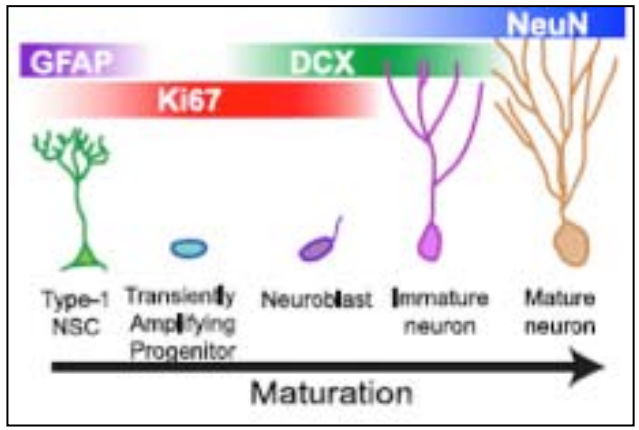
Cours 4-11-2013

Notch1 Is Required for Maintenance of the Reservoir of Adult Hippocampal Stem Cells

Jessica L. Ables,[1] Nathan A. DeCarolis,[1] Madeleine A. Johnson,[1] Phillip D. Rivera,[1] Zhengliang Gao,[2] Don C. Cooper,[3] Freddy Radtke,[4] Jenny Hsieh,[2] and Amelia J. Eisch[1]

10484 • The Journal of Neuroscience, August 4, 2010 • 30(31):10484–10492



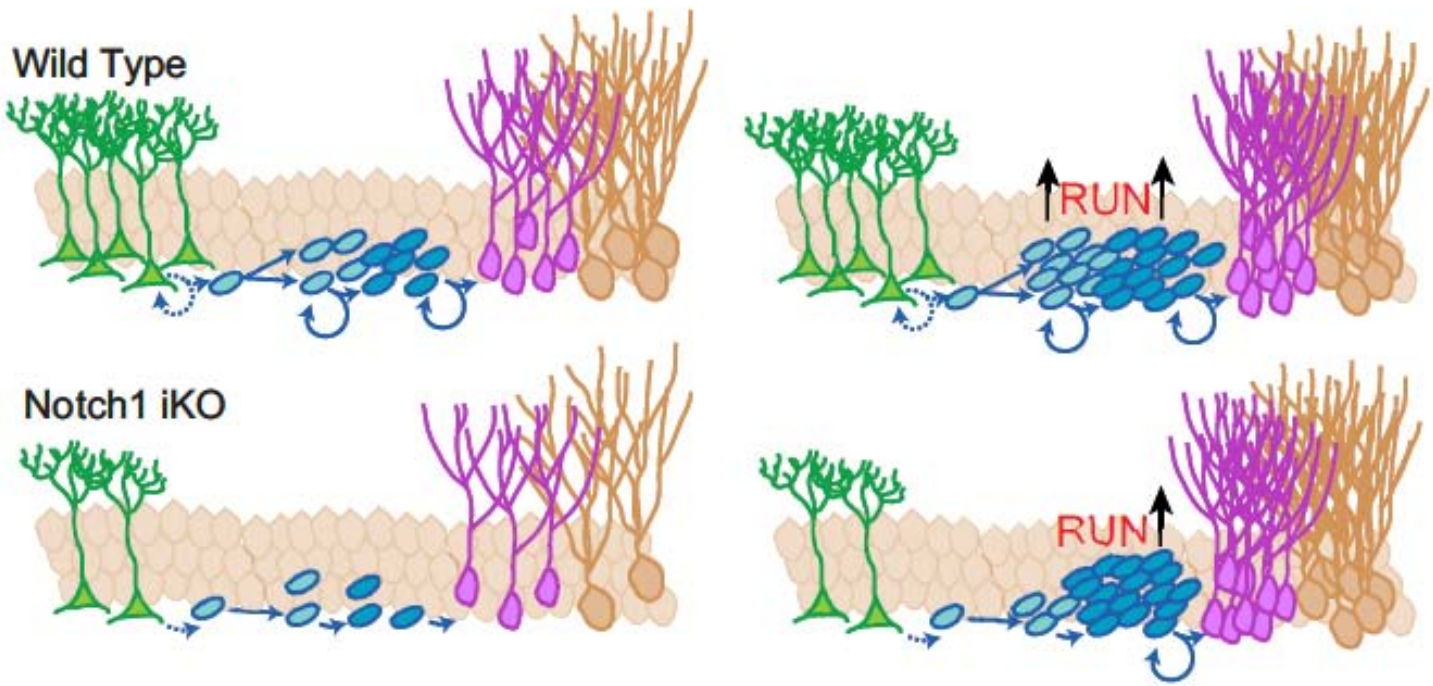


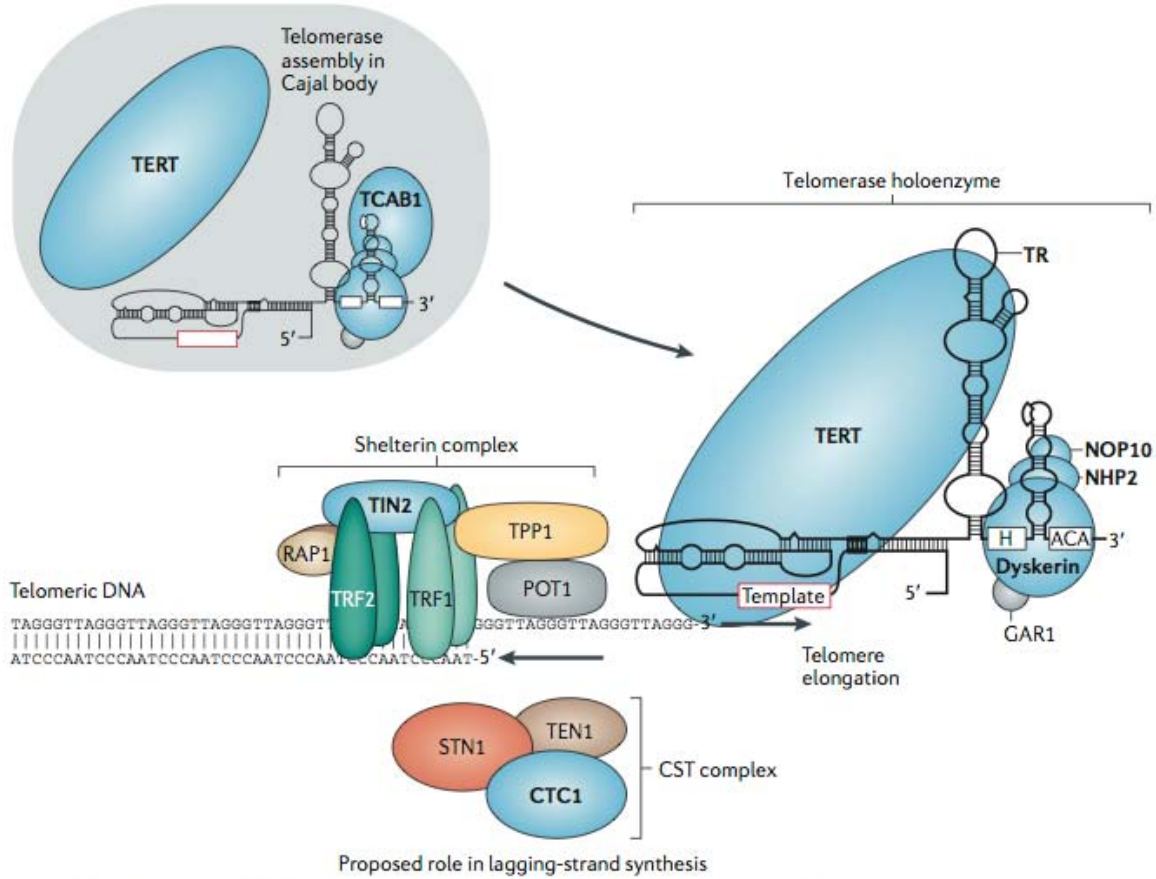
Figure 7. Proposed model of Notch1 in regulating adult neurogenesis under basal conditions and after physical activity. Without Notch1, self-renewal and expansion of nestin-expressing cells is disrupted and the net number of adult-generated dentate gyrus neurons is decreased. Physical activity increases adult-generated neurons in WT and Notch1 iKO mice by increasing neuroblast proliferation. However, physical activity does not rescue Type-1 NSC or TAP number in Notch1 iKO mice.

NO SPORT

The telomere syndromes

Nature Reviews Genetics
2012 vol. 13 (10) pp. 693-704

Armanios M, Blackburn EH



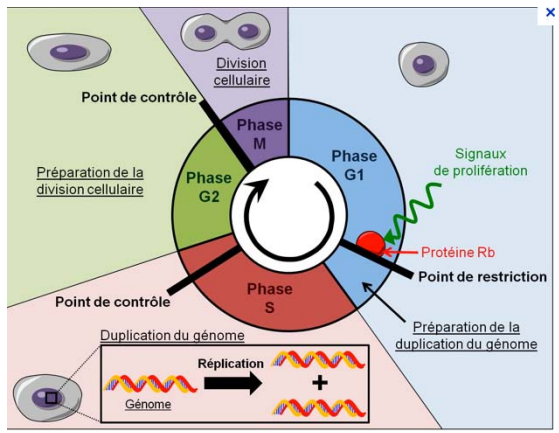
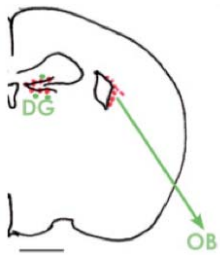


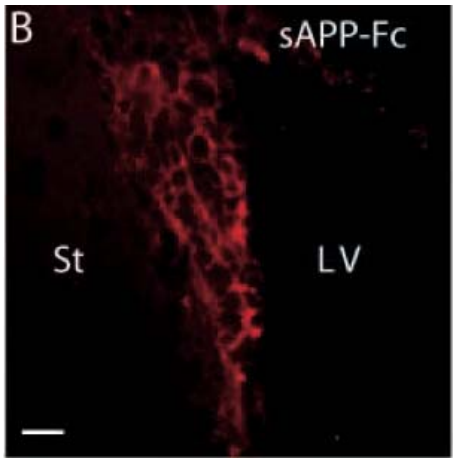
Figure 1 | **Telomerase and telomere components involved in human monogenic telomere syndromes.** Components for which mutations have been identified in telomere syndromes are indicated in bold type and shaded in blue. Shelterin complex components are made up of six component proteins — telomere repeat-binding factor 1 (TRF1), TRF2, repressor/activator protein 1 (RAP1), TRF1-interacting nuclear protein 2 (TIN2), TIN2-interacting protein 1 (TPP1) and protection of telomeres 1 (POT1) — which are essential for telomere protection and for regulating telomere elongation. The telomerase enzyme complex is comprised of TERT (the reverse transcriptase) and TR (the essential RNA component that contains a template for telomere repeat addition). TR contains a 3′ H/ACA box motif that binds the dyskerin protein, which is part of a larger dyskerin complex that also consists of NHP2, NOP10 and GAR1. Note that for simplicity, one dyskerin complex is shown per TR molecule, although two copies are now thought to bind each TR. Telomerase Cajal body protein 1 (TCAB1) binds a Cajal body localization motif in TR and has a role in TR trafficking and biogenesis. In the Cajal body, TR and TERT assemble into a functional holoenzyme complex. The CST complex has three components — conserved telomere protection component 1 (CTC1), suppressor of cdc thirteen 1 (STN1) and telomeric pathway with STN1 (TEN1) — which are thought to function in part in telomere lagging-strand synthesis. Figure adapted, with permission, from REF. 13 © (2009) Annual Reviews.

