5 Zusammenfassung

Der Gyrus dentatus ist das primäre Eingangstor der Hauptafferenzen in den Hippocampus und repräsentiert eine von insgesamt nur zwei im Gehirn von Säugetieren existierenden Regionen in denen adulte Neurogenese stattfindet. Während seiner Entwicklung erlangt der Gyrus dentatus durch die Etablierung einer neuen neurogenen Nische (tertiäre Matrix) die Fähigkeit zur fortgesetzten postnatalen Neurogenese. Neurogenese wird durch eine Vielzahl von Transkriptionsfaktoren gesteuert, die sowohl die Proliferation und Differenzierung als auch das Überleben der Progenitorzellen und unreifen Neurone kontrollieren. Bcl11b kodiert für einen hochkonservierten Zinkfinger-Transkriptionsfaktor, der sowohl während der Entwicklung als auch im adulten Hippocampus exprimiert wird. Bcl11b Null-Mutanten sterben kurz nach der Geburt. Um die Funktionen von Bcl11b auch im postnatalen Hippocampus bestimmen zu können, wurde ein Mausstamm verwendet, bei dem Bcl11b konditionell im Vorderhirn deletiert wird. Durch die Phänotypanalyse dieser postnatal lebensfähigen Mutanten konnte ich zeigen, dass Bcl11b essentielle Funktionen während der postnatalen Entwicklung des Gyrus dentatus besitzt: Während die pränatale Entwicklung des Hippocampus in Bcl11b Mutanten normal verläuft, ist die postnatale Neurogenese von Körnerzellen innerhalb der sekundären neurogenen Nische Bcl11b-abhängig. Bcl11b ist einerseits an der Kontrolle der Proliferation der Progenitorzellen der tertiären Matrix beteiligt, andererseits wird Bcl11b auch für die späte Differenzierung der unreifen Neurone im postnatalen Gyrus dentatus benötigt. Der Funktionsverlust von Bcl11b führt in den Mutanten sowohl zu einer signifikanten Reduktion mitotisch aktiver Progenitorzellen als auch einer vermehrten Anzahl unreifer und vermehrt apoptotischer Neurone in der Körnerzellschicht. Die Folge ist ein verkleinerter Gyrus dentatus mit einer signifikanten Reduktion an Körnerzellen in Bcl11b Mutanten. Durch Verhaltensexperimente konnte ich ferner zeigen, dass die gestörte postnatale Neurogenese mit einem eingeschränkten räumlichen Lernverhalten der mutanten Mäuse im Radiallabyrinth assoziiert ist.

Meine Untersuchungen zeigen damit erstmals essentielle Funktionen des Transkriptionsfaktors Bcl11b während der postnatalen Neurogenese des Gyrus dentatus und der Ausbildung der normalen Hippocampusfunktion bei Lern- und Gedächtnisprozessen.

Summary

The dentate gyrus is the primary afferent pathway into the hippocampus and represents one of two locations with continuing neurogenesis in the adult mammalian brain. During development the dentate gyrus acquires the capacity for ongoing neurogenesis by generating a new neurogenic niche (tertiary matrix). Neurogenesis is regulated by a network of transcription factors that control proliferation, differentiation, as well as survival of the progenitor cells, and immature neurons. Bcl11b encodes a highly conserved zinc finger transcription factor that is expressed in the developing and adult hippocampus. Mice with a null-mutation of the Bcl11b gene die shortly after birth. To determine the role of Bcl11b in the postnatal hippocampus, conditional mutagenesis of the Bcl11b gene in the forebrain was employed. Analysis of these viable mice demonstrates that Bcl11b has essential functions during postnatal development of the dentate gyrus: Bcl11b is dispensable for the prenatal hippocampal development, however postnatal neurogenesis of dentate granule cells from the secondary neurogenic niche depends on Bcl11b. Bcl11b is involved in the control of the proliferating progenitor cells of the tertiary matrix as well as the terminal differentiation of immature neurons. As a consequence, proliferating progenitor cells are significantly depleted in mutants and numbers of immature neurons are increased, which, in turn, fail to undergo appropriate terminal differentiation. In addition, impaired postnatal neurogenesis is associated with an elevated apoptotic cell death in the granule cell layer leading to significant reduction of the dentate gyrus size and cell number at the end of the development.

Moreover, the affected postnatal development of the dentate gyrus in the mutants is accompanied by an impairment of spatial learning in the radial arm maze.

The data presented here revealed for the first time an essential role for Bcl11b in regulating neurogenesis during the postnatal development of the dentate gyrus, which is necessary for proper hippocampus function in learning and memory processing.

