Microtubule associated proteins and plasticity in the developing and diseased brain

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COLOR FIGURES
Color Figures

Figure 4. Adult neurogenesis in the hippocampal DG

A. Nissl stained dentate gyrus. In a thin layer of cells on the border of the granular cell layer (GCL) and the hilus called the subgranular zone (SGZ) remain stem cells which continuously produce new neurons. After a daughter cell has left the cell cycle, it migrates into the GCL where it becomes a fully functional neuron in about 4 weeks time. Proliferating cells can be stained using Ki-67 antibodies. Immature neurons (of 3 days to 21 days old) can be stained using doublecortin antibodies. After (Christie and Cameron, 2006)

B. The thre synaptic circuitry of the hippocampus. Direction of signalling and synaptic transmission is indicated by arrows in axonal projections. LPP: lateral perforant path; MPP: medial perforant path; MF: mossy fibers; AC: anterior commissure; SC: schaffer collaterals

Abbreviations: V3; 3rd ventricle, H; hypothalamus, OV; optic vesicle; DD (T): dorsal diencephalon (thalamus). Scale bar in A is 100 μm. Scale bar in D is 10 μm.
DRG (right arrow in K) and is also seen in fiber bundles of the vagal nerve oriented towards the pericardial cavity (left arrow in K). DCL is not only found in DRGs, albeit at generally lower levels, but also in rostrocaudally oriented fibers (arrowhead in J), but not in cellular profiles, nor in apoptotic cells (arrow in J). Scale bars in B, D and N are 10 μm. Scale bar in J is 20 and in L is 250 μm.

Figure 5. Multiple Immunofluorescent analysis of DCL and DCX expression in the neocortex and spinal cord at E11.

Fluorescent double labelings of the neuroepithelium [A] confirm the differential expression pattern of DCX and DCL. DCX is expressed at particularly high levels in the VZ (arrows) and at considerably lower levels in the PP. DCX is mainly more robustly expressed in the PP. In the spinal chord (D) DCX and DCL partly overlap in what appears to be tangential fibers, whereas DCL is additionally, and selectively, expressed in radial fibers. Scale bars in C and D are 50 and 12 μm, respectively.

Figure 6. DCL expression in neuronal tissues at E13.

Compared to E11 and DCX levels (Fig A and D), DCL expression in the VZ is reduced at E13 (Fig B and E). The overall expression pattern of DCL in other areas like the spinal cord DRGs, thalamus, pons and CP in the midbrain (B) is generally comparable to that of DCX at this age (A), but differs from vimentin expression at this age (C) that is strongly reduced e.g. in the thalamus and hypothalamus. Higher magnifications of the developing neuroepithelium surrounding the 3V show extensive DCL expression in the CP (D) and a strong reduction in DCL (E) expression in the CP. IZ. Strikingly, DCL expression was completely absent in the VZ. This contrasts with vimentin, that is expressed in CP and VZ (F).

Additional regions that showed considerable DCL expression were the olfactory epithelium (OE) [G and H] where high levels were found in the outer layer close to the nasal cavity (NC); as well as in radial fibers oriented towards the outer layer (H). DCX is not expressed in this region (not shown). In the developing pons (P in A) both DCX (I) and DCL (J) are expressed in tangentially (arrowheads) and radially (arrows) oriented fibers. Also in optic fibers (OF) of the developing eye (K), DCX (K) and DCL (L) expression was found, with lower levels for DCL. In the basal layer of the developing retina only DCL and not DCX was expressed, often in association with mitotic cells (arrows, higher magnification in inset in L).

Scale bar in A is 1 mm. Scale bar in E, J and L is 50 μm. Scale bar in G is 250 μm. Scale bar in H is 10 μm. Abbreviations: ctx: cortex; bg: basal ganglia; thal: thalamus; ht: hypothalamus; mb: midbrain; C: cerebellum; p: pons; nc: nasal cavity.

Figure 7. Differential expression of DCX and DCL in spinal cord and dorsal root ganglia at E13.