Soluble form of amyloid precursor protein regulates proliferation of progenitors in the adult subventricular zone

Development 131, 2173-2181
Published by The Company of Biologists 2004
doi:10.1242/dev.01103

Isabelle Caillé[1], Bernadette Allinquant[1], Edmond Dupont[1], Colette Bouillot[1], Andreas Langer[2], Ulrike Müller[2] and Alain Prochiantz[1,*]

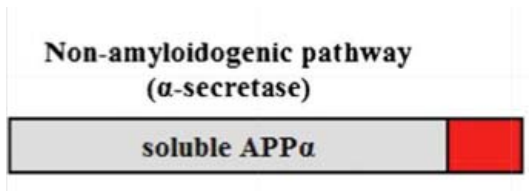


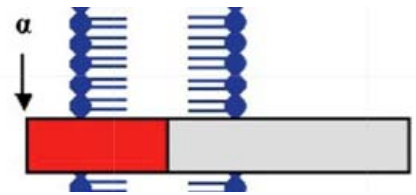


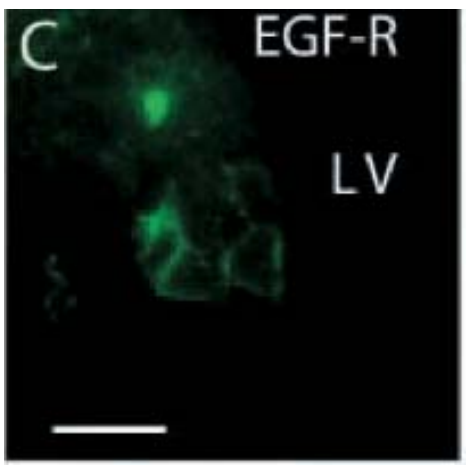
Clinics (Sao Paulo). 2011 June; 66(Suppl 1): 45–54.
doi: 10.1590/S1807-59322011001300006
PMCID: PMC3118437

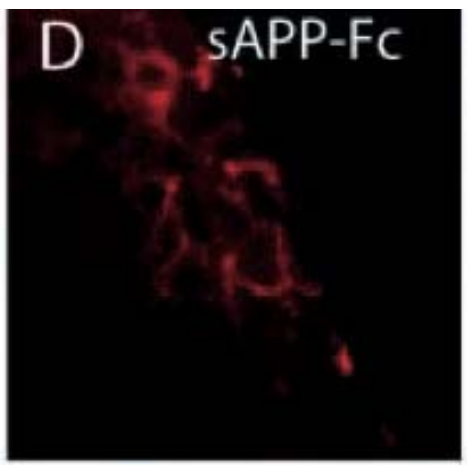
Insights into Alzheimer disease pathogenesis from studies in transgenic animal models

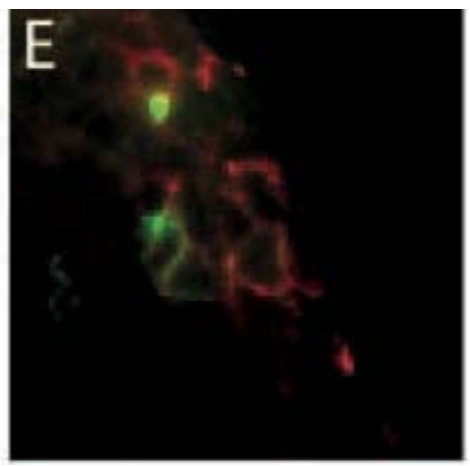
Evelin L Schaeffer,[I] Micheli Figueiró,[I] and Wagner F Gattaz[I]

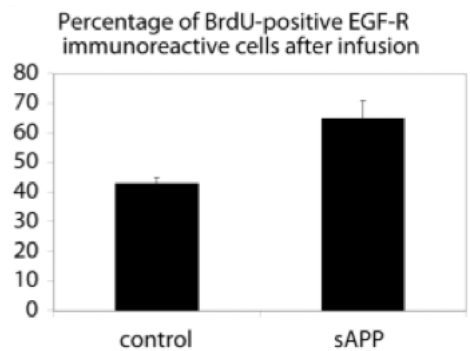












The telomere syndromes

Nature Reviews Genetics
2012 vol. 13 (10) pp. 693-704

Armanios M, Blackburn EH

Table 1 | **Disease spectrum, frequency of gene mutations and mechanism of telomere shortening in telomere syndromes**

Gene	First diagnosis	Mutation frequency (%)	Mechanism of telomere shortening	Refs
TERT; *TR*	Familial IPF	8–15	• Partial loss-of-function • Haploinsufficiency	36, 38, 39, 41, 54, 56, 68, 73, 74, 77, 111, 116
	Sporadic IPF	1–3		
	Aplastic anaemia	3–5		
	Autosomal dominant dyskeratosis congenita	10*		
	Familial MDS–AML	20		
DKC1	*De novo* dyskeratosis congenita	?	• Partial loss-of-function • Decreased TR stability and biogenesis	9, 11, 124, 125
	X-linked recessive dyskeratosis congenita	15–25*		
	Hoyeraal–Hreiderasson syndrome	?		
TINF2	*De novo* dyskeratosis congenita	15–25*	• Not completely understood • Probably dominant-negative mutations	62, 126, 127
	Autosomal-dominant dyskeratosis congenita	Rare		
	Hoyeraal–Hreiderasson syndrome	Rare		
	Revesz syndrome	Rare		
NOP10	Autosomal-recessive dyskeratosis congenita	‡	Presumed loss of telomerase function	61
NHP2	Autosomal-recessive dyskeratosis congenita	‡	Presumed loss of telomerase function	60
TCAB1	Autosomal-recessive dyskeratosis congenita	‡	Impaired TR trafficking; loss-of-function	63
CTC1	Coats plus syndrome	90	Loss-of-function	22, 64, 66, 67
	Autosomal-recessive dyskeratosis congenita	?		

*Refers to frequency of total dyskeratosis congenita patients. ‡Only two cases have been reported for each of these genes in the literature to date. AML, acute myeloid leukaemia; *CTC1*, conserved telomere protection component 1; *DKC1*, dyskeratosis congenita 1; IPF, idiopathic pulmonary fibrosis; MDS, myelodysplastic syndrome; *TCAB1*, telomerase Cajal body protein 1; *TINF2*, TRF1-interacting nuclear factor 2.

The Hallmarks of Aging

Cell 153, June 6, 2013 ©2013 Elsevier Inc.

Carlos López-Otín,[1] Maria A. Blasco,[2] Linda Partridge,[3,4] Manuel Serrano,[5,*] and Guido Kroemer[6,7,8,9,10]

Figure 1. The Hallmarks of Aging
The scheme enumerates the nine hallmarks described in this Review: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

Telomeres and age-related disease: how telomere biology informs clinical paradigms

J Clin Invest
2013 vol. 123 (3) pp. 996-1002

Armanios M

Telomere syndrome manifestations that overlap with human age-related phenotypes

High-turnover compartments	Low-turnover compartments
Hair graying	Idiopathic pulmonary fibrosis
Hair loss	Emphysema
Nail ridging	Liver fibrosis and cirrhosis
Periodontal disease	Impaired glucose tolerance
Thrombocytopenia	Defective insulin secretion
Decreased bone marrow cellularity	Insulin resistance
Immunosenescence	Osteoporosis
Gastrointestinal intraepithelial lymphocytosis	
Increased cancer risk	
Chemotherapy intolerance	

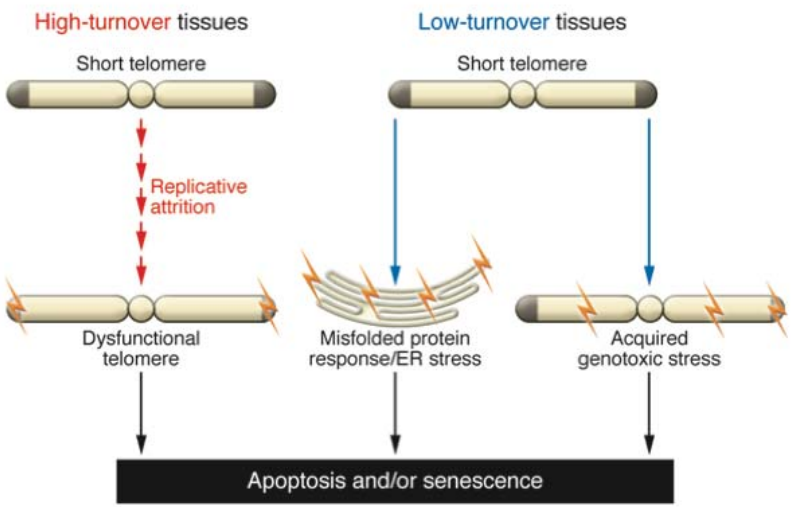
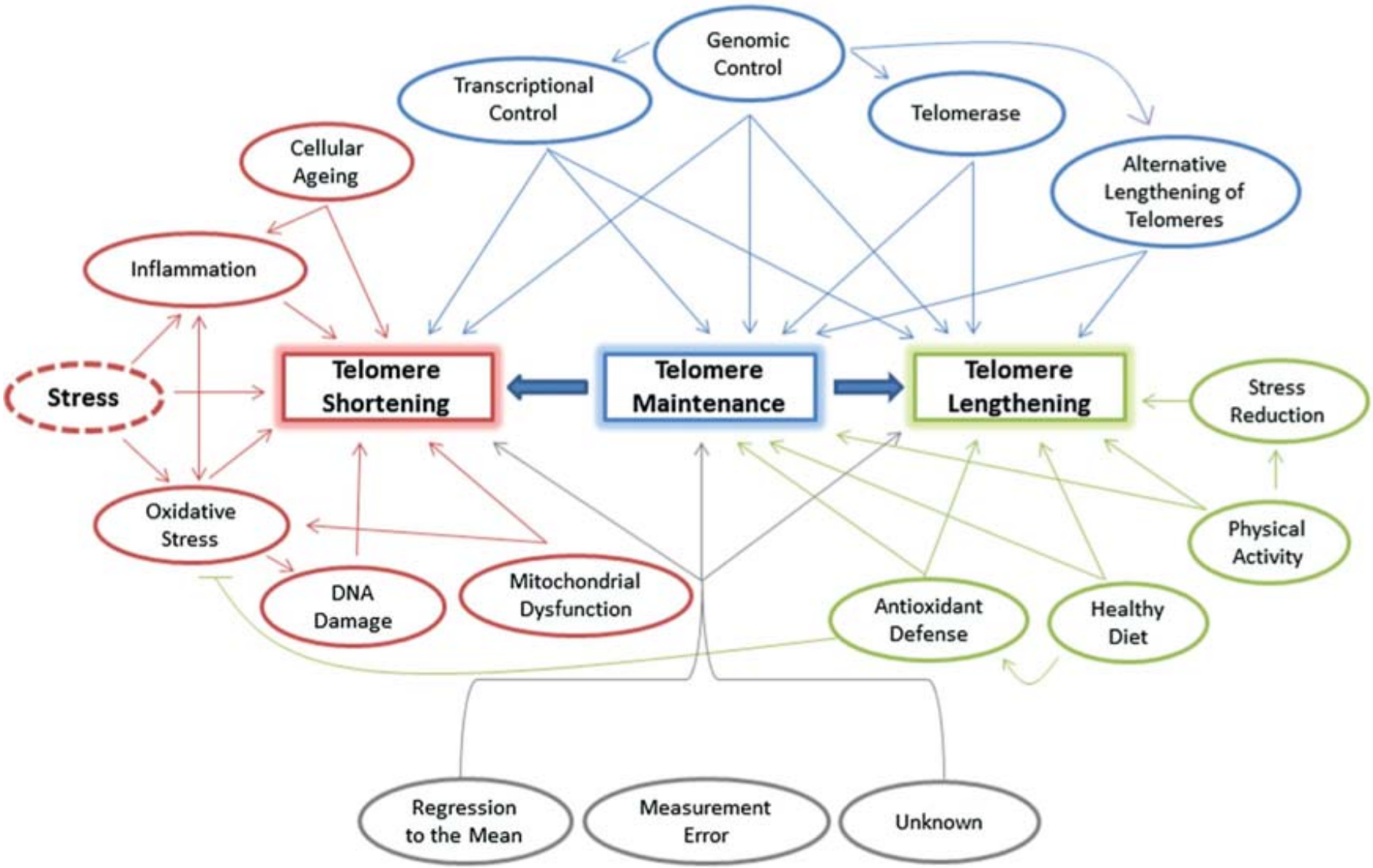


Figure 2
Model for understanding the mechanisms of telomere-mediated disease in high- and low-turnover tissues. In high-turnover tissues (left), cell replication is the primary determinant of disease onset. In contrast, in low-turnover tissues (right), other genetic and acquired hits contribute to disease onset. In both cases, telomere dysfunction induces apoptosis and/or senescence. The senescence phenotype may be associated with gene expression changes, mitochondrial dysfunction, aberrant Ca^{2+} signaling, and the SASP.