6 Literatur

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7 Anhang

Im Anhang befinden sich das Abkürzungsverzeichnis, meine Danksagung, ein tabellarischer Lebenslauf und die eidesstattliche Erklärung über die eigenständige Anfertigung der vorliegenden Arbeit.

Abkürzungsverzeichnis

Abb.	Abbildung
AS	Aminosäuren
AP	Alkalische Phosphatase
BCIP	5-Bromo-4-Chlor-3-Indolylphosphat
bp	Basenpaare
BSA	(engl.: bovine serum albumin) Rinderserumalbumin
°C	Grad Celsius
ca.	circa
cDNA	(engl.: complementary DNA) komplementäre DNA
cRNA	(engl.: complementary RNA) komplementäre RNA
Cy2	Cyanin
Cy3	Indocarbocyanin
Cy5	Indodicarbocyanin
dCTP	Deoxycytidintriphosphat
DEPC	Diethylpyrocarbonat
DIG	Digoxigenin
DMSO	Dimethylsulfoxid
DNA	(engl.: desoxyribonucleic acid) Desoxyribonukleinsäure
dNTPs	Desoxyribonukleosidtriphosphate
DTT	Dithiothreitol
E	Embryonalstadium (Tag der Embryonalentwicklung nach Vaginalpfropfen)
EDTA	(engl. ethylenendinitrilotetraacetic acid) Ethylendinitrilotetraessigsäure
EST	(engl.: expressed sequence tags) exprimierte Sequenzstellen
et al.	et alteres
g	Gramm
β-gal	β-Galaktosidase
x g	Erdbeschleunigung
h	Stunden
IPTG	1-Isopropyl-β-D-1-thiogalactopyranosid
kb	Kilobasenpaare
l	Liter
LB	Luria Broth
m	milli
M	Molarität
MDC	Max-Delbrück Zentrum für Molekulare Medizin
MilliQ-H_2O	Wasser aus Ultrafiltrationsanlage (Milli-Q UF Plus; Millipore)
min	Minuten
µ	Mikro
mRNA	(engl. messenger RNA) Boten-Ribonukleinsäure
n	nano
NBT	Nitroblautetrazoliumchlorid

Neo	Neomycin
OD	optische Dichte
P	postnatales Stadium (Tag nach der Geburt)
pBS	pBluescript SK II (+)
PBS	(engl. phosphate buffered saline) phosphatgepufferte Salzlösung
PCR	(engl.: polymerase chain reaction) Polymerase-Kettenreaktion
PFA	Paraformaldehyd
PNS	Peripheres Nervensystem
RNA	(engl.: ribonucleic acid) Ribonukleinsäure
RNase	Ribonuclease
rpm	(engl.: revolutions per minute) Umdrehungen pro Minute
RT	Raumtemperatur
RT-PCR	Reverse Transkriptions-PCR
RZPD	Deutsches Ressourcenzentrum für Genomforschung (Berlin)
s	Sekunden
s.	siehe
SDS	Natriumdodecylsulfat
SSC	(engl.: standard saline citrate) Standard-Zitronensäuresalz
Tab.	Tabelle
TBS	(engl.: tris buffered saline) Tris-gepufferte Salzlösung
TE	Tris-EDTA
Tris	2-Amino-2-(hydoxylmethyl)-1,3-propandiol
tRNA	Transfer-Ribonucleinsäure
U	(engl.: Units) Einheiten
UTR	(engl. untranslated region) nicht-translatierte Region
üN	über Nacht
v.a.	vor allem
VE-Wasser	vollentsalztes Wasser
Vol.	Volumen
WT	Wildtyp
X-Gal	5-Brom-4-Chlor-3-Indolyl-β-D-Galactopyranosid
z.B.	zum Beispiel
ZNS	Zentrales Nervensystem

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Lebenslauf

Aus Datensicherheitsgründen wird der Lebenslauf online nicht veröffentlicht.

Eidesstattliche Erklärung

Hiermit erkläre ich eidesstattlich, dass ich die vorgelegte Dissertation selbstständig und ohne unerlaubte Hilfe angefertigt habe. Die genutzte Hilfe und die verwendeten Hilfsmittel und Quellen habe ich vollständig angegeben. Abbildungen, die anderen Quellen unverändert entnommen oder diesen entlehnt wurden, sind mit der Quellenangabe gekennzeichnet. Ich versichere, dass ich mich nicht anderwärtig um einen Doktorgrad beworben habe oder einen entsprechenden Doktorgrad besitze. Diese Dissertation habe ich keinem anderen Fachbereich oder keiner anderen Universität vorgelegt. Die Bestimmungen der Promotionsordnung des Fachbereichs Biologie, Chemie, Pharmazie der Freien Universität Berlin sind mir bekannt.

Heike Brylka