Sagittal section showing DCX to be primarily expressed in the upper DRGs in fibers with a dorso-ventral orientation (arrow in A, C), whereas DCL is abundant in more caudally located, rostrocaudally orientated fibers (B, D). Scalebar in B is 500 μm. Scalebar in D is 50 μm.

Figure 8. DCL expression at E15 and E17.

Whereas DCX expression in the neuroepithelium remains high in MZ/PP and IZ (A), DCL expression (B) in the lateral epithelium of the lateral ventricles has further declined. Vimentin (C) is weakly expressed throughout the neuroepithelium but especially high in the VZ. Although in the CNS, DCX expression is higher than expression of DCL. DCL expression exceeds that of DCX in the developing tongue. DCL and DCX positive cells reside at the tongue base in fibers orientated in different directions (I and D). At E17, DCL expression has further declined (G) and is nearly undetectable in the ventricular zone. DCX (F) is now also expressed in the MZ. Vimentin expression remains stable (H). Scale bar in C is 10 μm. Scale bar in E indicates 100 μm. Scalebar in G is 50 μm.

Figure 9. Summary of the observed findings.

This scheme summarizes the main observations in this study. A. Spatial distribution of DCX, DCL and vimentin at E11 and E13. B. Level of DCX and DCL expression during development.

Chapter 3

Figure 2. Tau expression affects proliferation, differentiation and axonal outgrowth in primary hippocampal cultures from tau-KOKI mice

A. Western blotting for total tau (antibody tau5) and human tau (antibody HT-7) in cell lysates from non-transgenic (WT) and tau-KOKI primary hippocampal cultures analyzed at 4 DIV and 10 DIV. Asterisks denote unspecific bands reacting with the secondary antibodies. Apparent molecular weight as indicated (kDa). Tau is expressed at 10 DIV but not at 4 DIV in tau-KOKI cultures, in WT cultures the predominant tau isoform is of the 4R variant. 

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B. Immunocytochemical staining for total tau (antibody tauS) and human tau (antibody HT7) shows again that tau is expressed at 10 DIV but not at 4 DIV in tau-KOKI primary cultures.

C. The BrdU labeling index (LI) in hippocampal cell cultures at 4 DIV is increased in tau-KOKI mice but normal at 10 DIV compared to non-transgenic (WT) mice at 4 and 10 DIV.

D. The percentage of NeuN positive cells is decreased in hippocampal cell cultures from tau-KOKI mice at 4 DIV but increased at 10 DIV compared to non-transgenic mice (WT).

E. The percentage of nestin positive cells in hippocampal cell cultures from tau-KOKI is increased at 4 DIV but decreased at 10 DIV compared to non-transgenic (WT) mice.

F. Representative BrdU, NeuN and nestin staining of primary hippocampal cultures from tau-KOKI mice at 4 DIV.

G. Relative neurite protein levels are decreased in hippocampal cell cultures from tau-KOKI at DIV 4 but normal at DIV 10 compared to non-transgenic (WT) mice.

H. Representative axon-specific staining with antibody SMI-312 showing delayed axonal outgrowth in primary hippocampal cultures from tau-KOKI mice at 4 DIV, which is completely restored at 10 DIV compared to non-transgenic (WT) mice.

In total, more than 1500 cells per group were scored from at least 3 different cell culture preparations. Data presented as normalized average OD values ± SEM. Statistical analysis by Mann-Whitney test, * = p = 0.05 and ** = p = 0.01 relative to control.

**Figure 7A.** Pictures of the immunohistochemical markers doublecortin (DCX), staining young migrating neurons, and BrdU, a marker for survival, used to label 3-4 wks old cells.

**Chapter 4**

**Figure 1.** Immunohistochemistry for human tau and phosphorylated tau in the hippocampus of young nontransgenic and tau-4R and tau-P301L transgenic mice.

Human protein tau was detected with mAb H7 in the hippocampal formation of tau-P301L and tau-4R transgenic mice [8 weeks of age] but not in nontransgenic mice (FVB/N). IHC with the phosphorylation-specific antibodies AD2, AT8, and AT180 demonstrated less phosphorylation in tau-P301L mice. Except for IHC with H7, all sections were counterstained with hematoxylin (original magnification, 5x).