Early life stress and telomere length: investigating the connection and possible mechanisms: a critical survey of the evidence base, research methodology and basic biology

Shalev I

Bioessays
2012 vol. 34 (11) pp. 943-52



Variation in neural development as a result of exposure to institutionalization early in childhood

Sheridan MA, Fox NA, Zeanah CH, McLaughlin KA, Nelson CA

Laboratories of Cognitive Neuroscience, Division of Developmental Medicine, Boston Children's Hospital, Boston, MA 02115.

We used structural MRI and EEG to examine brain structure and function in typically developing children in Romania (n = 20), children exposed to institutional rearing (n = 29), and children previously exposed to institutional rearing but then randomized to a high-quality foster care intervention (n = 25). In so doing, we provide a unique evaluation of whether placement in an improved environment mitigates the effects of institutional rearing on neural structure, using data from the only existing randomized controlled trial of foster care for institutionalized children. Children enrolled in the Bucharest Early Intervention Project underwent a T1-weighted MRI protocol. Children with histories of institutional rearing had significantly smaller cortical gray matter volume than never-institutionalized children. Cortical white matter was no different for children placed in foster care than never-institutionalized children but was significantly smaller for children not randomized to foster care. We were also able to explain previously reported reductions in EEG α-power among institutionally reared children compared with children raised in families using these MRI data. As hypothesized, the association between institutionalization and EEG α-power was partially mediated by cortical white matter volume for children not randomized to foster care. The increase in white matter among children randomized to an improved rearing environment relative to children who remained in institutional care suggests the potential for developmental "catch up" in white matter growth, even following extreme environmental deprivation.

Proc Natl Acad Sci USA
2012 vol. 109 (32) pp. 12927-32

☆☆☆☆☆

Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys

Feng X, Wang L, Yang S, Qin D, Wang J, Li C, Lv L, Ma Y, Hu X

State Key Laboratory of Brain and Cognitive Science, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan 650223, People's Republic of China.

Maternal separation (MS), which can lead to hypothalamic pituitary adrenal axis dysfunction and behavioral abnormalities in rhesus monkeys, is frequently used to model early adversity. Whether this deleterious effect on monkeys is reversible by later experience is unknown. In this study, we assessed the basal hair cortisol in rhesus monkeys after 1.5 and 3 y of normal social life following an early separation. These results showed that peer-reared monkeys had significantly lower basal hair cortisol levels than the mother-reared monkeys at both years examined. The plasma cortisol was assessed in the monkeys after 1.5 y of normal social life, and the results indicated that the peak in the peer-reared cortisol response to acute stressors was substantially delayed. In addition, after 3 y of normal social life, abnormal behavioral patterns were identified in the peer-reared monkeys. They showed decreases in locomotion and initiated sitting together, as well as increases in stereotypical behaviors compared with the mother-reared monkeys. These results demonstrate that the deleterious effects of MS on rhesus monkeys cannot be compensated by a later normal social life, suggesting that the effects of MS are long-lasting and that the maternal-separated rhesus monkeys are a good animal model to study early adversity and to investigate the development of psychiatric disorders induced by exposure to early adversity.

Proc Natl Acad Sci USA
2011 vol. 108 (34) pp. 14312-7

☆☆☆☆☆

Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood

Entringer S, Epel ES, Kumsta R, Lin J, Hellhammer DH, Blackburn EH, Wüst S, Wadhwa PD

Department of Pediatrics, University of California, Irvine, CA 92697.

Leukocyte telomere length (LTL) is a predictor of age-related disease onset and mortality. The association in adults of psychosocial stress or stress biomarkers with LTL suggests telomere biology may represent a possible underlying mechanism linking stress and health outcomes. It is, however, unknown whether stress exposure in intrauterine life can produce variations in LTL, thereby potentially setting up a long-term trajectory for disease susceptibility. We, therefore, as a first step, tested the hypothesis that stress exposure during intrauterine life is associated with shorter telomeres in adult life after accounting for the effects of other factors on LTL. LTL was assessed in 94 healthy young adults. Forty-five subjects were offspring of mothers who had experienced a severe stressor in the index pregnancy (prenatal stress group; PSG), and 49 subjects were offspring of mothers who had a healthy, uneventful index pregnancy (comparison group; CG). Prenatal stress exposure was a significant predictor of subsequent adult telomere length in the offspring (178-bp difference between prenatal stress and CG; d = 0.41 SD units; $P < 0.05$). The effect was substantially unchanged after adjusting for potential confounders (subject characteristics, birth weight percentile, and early-life and concurrent stress level), and was more pronounced in women (295-bp difference; d = 0.68 SD units; $P < 0.01$). To the best of our knowledge, this study provides the first evidence in humans of an association between prenatal stress exposure and subsequent shorter telomere length. This observation may help shed light on an important biological pathway underlying the developmental origins of adult health and disease risk.

Proc Natl Acad Sci USA
2011 vol. 108 (33) pp. E513-8

☆☆☆☆☆

New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory?

Wei Deng, James B. Aimone* and Fred H. Gage*

NATURE REVIEWS | NEUROSCIENCE
VOLUME 11 | MAY 2010 | 339

Notch1 Is Required for Maintenance of the Reservoir of Adult Hippocampal Stem Cells

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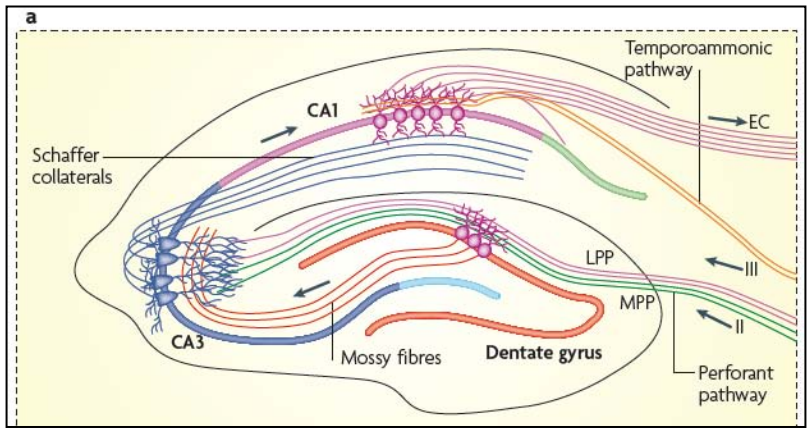
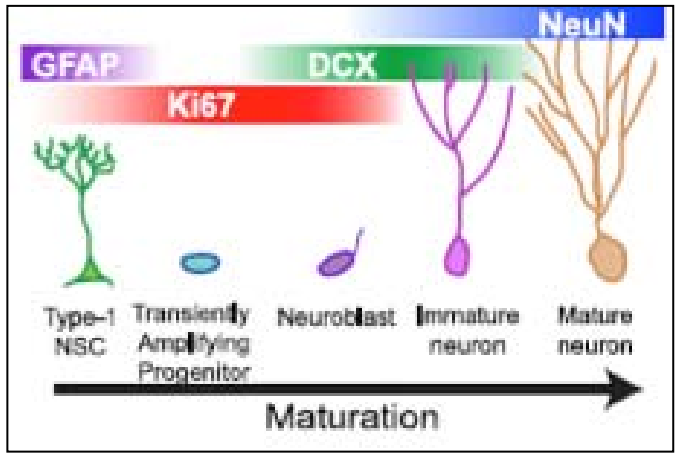
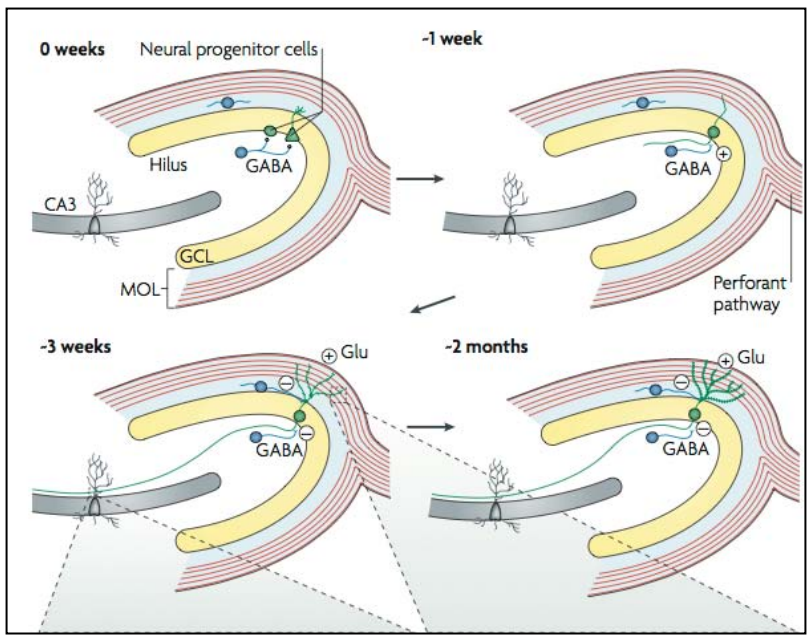
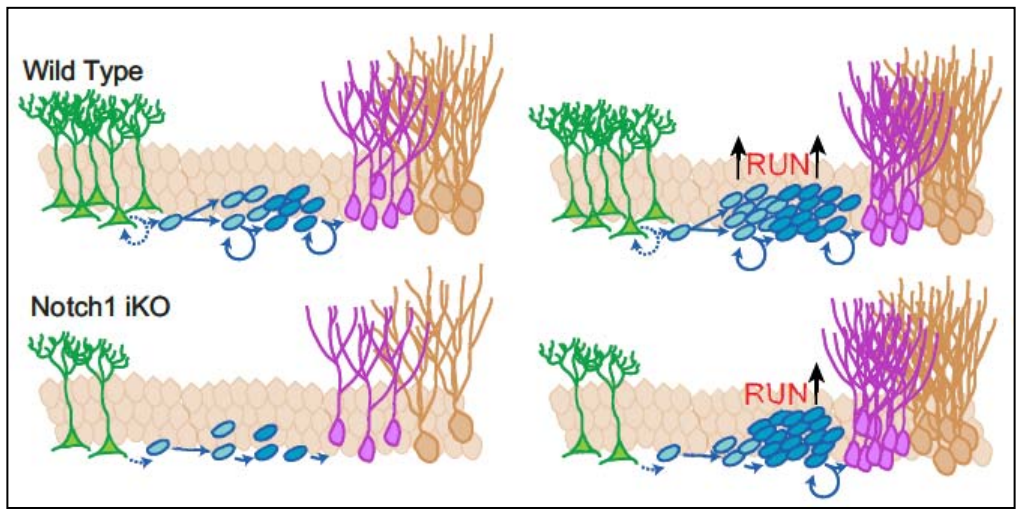
10484 • The Journal of Neuroscience, August 4, 2010 • 30(31):10484–10492









