# WORKSHOP: CELL CYCLE ABNORMALITIES IN SCHIZOPHRENIA

## CELL CYCLE DISTURBANCES IN SCHIZOPHRENIA: THE JOURNEY SO FAR

Hans-Gert Bernstein, Esther Stürze, Bernhard Bogerts

Department of Psychiatry, University of Magdeburg

**Abstract**

As an introduction to the Pula Workshop „Schizophrenia and Cell Cycle Disturbances", we give a short survey on the current knowledge about the impact of cell cycle disturbances in schizophrenia. While the existence of reduced adult neurogenesis in schizophrenia is supported by various studies, less is known about such disturbances in non-neural cells (for example, in oligodendrocytes). We herein try to show that both impaired neuronal and oligodendroglial cell cycles might contribute to the pathophysiology of schizophrenia, and that antipsychotic treatment might be a way to „normalize" cell cycle abnormalities.

Schizophrenia is a chronic and disabling mental illness affecting several millions of people worldwide. The etiopathogenesis of the disease, however, remains enigmatic, and various competing hypotheses have been proposed to explain its origin. Amongst these, the proposition that schizophrenia may have its roots in early brain development has gained much attention. During the past decade the scientific community has witnessed a considerable progress in the understanding of normal neural development and neurogenesis, and convincing evidence has accumulated in favour of abberant neurodevelopment in schizophrenia[1]. This neurodevelopmental theory, however, leaves some vital questions unanswered. For example, how can a purely neurodevelopmental disorder manifest for the first time in an adolescent or an adult[2]? It soon became clear that certain „disease-shaping" pathomechanisms must still be active in the adult human brain, which contribute to the development and/or progression of the disease. So far, mainly neurodegenerative and immune processes have been blamed to be responsible for this[3].

Department of Psychiatry, University of Magdeburg Leipziger Str. 44, D-39120 Magdeburg, Germany

### *Why do we assume that cell cycle disturbances may be of relevance for schizophrenia?*

The discovery of neurogenesis in the postnatal brain has added a new, intruiging aspect to the discussion about the origin of schizophrenia. It is now beyond any doubt that in circumscribed brains areas, particularly in the dentate gyrus and the subventricular zone, functional neurons are generated throughout the entire lifespan[4]. This phenomenon has been termed adult neurogenesis. Although the actual physiological role of this process remains largely unknown, ist functioning is obviously necessary to maintain normal brain function. Hence, disturbancees of adult neurogenensis (or, more precisely, neural stem cell proliferation) might significantly contribute to neuropsychiatric disorders, including schizophrenia. Indeed, numerous animal studies and investigations in humans give now reason to suppose that decreased, and not increased[5], hippocampal cell proliferation may be part of the pathophysiology of schizophrenia. This reduced birth of new neurons may contribute to to disease-related smaller hippocampal volumes, considerable cognitive deficits as well as to delusions and hallucinations[6].

***How is the cell cycle controlled, and do the controlling agents show abnormal levels in schizophrenia?***

Little is currently known about cell cycle regulating proteins in the adult hippocampus and other brain areas. In all mammalian cells including neural stem cells, cellular proliferation is mainly controlled during the G1 phase of the cell cycle. Cyclins are cell cycle proteins known to be positive regulators of the cell cycle. The cyclins D and E are present in the adult subgranular zone and hippocampus[7]. Both cyclins D1 and D2 have been found upregulated in schizophrenia (8, 9). Interestingly, cyclin D2 was identified as a part of the regulatory network of glutamic acid decarboxylase (GAD67), an enzyme which is profoundly dysregulated in schizophrenia[8].