**Figure 7.** Newborn cells and survival in young tau-P301L transgenic mice.

Different markers were examined to define putative changes in cell genesis and/or turnover. A, D. Immunohistochemistry for doublecortin marks young neurons. B, E. BrdU was analyzed 4 weeks after injection as a measure of cell age (see Results for details). C. Immunohistochemistry for the Ki-67 antigen as a marker of proliferating cells. A-C show an overview of the dentate gyrus, and representative individual cells or groups of cells are illustrated in D and E. Sections were counterstained with hematoxylin.

**Chapter 5**

**Figure 7.** Glial Fibrillary Acidic Protein (GFAP) Immunohistochemistry

A. Very little signal is present in the CA1 area of a control subject immunostained for GFAP.

B. Conversely, abundant glial and many GFAP positive reactive astrocytes (arrow) are present in CA1 and cortical grey matter of an AD patient. C. Abundant glia staining is seen in the hilus and SGZ of most of the AD patients with only occasionally glial activation apparent in the molecular layer. D. In most controls subjects, very little glial activation was found in the SGZ, GCL or molecular layer.

E. In AD patients, abundant glial activation in the SGZ (arrows) and hilus was often observed.

F. Detail of E showing clusters of GFAP positive astrocytes (arrows) present in the SGZ.

(G) and hilus (H). Often GFAP positive protrusions were extended and traversed through the GCL into the molecular layer. I. Only in a few cases, abundant activation of GFAP positive astrocytes was seen within the GCL and the molecular layer.

SGZ: Subgranular zone, mol: molecular layer, H: hilus, GCL: granular cell layer. Magnification in A, B, D, E, M, H and f: 250x, C: 100x, F and G: 400x

**Fig 8.** DCX Immunohistochemistry

A. Representative illustration of the arrangement of newly generated neurons in the two blades of the adult mouse dentate gyrus as shown by doublecortin immunohistomistry (perfused brain tissue). Prominent staining
of branching apical dendrites is visible that traverse the granular cell layer and cross the inner and middle molecular layers to often reach into the outer molecular layer (OML, arrows).

B. High magnification showing the typical distribution pattern of the microtubule associated protein doublecortin in rodent brain that is prominent in the soma as well as in the dendrites (arrowheads).

C. Representative illustration of a DCX positive neuron in the rat dentate gyrus (immersion fixed) after a 1 hour post mortem delay. A prominent reduction in immunoreactivity is apparent, not only in the soma, but even more so in the dendrites.

D. DCX immunoreactivity of a rat brain with a PMD of 8 hours, showing only some DCX staining of the soma (arrows) remaining in the GCL, yet very little. If any, dendritic staining remains present. *: hilus

E. At 12 h PMD, DCX soma staining is very weak in rat brain, while an additional, granular staining pattern is apparent in the SGZ and hilus (arrows).

F. High magnification of newly born neurons in the SGZ/GCL after 3 h PMD, illustrating poor dendritic staining (arrowhead).

G. High magnification of a DCX positive, newly born neuron in the rat DG after a PMD of 8 hours. Note the presence of a nucleolus (arrow) and the complete absence of dendritic staining, as compared to figs A and B.

H. Illustration of probably the remnant of a DCX positive cell, in the SGZ after a PMD of 12 h. The hilar region of a rat at a PMD of 8 h, illustrating the occurrence of an abundant granular staining DCX-IR pattern (arrows).

J. DCX positive cell clearly positioned in the SGZ of the human DG of an Alzheimer patient.

K. Higher magnification of J.

L. Illustration of the granular pattern of DCX immunostaining in the human hippocampus, that was mainly found in the SGZ (arrows)/hilus area.

M. DCX positive soma in the hilar/SGZ border of an AD patient. The arrow indicates the presence of a nucleolus. The inset shows a similar example in the hilus.

N. DCX staining in the hippocampal SGZ of an AD patient, showing both granular staining (arrows) and an occasional cellular profile.

Magnifications in A: 100x; B, I and L: 400x; C, F, G, H, K, M and N: 1000x; D and E, J: 250X

ADDENDUM

Figure 2. DCL is a MAP.