Dynamics of Hippocampal Neurogenesis in Adult Humans

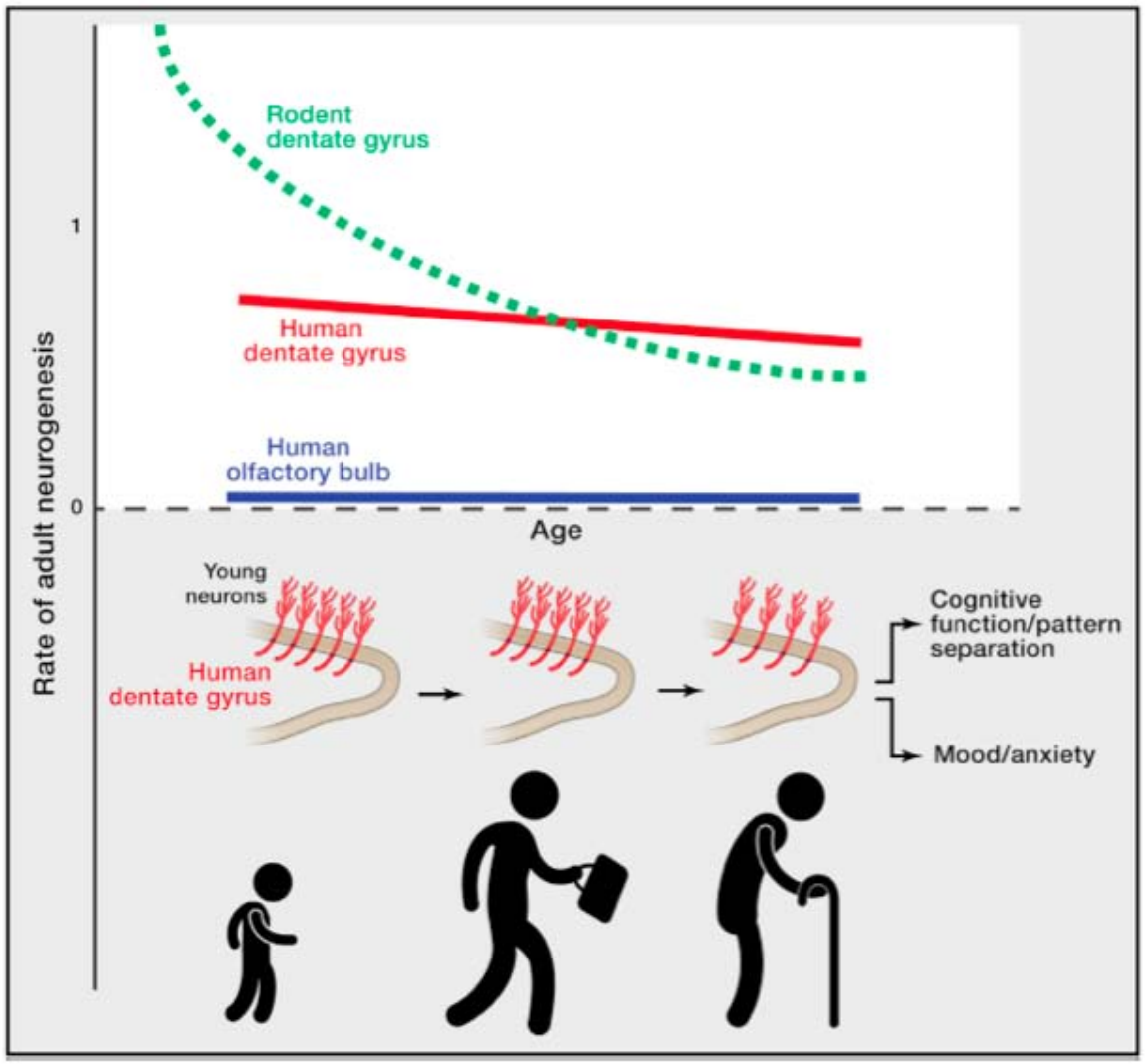
Kirsty L. Spalding,[1,8] Olaf Bergmann,[1,8] Kanar Alkass,[1,2] Samuel Bernard,[3] Mehran Salehpour,[4] Hagen B. Huttner,[1,5] Emil Boström,[1] Isabelle Westerlund,[1] Céline Vial,[3] Bruce A. Buchholz,[6] Göran Possnert,[4] Deborah C. Mash,[7] Henrik Druid,[2] and Jonas Frisén[1,*]

Cell 153, 1219–1227, June 6, 2013 ©2013 Elsevier Inc.

(Radio)active Neurogenesis in the Human Hippocampus

Mazen A. Kheirbek[1,3,*] and René Hen[1,2,3,*]

Cell 153, June 6, 2013 ©2013 Elsevier Inc.



Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia

Susanne A. Wolf[a,*], Andre Melnik[a], Gerd Kempermann[b,c]

Brain, Behavior, and Immunity 25 (2011) 971–980

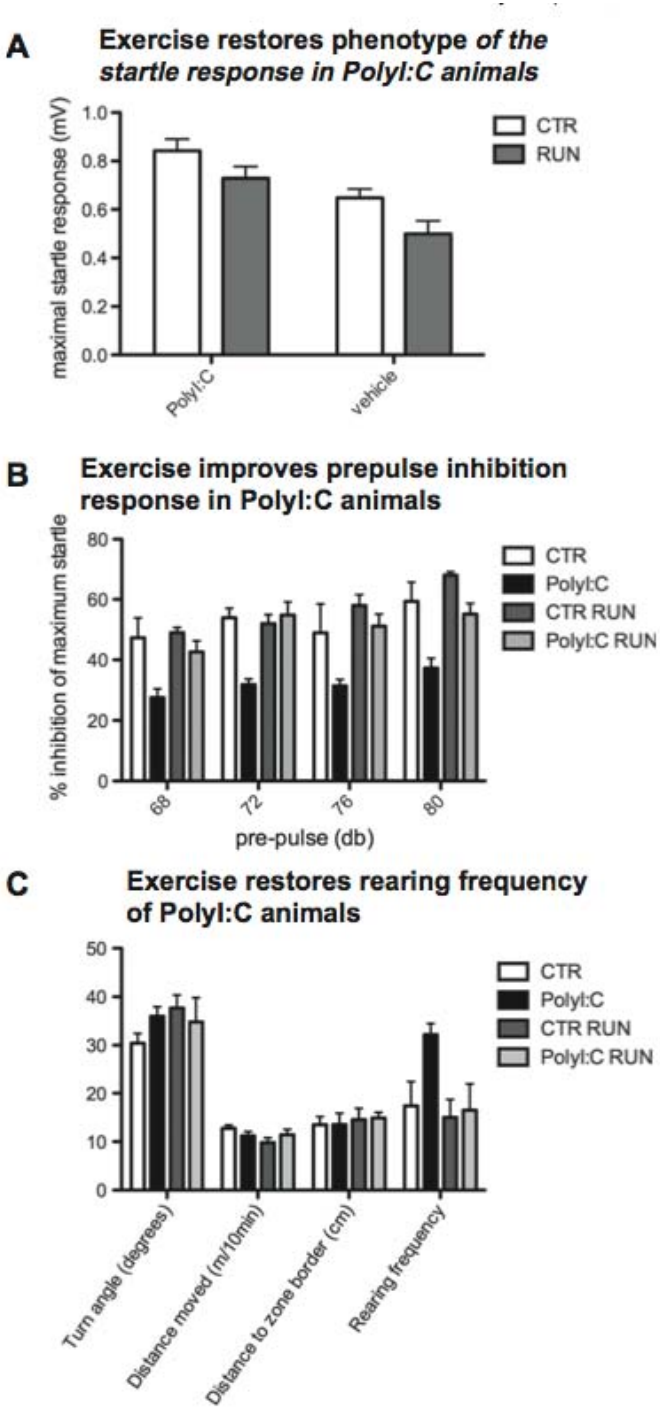
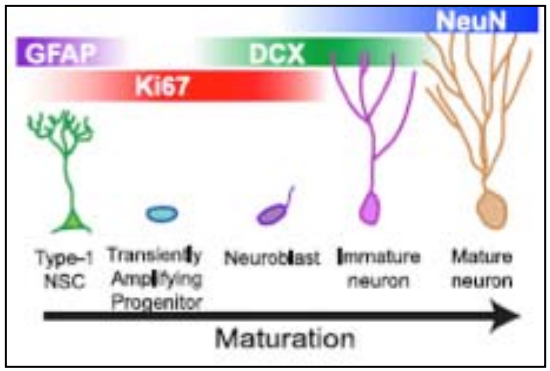


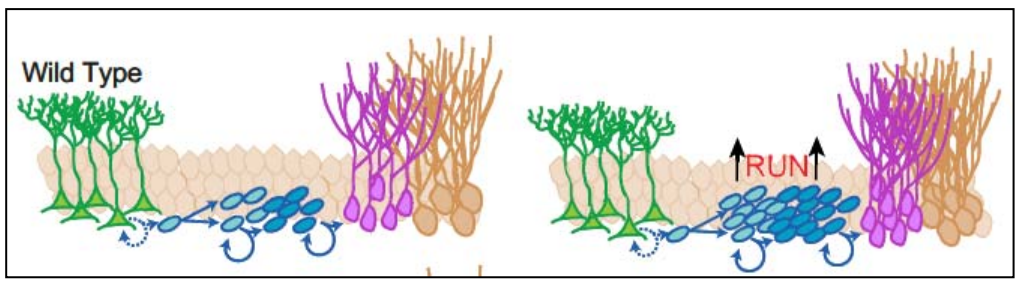
Fig. 1. Behavioral improvements in Polyl:C offspring after physical activity. We used pre-pulse inhibition of the startle response (PPI) at postnatal day 60 to verify the schizophrenic phenotype of the mice subjected to Polyl:C in utero. Moreover we used the open field test to measure differences in general motor behavior between the groups. Both tests revealed a rather hypoactive behavior of the Polyl:C group compared to CTR. (A) The overall response to the startle of 100 dB was increased in the Polyl:C group. The voluntary wheel running decreased the startle response in both groups bringing the Polyl:C RUN group toward CTR level and thus restoring the phenotype. (B) The same could be seen in the pre-pulse inhibition. The Polyl:C animals showed only a 30% inhibition of the startle compared to CTR with 50% of inhibition. Exercise increased the inhibition of Polyl:C RUN to 50% in average thus restoring the phenotype in this measure as well. No differences were seen between CTR and CTR RUN. (C) In the open field test both Polyl:C and CTR RUN showed an increase in head turns paralleled by a decrease in the total distance moved compared to CTR. Increased head turns could be interpreted as either greater interest in the environment or higher level of distractibility leading to the conclusion that these parameters alone are not sufficient in monitoring motor behavior. When we look at the frequency of rearing we do see an approximately 50% increase in the Polyl:C group compared to all other groups. Exercise brought the rearing frequency back to CTR level in the Polyl:C RUN group. Since running had no effect on the CTR animals, rearing frequency in addition to head turns demonstrate a rather hypoactive phenotype in the Polyl:C group.

Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia

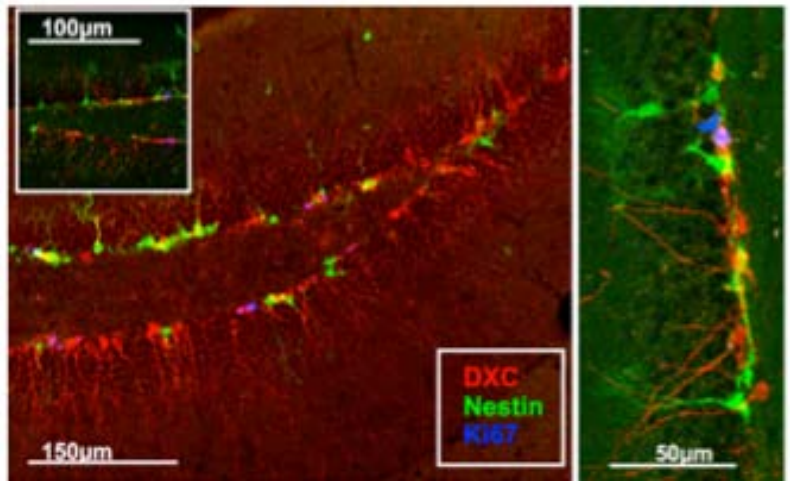
Brain, Behavior, and Immunity 25 (2011) 971–980

Susanne A. Wolf [a,*], Andre Melnik [a], Gerd Kempermann [b,c]

