative neuroepithelial zones (Diaz *et al.*, 1997), resulting in an overall proliferative effect of DA on neural progenitors.

In the adult brain, DA fibers extending from the substantia nigra to the striatum also contact the transit-amplifying C cells in the SVZ (Hoglinger *et al.*, 2004). D2-like receptors are expressed predominantly on transit-amplifying C cells (Coronas *et al*., 1997).

The DA loss in the nigro-striatal pathway results in decreased proliferation in the adult rodent SVZ. These findings have been reported in 6-hydroxydopamine (6-OHDA)-lesioned rats by several groups (Baker *et al.*, 2004; Hoglinger *et al.*, 2004; Winner *et al.*, 2006). In addition, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-injected mice have a reduction in numbers of proliferating cells in the SVZ. Here a decrease in PCNA-positive cells in the SVZ was noted shortly after the MPTP injection. Interestingly, the number of PCNA-positive cells returned to baseline during the DA reinnervation (Hoglinger *et al.*, 2004), indicating a correlation between DA depletion and reduction of proliferating cells in the SVZ. The decrease in newly generated SVZ progenitor cells with a nigro-striatal DA deficit can be reversed by DA stimulation. The important result is that specific DA D3 receptor stimulation increases SVZ proliferation.

Effects of a similar size can be achieved by two frequently used DA agonists (ropinirole and pramipexole), which indicates that these two DA agonists have a regenerative effect (Hoglinger *et al.*, 2004; Winner *et al.*, 2009). Moreover, toxin-induced models show an increase in dopaminergic neurogenesis in the OB glomerular layer, which has been described for the MPTP (Yamada *et al.*, 2004) and 6-OHDA (Winner *et al.*, 2006) models. This finding is of particular interest because an increase in dopaminergic olfactory neurons has been described in the OB of patients with PD (Huisman *et al.*, 2004), which seems to parallel these experimental findings but could only partially be confirmed in a recent study (Huisman *et al.*, 2008). Indications of decreased numbers of dividing SVZ cells/EGF-receptor-expressing cells in patients with PD have also been independently reported (Hoglinger *et al.*, 2004; O' Keeffe *et al.*, 2009).

Common characteristics

Taking into account the low numbers of newly generated DG neurons in an aging brain compared with the vast number of degenerating neurons in many brain regions, including, for example, the entorhinal cortex and neocortex in AD, it is unlikely that these newly generated neurons in the DG or SVZ/OB will be able to achieve global repair. However, given the crucial role of the hippocampus in processing information and specifically pattern separation (Clelland *et al.*, 2009; Creer *et al.*, 2010), it may be that, given that the initial deleterious stressors involved have been removed, stimulating DG adult neurogenesis might have some therapeutic potential.

In addition, the seeming discrepancies between increased and decreased proliferation in some human and transgenic animal models might be explained by studying in detail the different NSC populations and radial glial cells and ruling out their proliferative potential under diseased conditions. Recently, glial and immune cells have been shown to have increasing importance in these diseases (Glass *et al.*, 2010). In addition, there are indications that knock-down of toll-like receptor 4 (Rolls *et al.*, 2007) and toll-like receptor 3 has a positive impact on adult neurogenesis and memory (Okun *et al.*, 2010).

An additional common aspect is the process of protein aggregation in these diseases. It seems that oligomerization and early aggregates have a stronger toxic effect in AD, HD and PD. The interplay between NSCs and oligomers will require future studies. In addition, dissecting the intracellular and extracellular as well as stem cell autonomous vs. non-autonomous actions on NSCs will clarify the different actions of proteins. Again, the interaction of aggregating proteins with glial cells and reactive gliosis seems to have a common but as yet barely understood effect on NSCs.

Investigating the role of adult NSCs is a way to understand disease pathology at different stages of neuronal development. The classical neuropathological hallmarks of AD, PD and HD are late-stage effects and therefore do not reflect early disease mechanisms.

There is a need for early-stage disease models, as they will be important for testing compounds and therapies at a presymptomatic or early symptomatic stage. Imaging techniques for *in-vivo* measurements of adult neurogenesis combined with other biomarkers used to determine early stages of the disease might open up a totally new avenue of early diagnosis.

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Abbreviations

Aβ, amyloid-β; AD, Alzheimer's disease; APP, amyloid precursor protein; BrdU, bromodeoxyuridine; DCX, doublecortin; DG, dentate gyrus; HD, Huntington's disease; hWT, human wild-type; NSC, neural stem cell; OB, olfactory bulb; PD, Parkinson's disease; PCNA, proliferating cell nuclear antigen; PSEN, presenilin; SVZ, subventricular zone; 3× Tg-AD, triple transgenic mice.

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