To confirm DCL is a MAP, three experiments were conducted. Firstly, expression of DCL in transfected COS-1 cells resulted in a fibrillar somal staining pattern overlapping the microtubular distribution (Panel I A-C). Overexpression of DCL lead to clear bundling of microtubule filaments (see also Fig. 6). Secondly, exposure to 10 mg colchicine, a compound that depolymerizes and disrupts tubulin microtubules, revealed around 90% of the DCL transfected cells to be resistant to 1-hr colchicine treatment (Panel I D+F).

Legend: Green represents DCL; red represents -tubulin and yellow indicates co-localization. Blue represents nuclear DNA. Arrows in F indicate DCL-associated microtubule bundles, which are resistant to colchicine treatment. Also note the clear association of DCL with a centrosome in A. Scale bar is 10 μm.

Figure 6. Immunocytochemical analysis of DCL and DCX protein expression in the embryonic brain.

A. At ED 11, DCL protein (sagittal section) is found throughout the telencephalon and diencephalon (left and right, respectively). DCL is found in the outer layers close to the pia as well as in the inner VZ (arrowheads; see also below). Non-neuronal tissue like the mandibular component of the first branchial arch (M) e.g., is devoid of any signal. IV: fourth ventricle. Bar represents 150 μm.

B + C: Adjacent transversal (coronal) sections from the early neuroepithelium at ED 9 immunostained for DCX (B) and DCL (C). DCX is absent at this age (arrowheads in B), whereas DCL is abundantly expressed in the inner ependymal (upper 2 arrows in C) and outer, early preplate/MZ region (lower arrow pointing leftward in C). Bar represents 25 μm.

D. Sagittal section of the neuroepithelium of the neural tube at ED11, showing abundant expression at the luminal border (arrowheads), while in the developing neuronal tissue, various mitotic cells express DCL (arrows). Bar represents 70 μm.

E. Detail of a DCL+ mitotic cell in the neocortical V2. Arrowhead points to the chiasmata oriented in the midline cleavage plane. Bar represents 5 μm.

F. DCL expression in the neuroepithelium and V2 (arrowhead on the left) of the early telencephalon at ED10. Many DCL+ processes extend radially towards the pial surface (arrowheads in upper left corner). In the preplate (arrowhead on the right), DCL is also found in tangentially orientated processes. DCL+ mitotic cells in the V2 are also visible (arrows). Bar represents 15 μm.

G. Immunostaining for the intermediate filament protein vimentin that identifies neurogenic radial glia, shows immunopositive cellbodies (arrow) in the lumenal surface (asterisks) and radial processes running through the V2 and SVZ (ED11).

H+I. Transversal cross-sections illustrating the differential, yet partly overlapping distribution of DCX and DCL. DCX is expressed at ED11 (H) in the upper preplate and CP/MZ (arrow). In contrast, DCL is already strongly...
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expressed at ED9 (I) in the VZ/ependymal layer (arrowhead to the left), with DCL+ radial processes extending towards the IZ (arrowhead on the right). The ventricular layer [asterisk in H] is devoid of DCX, but not of DCL signal. Bar represents 5 μm.

J: Detail of the VZ at ED9 showing DCL expression in processes radially extending into the SVZ and IZ (middle arrowhead). Also a mitotic cell lacking DCL expression between the chromosomes (right arrowhead) is visible. Bar represents 12 μm.

K: Detail of the VZ showing DCL+ dividing cells, that appear to be in telophase (left) and anaphase (middle), with a vertical cleavage plane. The cell on the left is likely in telophase or may represent two cells in interphase. A DCL+ cell on the right is visible with DCL expression between the chromosomes, with a horizontal cleavage orientation (arrowheads). Bar represents 8 μm.

L: DCL immunoreactivity in the VZ at ED11, in prophase and telophase cells (arrowheads) and in a blast-like precursor cell in metaphase/anaphase (arrow). Bar represents 10 μm.

M: Two DCL+ mitotic cells in the neuroepithelium displaying expression between chromosomes (upper arrow) as well as in structures resembling centrosomes (lower arrows). Bar represents 1.5 μm.