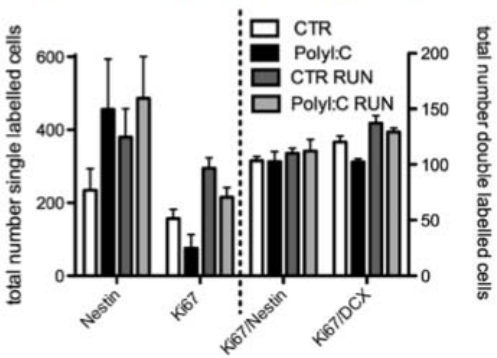




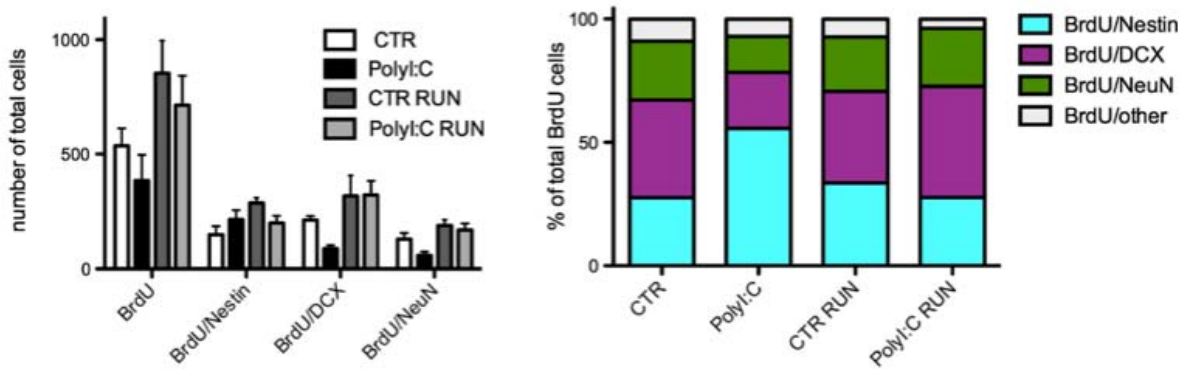
A **Expression of early neuronal markers in the dentate gyrus of the hippocampus**



B ***in utero*** **PolyI:C decreases neuronal progenitor proliferation in the adult hippocampus**



C ***in utero*** **PolyI:C slows down neuronal maturation in the adult hippocampus**

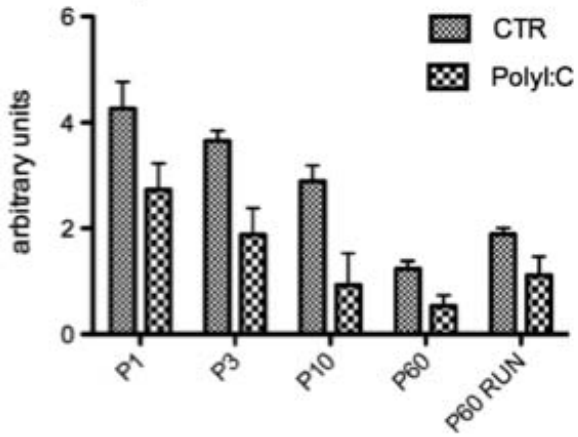


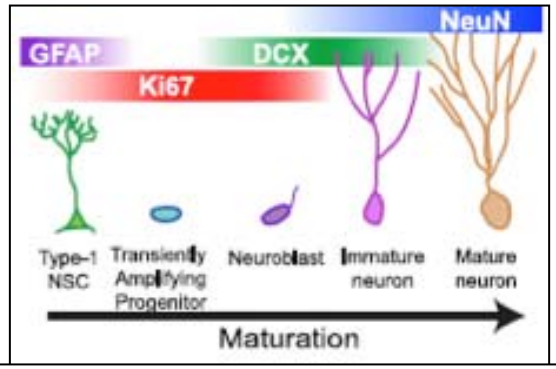
Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia

Brain, Behavior, and Immunity 25 (2011) 971–980

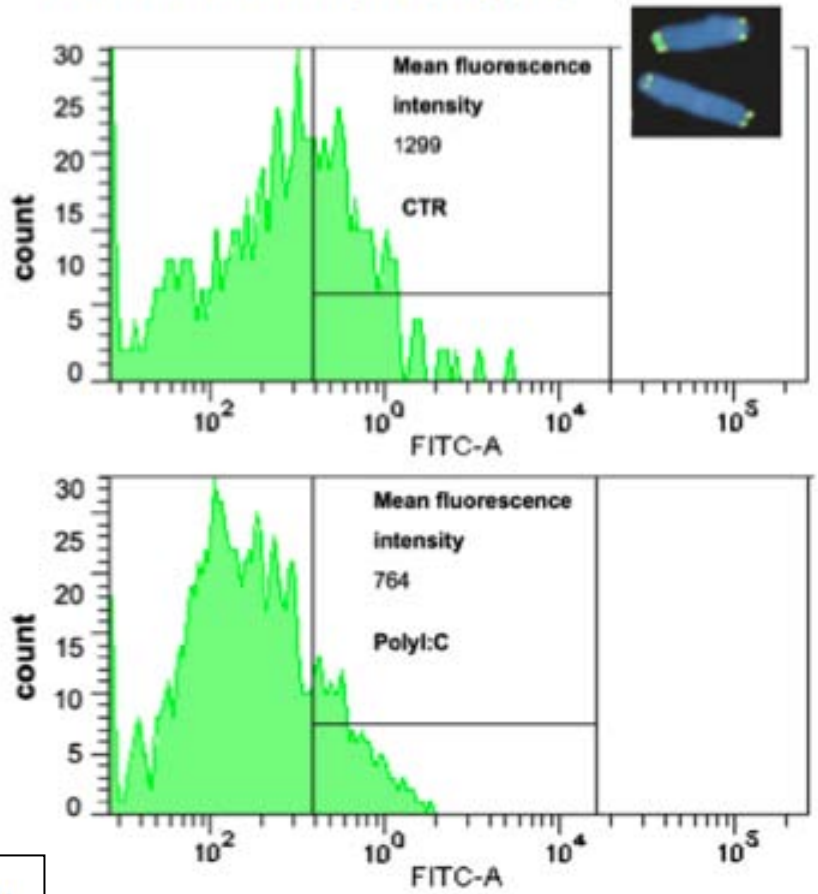
Susanne A. Wolf [a,*], Andre Melnik [a], Gerd Kempermann [b,c]

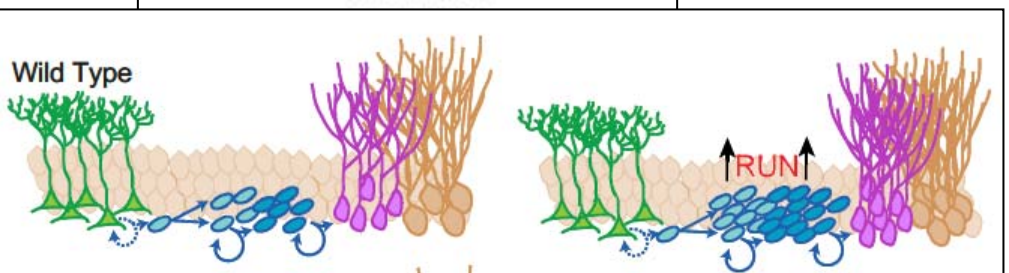
A **Exercise restores postnatal low telomerase activity levels in neuronal progenitor cells of Polyl:C animals**





B **Shorter telomere length in neuronal progenitor cells of adult Polyl:C progeny**





Adult neurogenesis and functional plasticity in neuronal circuits

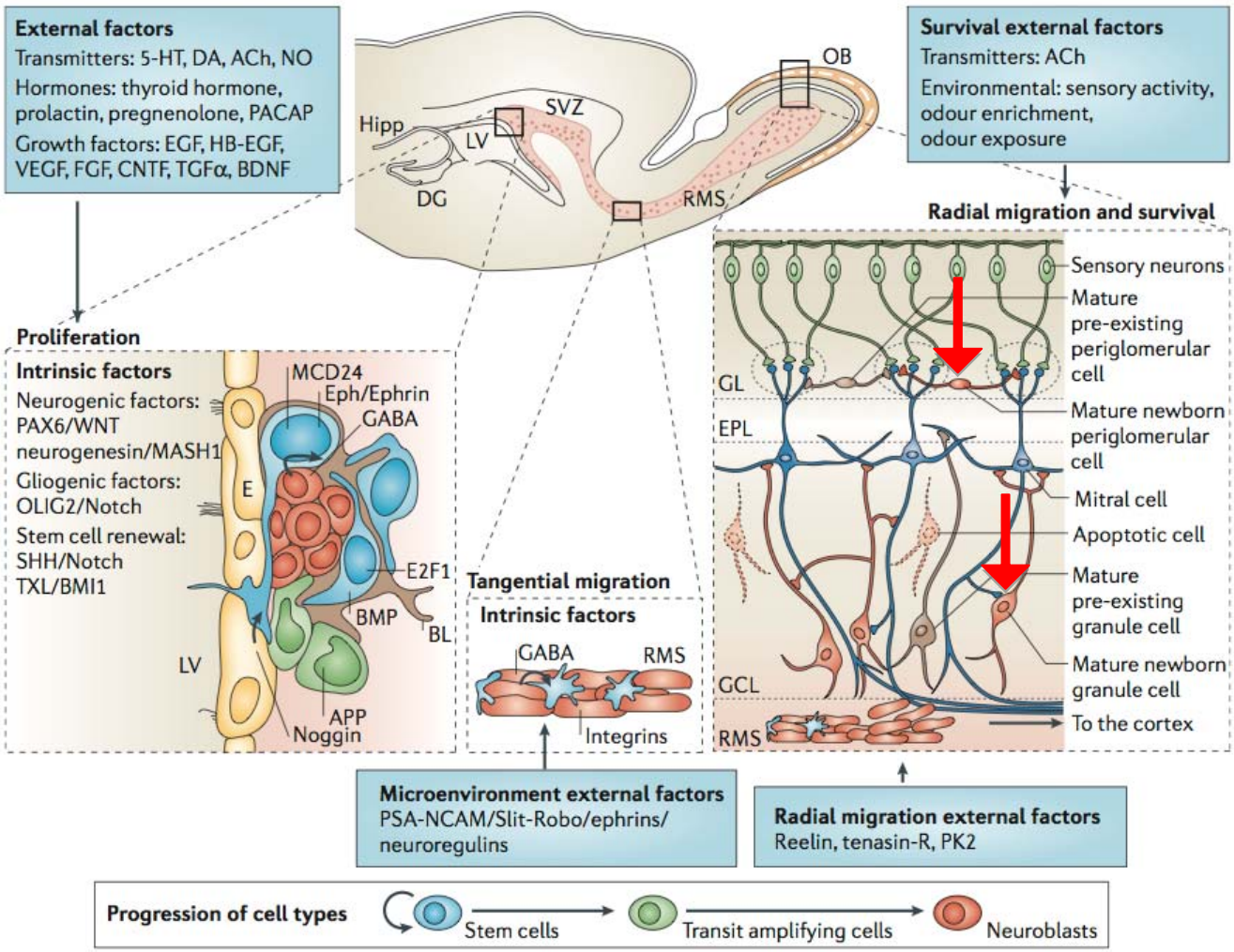
Nat Rev Neurosci
2006 vol. 7 (3) pp. 179-93

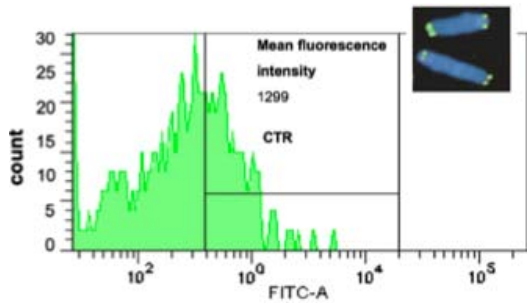
Lledo P, Alonso M, Grubb M

Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia

Susanne A. Wolf[a,*], Andre Melnik[a], Gerd Kempermann[b,c]

Brain, Behavior, and Immunity 25 (2011) 971–980





hippocampe cependant

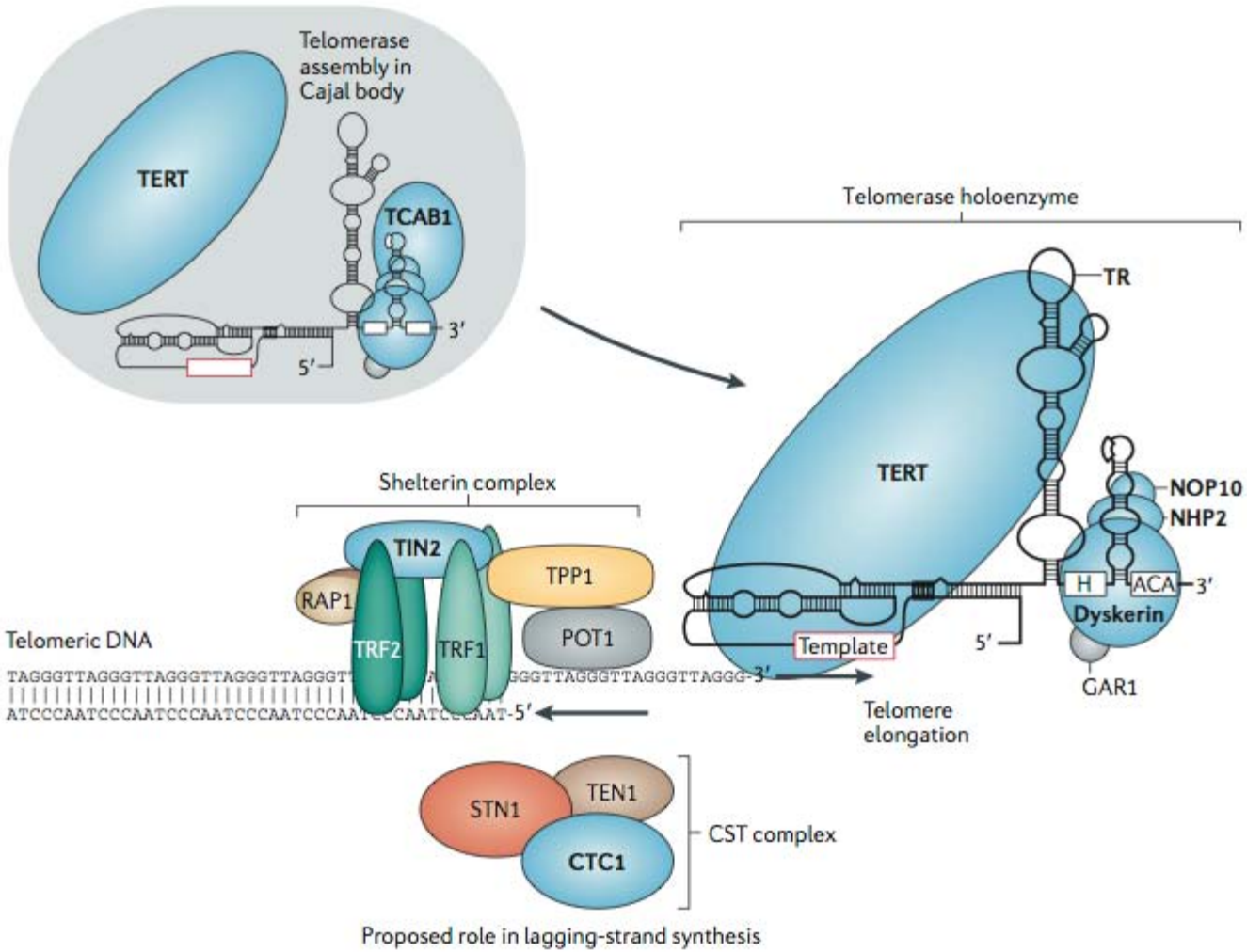
Periglomerular: TH

Granule Cells: GABA

The telomere syndromes

Nature Reviews Genetics
2012 vol. 13 (10) pp. 693-704

Armanios M, Blackburn EH

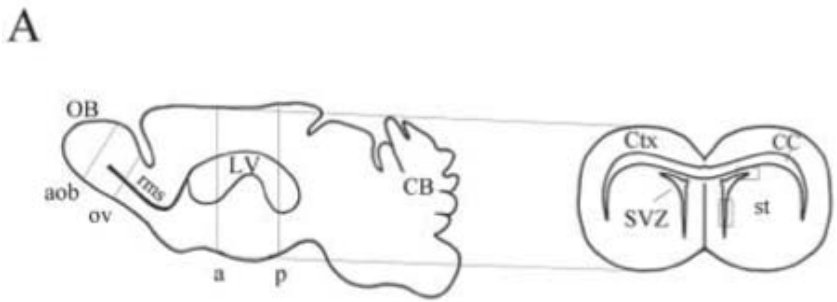


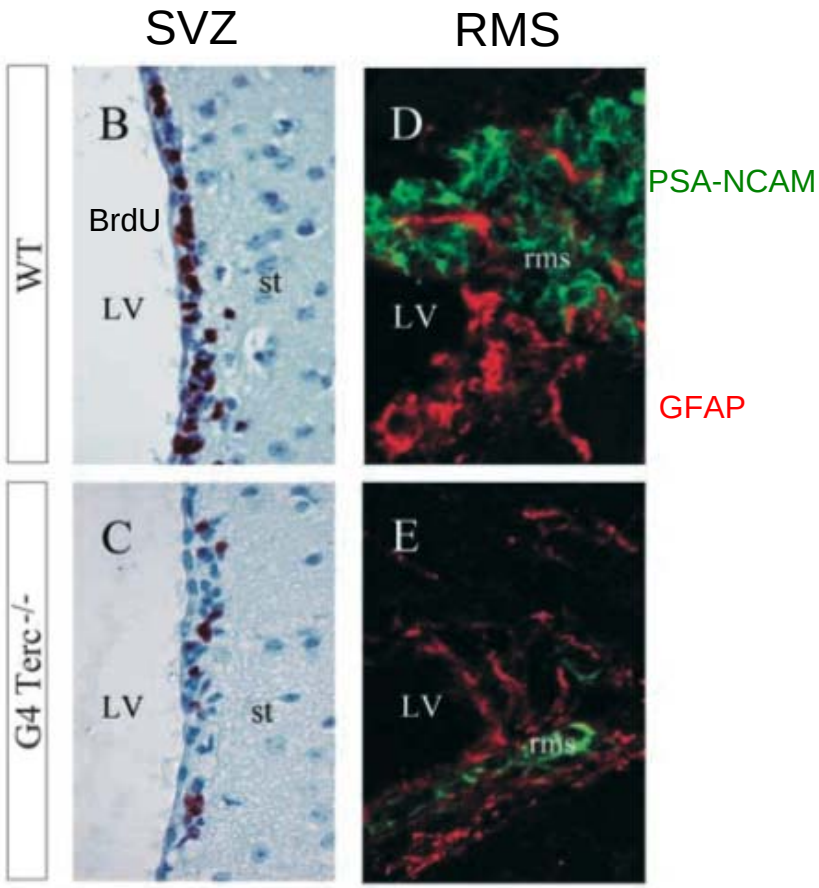
Proposed role in lagging-strand synthesis

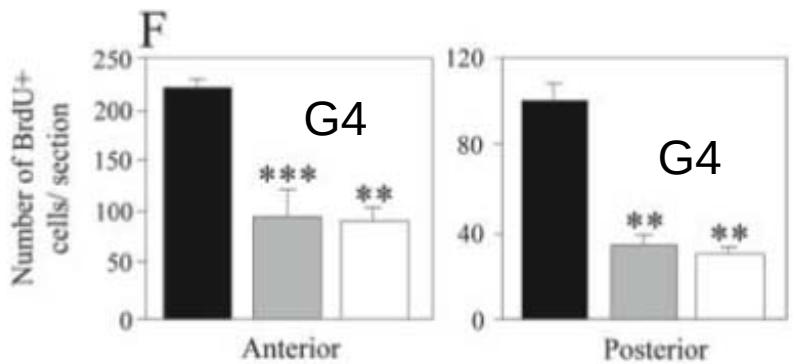
Telomere shortening and chromosomal instability abrogates proliferation of adult but not embryonic neural stem cells

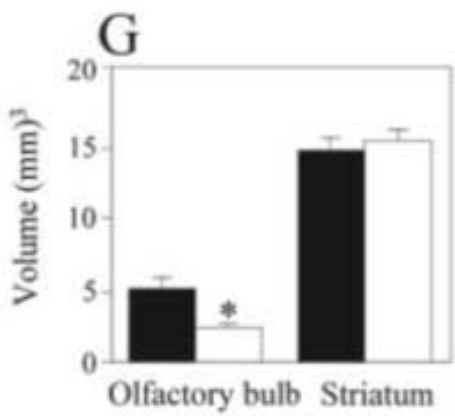
Ferrón S, Mira H, Franco S, Cano-Jaimez M, Bellmunt E, Ramírez C, Fariñas I, Blasco MA

Development
2004 vol. 131 (16) pp. 4059-70









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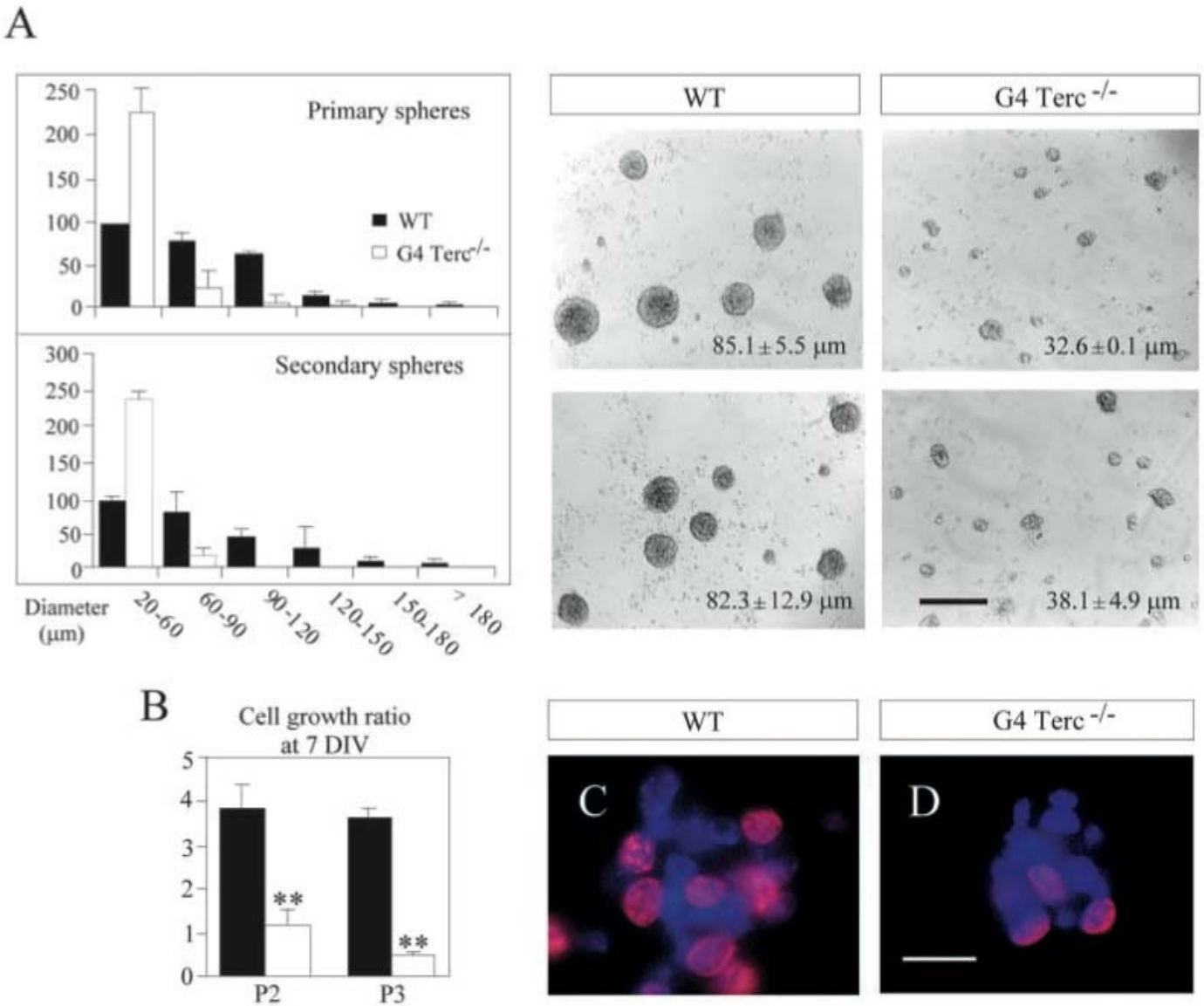