N+O: DCL immunoreactivity in dividing cells in anaphase II / telophase II (N) and in metaphase/anaphase I, with the chromosomes clearly visible (arrow in O), and in a radially extending process (arrowheads). Bars represent 1 μm.

**Figure 7. Confocal analysis of DCL and DCX protein expression in the embryonic brain.**

A-D: DCL expression in the VZ [ED10] (D) and in mitotic cells at the ventricular surface [arrow in D]. DCL, but not DCX [fig C], is associated with kinetochore microtubules (A; arrow) as well as polar microtubules [arrow in B]. Blue stain: Hoechst identified chromatin. Mitotic cells are DCX negative [inset C, see E,F,M,N&O], indicating a function of DCL at DCX at these ages. Bars represent 5 μm (A+B), and 12μm (D).

E-F: At E11, many DCL+ precursor cells (arrows) are found in the VZ and SVZ (arrows in F). These blast cells resemble those shown in Figure 5D, E and F, and are DCX negative, DCX+ processes are in close apposition to, but not overlapping with, the mitotic DCL positive blasts [inset E]. Bars represent 20 μm (F) and 5 μm (E).

G-J: Triple labeling of the neuroepithelial layer of an E13 mouse reveals expression of DCL in vimentin+ radial glial/neural precursors [merged image in J]. A mitotic cell oriented close to the ventricular surface is visible [H; arrow]. Bar represents 12 μm.

K-N: Triple labeling [E11] showing DCL expression in vimentin+ RGC throughout the neuroepithelium and VZ (upper arrowhead in K and M), and in neuroblasts in the SVZ/IZ (arrow on the left in K and M). This distribution pattern is distinctly different from DCX (shown in L), with weak expression in a.o. tangentially oriented migratory fibers in the VZ/SVZ, and expression in the early preplate/primitive plexiform zone [PP] (H). Only in the second proliferative layer between [SVZ and PPZ, where migrating precursors undergo M phase, are vimentin+ DCX+ and DCL+ triple labeled cells found [white: lower right arrow / cell on the left in N]. Precursors in the VZ/lower SVZ are only double positive for vimentin and DCL [pink cells; upper right arrow], P: pial surface. Bar represents 35 μm.

O: DCX and DCL colabeling of the spinal cord (E11) reveals DCL expression at upper and lower border regions (arrows) with long processes (arrowheads) extending radially, amidst of extensive (non-overlapping) DCX expression.

P: Unlike DCL, DCX expression is not expressed in vimentin+ RGC (2 lower arrows) in the neural tube at E11. Only very rarely is colabeling seen (upper arrow), indicating neuronal migration under guidance of RGCs. Bar in O and P represents 18 μm.

**Figure 9. DCL knock-down leads to deformation of mitotic spindles.**

I: Effectiveness of RNA interference to knock-down DCL.
Western blot analysis in N1E-115 cells with [1 to 3] and without [4] siRNA treatment performed in duplo. Three different siRNA molecules targeting DCL were used: siDCL-1 (lanes 1), siDCL-2 (lanes 2) and siDCL-3 (lanes 3). siDCL-2 and 3 induce an effective knock-down (80% and 90% respectively) while siDCL-1 failed to do so, and was subsequently used a control for the siRNA procedure. As a reference, the same membrane was re-stained with alpha-tubulin.

II: Confocal analysis of mitotic neuroblastoma cells treated with DCL siRNA. In non-treated mitotic cells [A-C], DCL [A] colocalizes with alpha-tubulin [B]. The merged image [C] indicates DCL association with polar and kinetochore microtubuli [arrow]. Transfection with siDCL-1 [D-F] failed to induce DCL knockdown [D], and left the mitotic spindle intact [E]. Effective DCL knockdown by siDCL-2 [G-I] or siDCL-3 [J-L] not only caused all immunoreactive DCL signal to disappear [G, J], but also induced collapse and deformation of the mitotic spindles H, K. Green=DCL, Red=alpha-tubulin. Yellow=merged. Scale bar: 10 μm.