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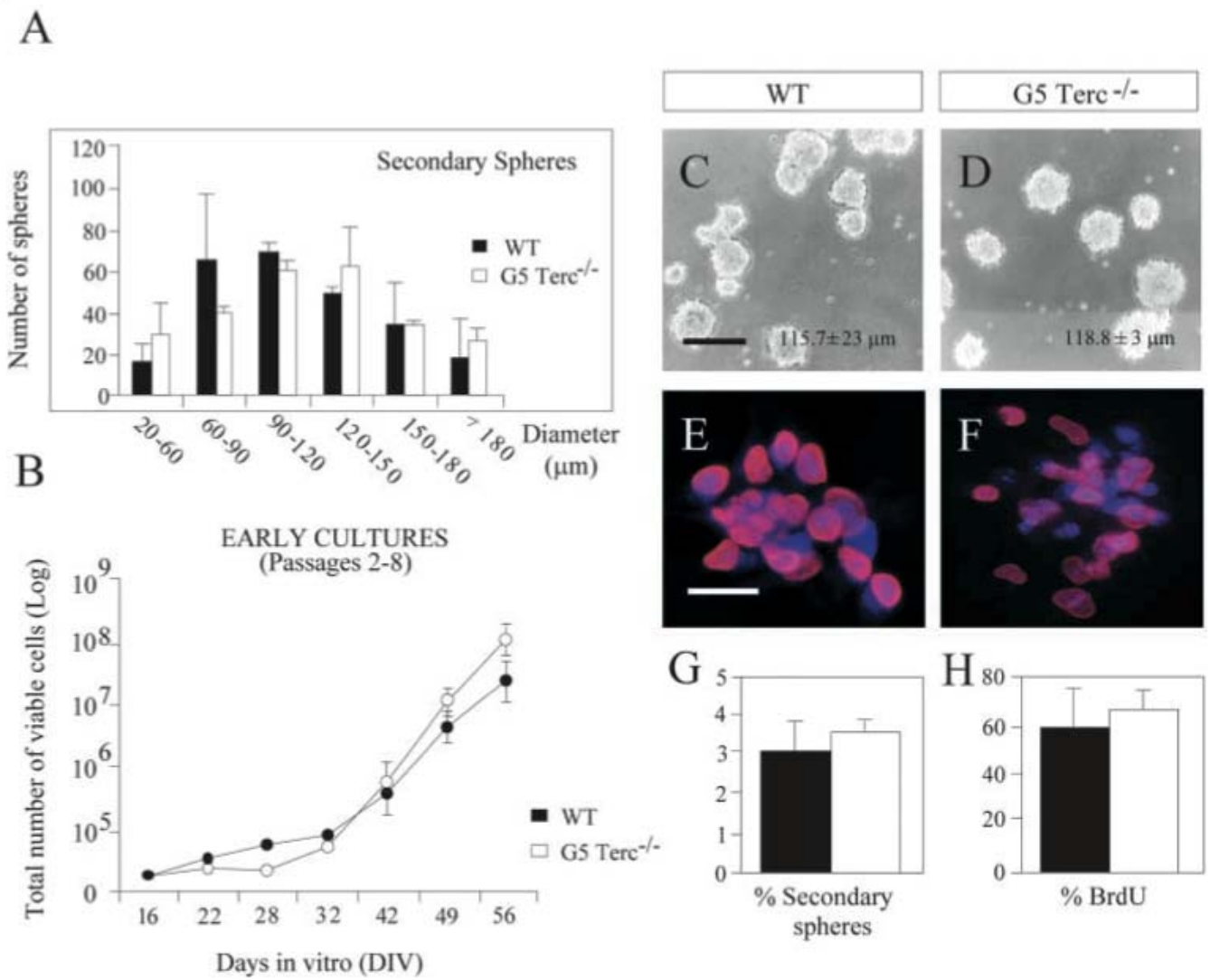

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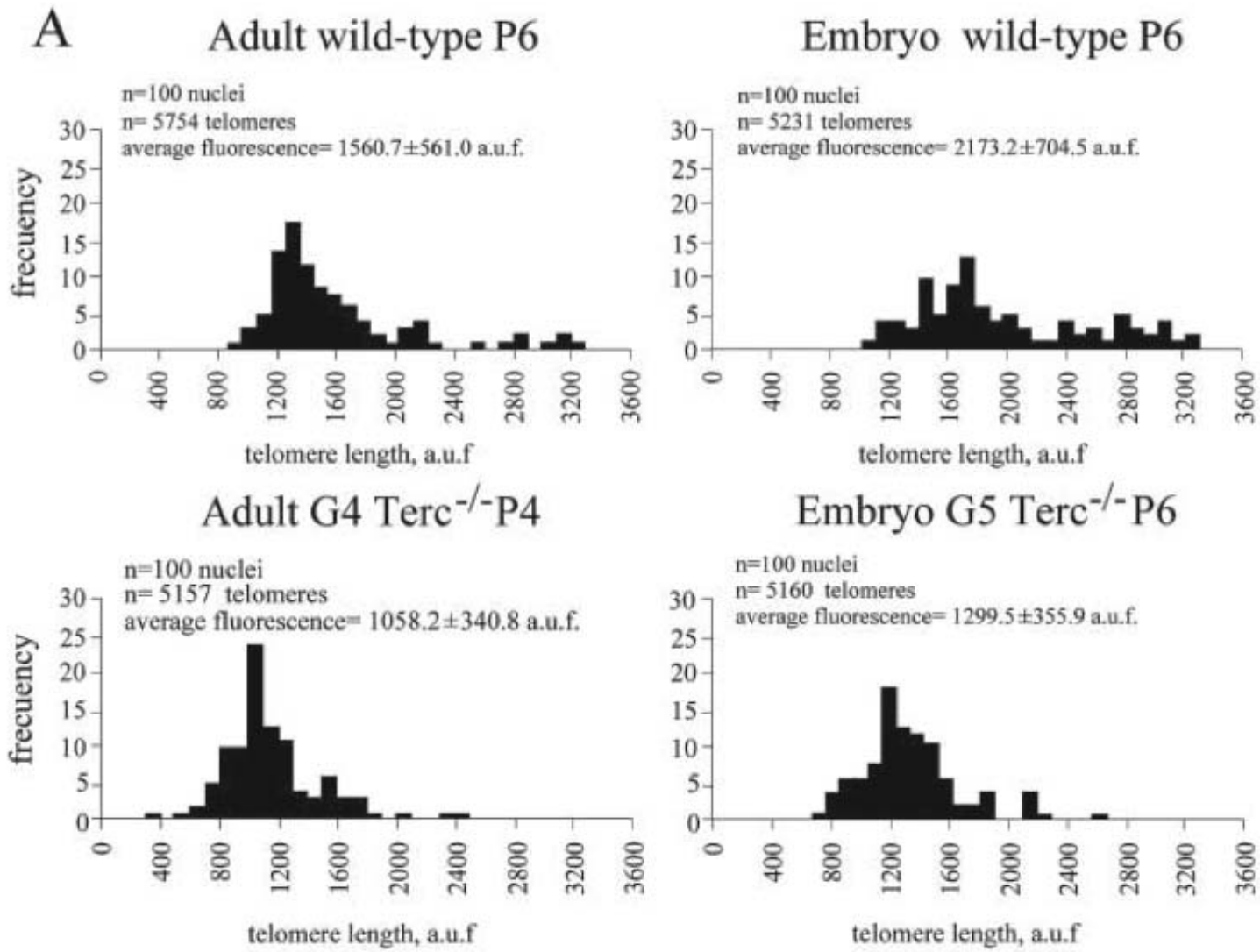

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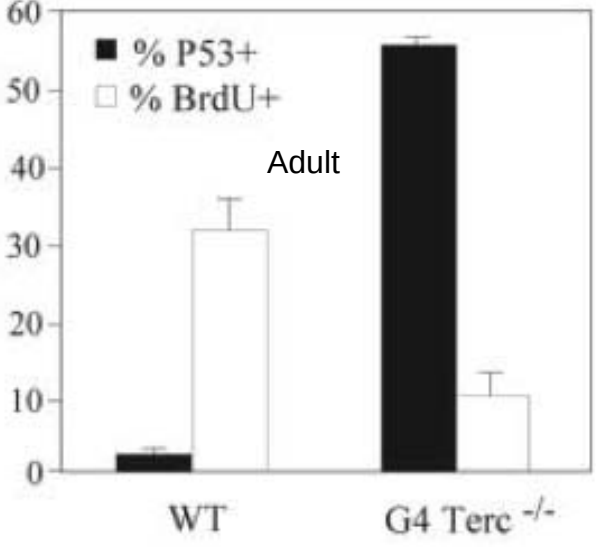
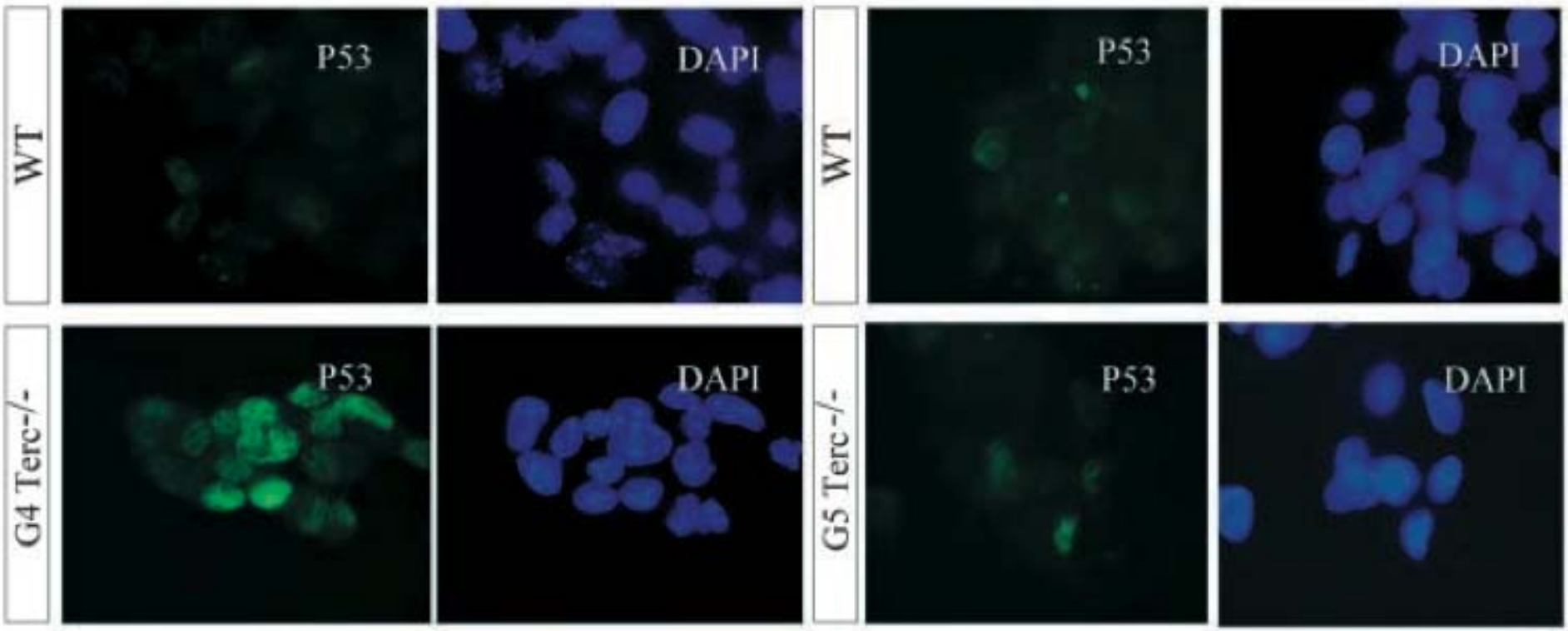


Adult

Embryo



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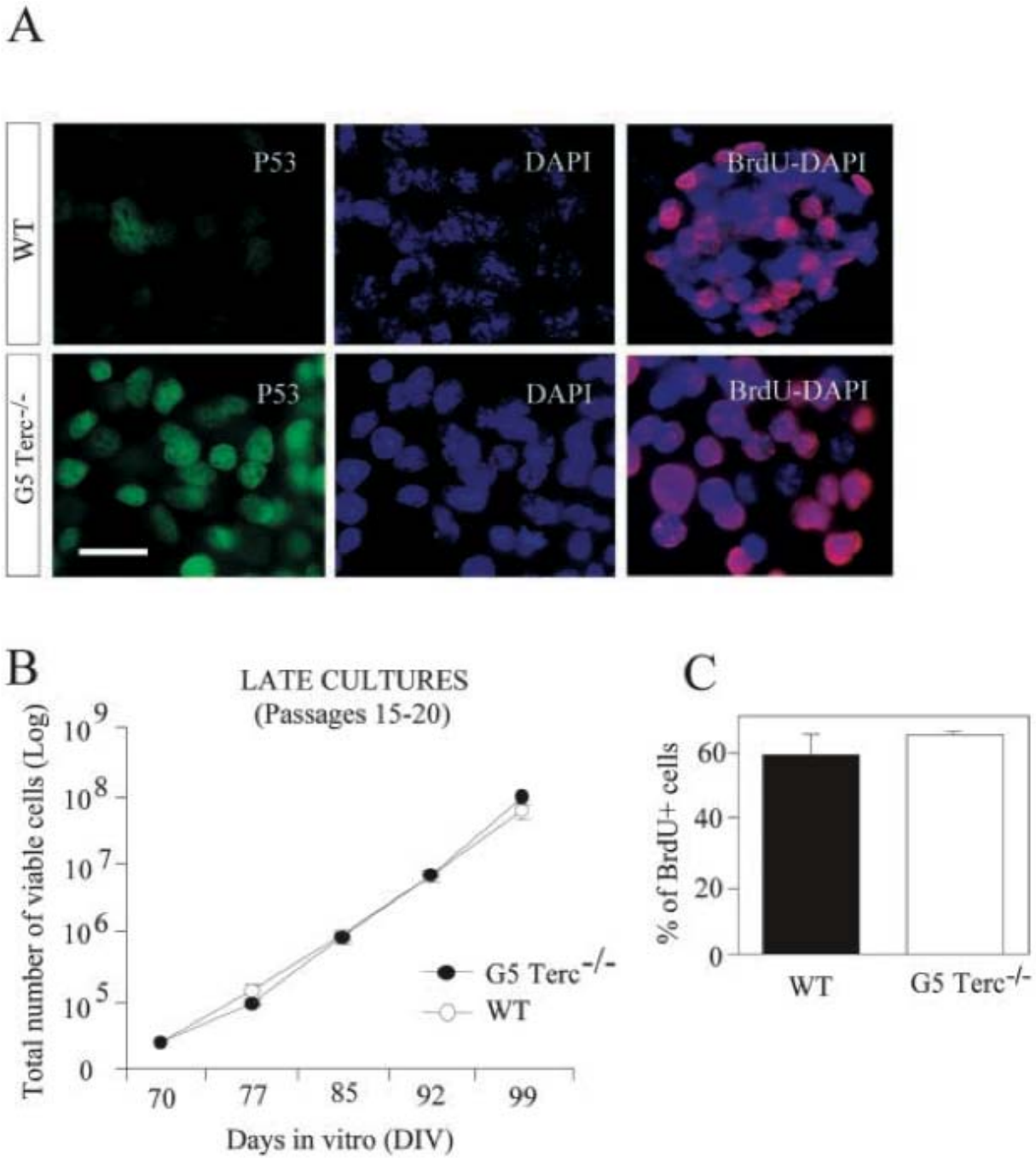
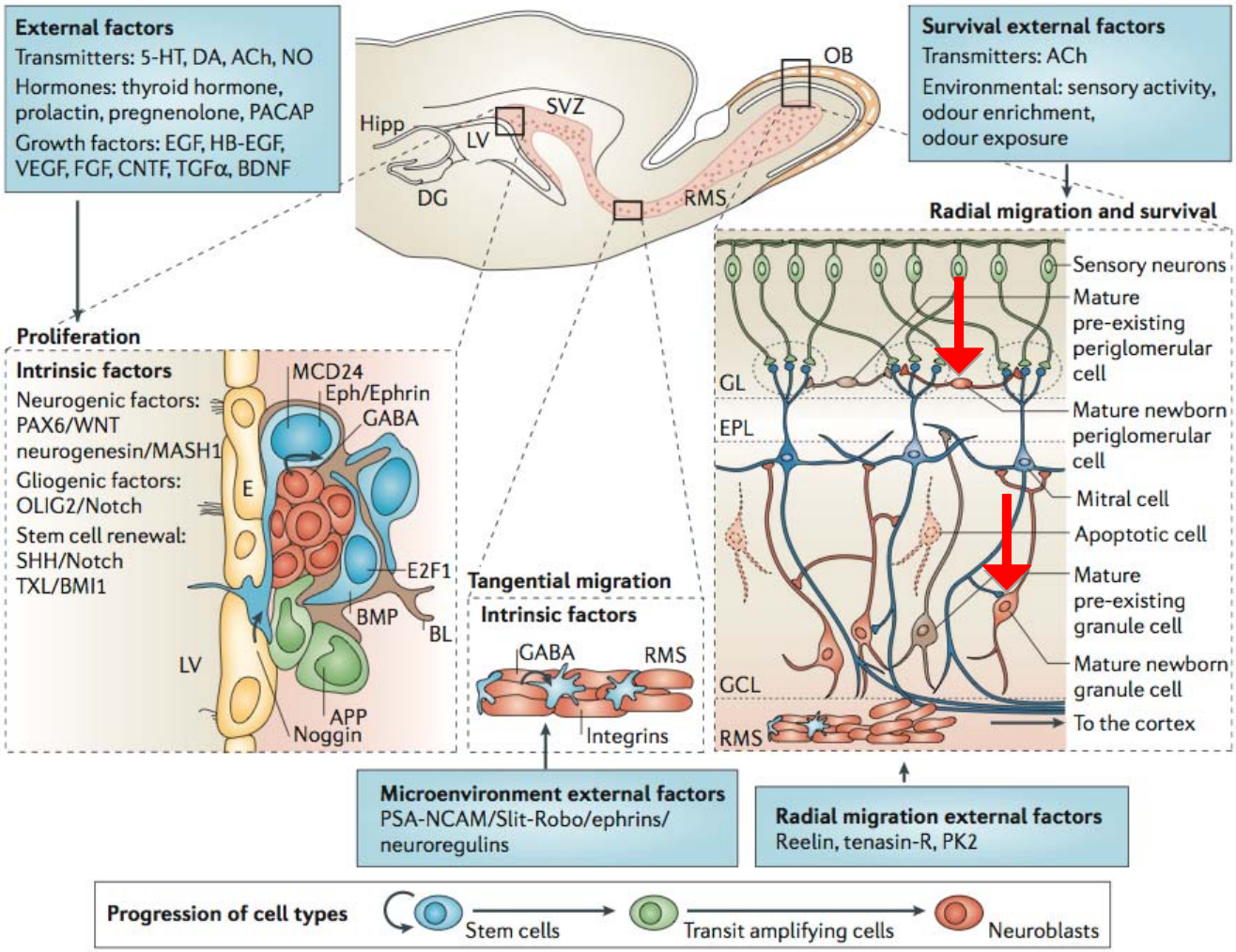


Adult neurogenesis and functional plasticity in neuronal circuits

Nat Rev Neurosci
2006 vol. 7 (3) pp. 179–93

Lledo P, Alonso M, Grubb M



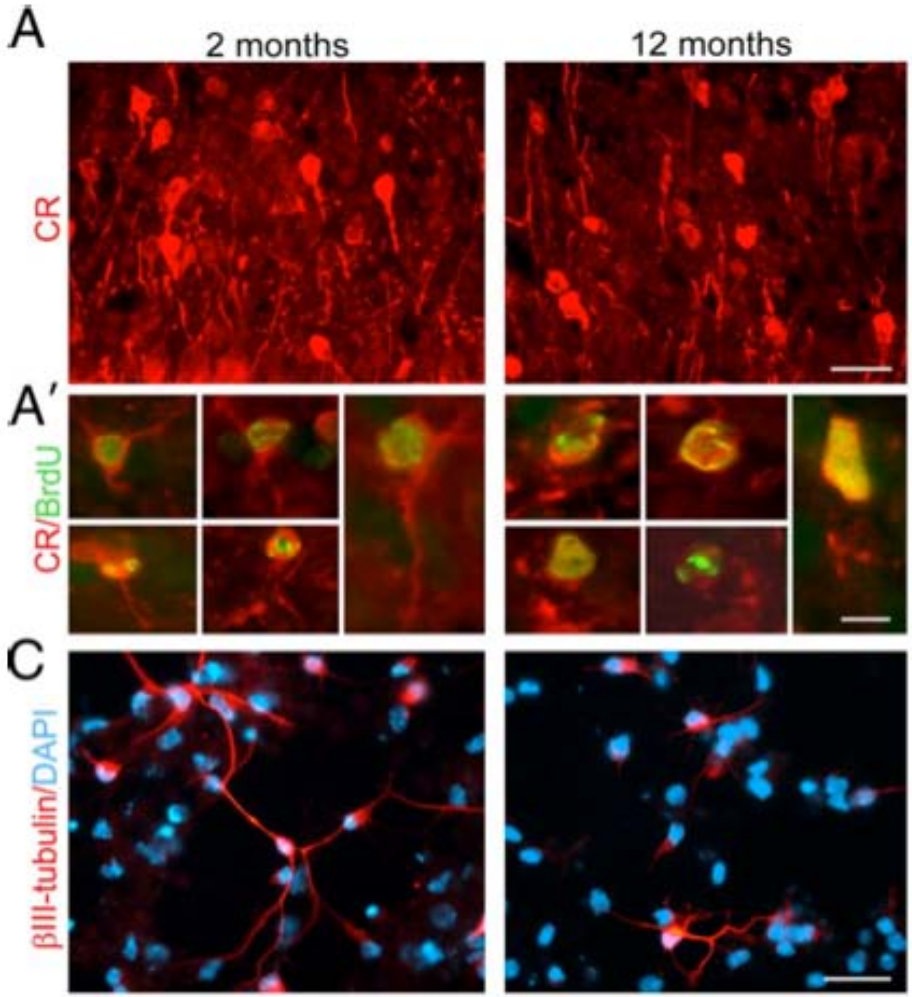
TH

GABA

Telomere shortening in neural stem cells disrupts neuronal differentiation and neuritogenesis

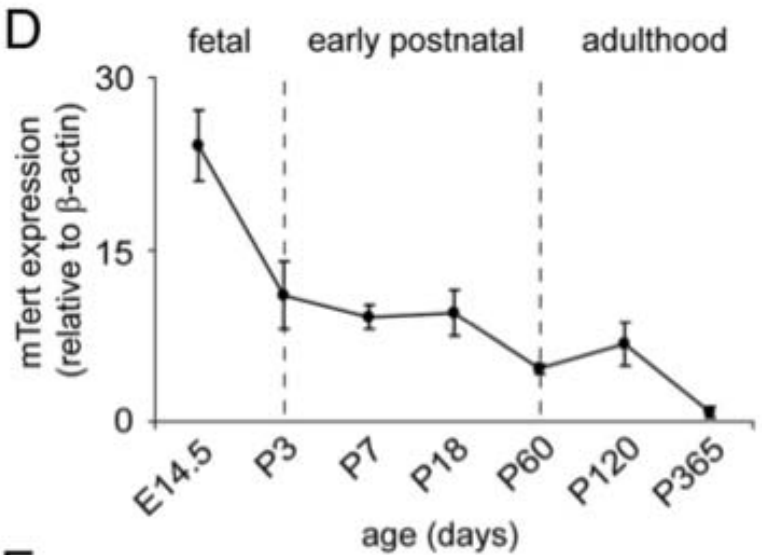
J Neurosci
2009 vol. 29 (46) pp. 14394-407

Ferrón SR, Marqués-Torrejón MA, Mira H, Flores I, Taylor K, Blasco MA, Fariñas I



B

	OB (granular layer)	
age (months)	2	12
LRC	43.9 ± 6.6	14.4 ± 1.8*
%LRC/CR	5.1 ± 0.6	1.6 ± 0.2**



E

	neurospheres	
age (months)	2	12
mTert expression (a.u)	2.2 ± 0.4	1.3 ± 0.3**
telomere length (a.u)	67.9 ± 3.2	52.5 ± 3.4*