**Figure 10. DCL overexpression in dividing COS-1 cells.**

A-C: A normally dividing COS-1 cell stained with alpha-tubulin is shown as reference ("ref" in inset). Overexpression of DCL [Green, A] leads to often unilateral, elongation of the mitotic spindle microtubules [B]. The mitotic spindle length, indicated by arrows, of transfected cells was enhanced compared to non-transfected cells (ref: reference length). DNA is stained with DAPI [blue].

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D-I: DCL overexpression in COS-1 cells during cell division revealed two phenotypes: one very similar (D-F) to wildtype COS-1 cells, in which DCL (D) largely colocalizes with α-tubulin (E). Similarly to the dividing N1E-115 cells, DCL (in green) is also associated with kinetochore microtubuli and overlaps with mitotic spindles (alpha-tubulin in red). The predominant other phenotype revealed a profound elongation and monopolar orientation of the mitotic spindles (G-I). Green=DCL (A, D, G), Red=alpha-tubulin (B,E,H), Yellow=merged (C, F, I). Scale bar is 10 μm.

*Figure 11. In utero electroporation of DCL reduces cell number in the SVZ/VZ and severely disturbs radial fiber organization.*

A: Control plasmids pCMV-YFP delivered into E 14.5 embryonic brain labeled many neural progenitors in SVZ/VZ (asterisks) and an extensive network of radial processes spanning the entire thickness of the cortex with a dense rim of pial endfeet (arrow, detail in J). Mismatch control plasmids revealed identical results (details in H).

B: Knockdown of DCL after pSuper-DCL183 delivery induced a profound reduction in SVZ/VZ precursor number and an almost complete ablation of the radial processes, with small cells in the IZ (arrowhead) and very few pial endfeet remaining (arrow).

C: DCL knockdown reduces DCL immunoreactivity (red). At the top right end border of a pSuper-DCL183 transfected zone, DCL is abundant, compared to the inner layers in the transfected zone on the left (asterisk), that are DCL negative. YFP+ cells are frequently accompanied by “dark holes”, devoid of DCL signal (arrow in C, and in C1 (only red channel shown)), indicating effective DCL protein knockdown. Control plasmids did not alter DCL immunoreactivity (C2 and also I).

D+E: After control plasmid delivery, the SVZ/VZ showed numerous dividing (arrows) and migrating precursors (inset), with straight radial fibers (arrowheads). DCL knockdown reduced progenitor number, with the remaining ones displaying an aberrant, disorganized and often multipolar cell shape (arrows, inset). Processes of these cells, if any, were aberrant and generally very short (arrowheads in E, inset).

F: Overview of the aberrant organization of cells in the PZ and the shortened and aberrantly oriented processes in IZ and CP after DCL knockdown.

G: Detail of a straight, long radial fiber in the IZ after control vector delivery.

H: A similar fiber after delivery of the pSuper-DCL183 mismatch control. A straight and long process with tight endfeet at the pial surface is seen (arrowhead).

I: Detail of a cell transfected with control vector, with a normally appearing process without any detectable effect on adjacent DCL immunoreactivity (red).

J: Details of the radial processes in the CP and their endfeet (arrowhead) at the pial surface after control plasmid delivery. Knockdown of DCL caused very few. If any endfeet to reach the pia (no detail shown, but see B and F).

K + L: Detail of the IZ after DCL knockdown (left is SVZ/VZ, to the right is CP), showing many aberrantly organized, shortened, curly, twisted, and occasionally obliquely oriented (lower right arrow in L) individual processes (arrows) and small cellular elements in the inner zones (arrowhead in K).

M: Example of a clearly disorganized cell shape in the SVZ/VZ after RNAi for DCL.

N: Numbers of electroporated cells in the proliferative zone (PZ) and IZ are significantly reduced in the PZ. In the CP, no differences were found (not shown).

Bars represent 20 μm (A), 15 μm (C+F), 10 μm (D+K), 3 mm (G,J,M,N,L) and 7 μm (H).
Chapter 1

Figure 3. Hippocampal layers and connectivity

Figure 4. Adult neurogenesis in the hippocampal DG
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Chapter 4

FVB/N      Tau-P301L      Tau-4R

HT7

AD2

AT180

AT8

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