Cyclin-dependent kinases, which control the cell cycle by negatively regulating cell cycle progression, which are. expressed in proliferating neural stem cells, are reduced in their expression in schizophrenia[8,10]. In addition, intracerebroventricular infusion of a non-selective cyclin-dependent kinase inhibitors decreases cell proliferation in the subgranular zone in rats[11]. Furthermore, the suppression of the expression of the gene Disrupted-in-Schizophrenia 1 (DISC 1) was shown to strongly reduce neural progenitor proliferation, leading to premature cell cycle exit and differentiation. DISC1 mediates this function by regulating glycogen synthase kinase-3 beta[12]. This might be of considerable importance for our understanding of schizophrenia, since DISC1 has repeatedly been linked with the disease. Lastly, adult neurogenesis is under control of neurotrophic factors, most of which are known to be altered in their expression in schizophrenia[13].

***Does antipsychotic treatment „normalize" the cell cycle disturbances in schizophrenia?***

Initially, reduced neurogenesis was detected in postmortem hippocampi of neuroleptic- treated, chronic schizophrenics[6,14], So, the spontaneous answer to this question would be a clear „No". In support of this failure, results from animal studies could be taken that show unchanged levels of stem cell proliferation after haloperidol treatment. One study, however, demonstrated an increase in adult neurogenesis upon treatment. In two studies it was found that chronic treatment with the atypical antipsychotic clozapine does not influence proliferation or survival of newborn cells in the hippocampal dentat gyrus, while acute adminstration doubled the number of BrdU-incorporating cells. Results with olanzapine are also contradictory (reviewed in ref. 6). Our group could show that repeated application of subanesthetic doses of the noncompetitive N-methyl-D-aspartate receptor antagonist ketamine, which has been shown to mimic model aspects of schizophrenia in animals, stimulates the hippocampal neurogenesis[15], and that both haloperidol and risperidone promote stem cell survival in rats ([16], and this symposium). Thus, further research is needed in order to get more conclusive answers as to whether or not antipsychotic treatment is helpful in „normalizing" cell cycle in schizophrenia (see also below).

***Abnormal cell cycles and schizophrenia – is it all with the neurons?***

The fascination of adult neurogenesis and ist possible disturbances in schizophrenia should not allow us to obscure our view of non-neural types in the brain, namely oligodendroglial cells. Schizophrenia is increasingly conceptualised as an illness of disturbed functional circuitry, and a wide range of white matter abnormalities have been revealed in schizophrenia. These include volume reductions, hypodensities, myelination defects, and especially alterations of density, morphology and gene expression profiles of the myelin-forming cells, oligodendrocytes and their progenitors (for recent review see ref. 17).

There are numerous reports about reduced oligodendrocyte density in schizophrenia, which may result from impaired mitoses of these cells. However, there is yet only circumstantial evidence in favour of disease-related oligodendrocyte cycle abnormalities in schizophrenia. In a recent, comprehensive analysis Katsel and colleagues[9] found that eight cell-cycle related antigens (including cyclins D1 and D2) are upregulated, and nine other antigens (indluding cyclin-dependent kinase inhibitors) are down-regulated in OLs isolated from postmortem brains of schizophrenics. Remarkably, the expression differences were more pronounced in anti-psychotic medication free patients with schizophrenia than in treated ones. The authors conclude that the normal patterns of

cell cycle gen and protein expression is disrupted in schizophrenia, and that this disruption may significantly contribute to oligodendroglial deficits observed in schizophrenia. In this study, a near-significant change was observed for prohibitin, a mitochondrial protein which is prominently involved in cell cycle control[18]. The number of prohibitin expressing neurons[19] and oligodendrocytes (this symposium) is increased in schizophrenia. It should be emphasized, however, that prohibitin is expressed in immature and mature (postmitotic) OLs . Thus, a possible influence of prohibitin on the cell cycle is by far not the only function of this multi-talented protein, which may be compromised in schizophrenia..

In sum, it becomes obvious that cell cycle disturbances are possibly not restricted to neurons, but might be a general phenomenon in schizophrenia[20], which deserves much more attention in future research.

## References


1. **WEINBERGER DR**. On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. Neuropsychopharmacology 1996; 14(3 Suppl):1S-11S.
2. GUPTA S, KULHARA P. What is schizophrenia: A neurodevelopmental or neurodegenerative disorder or a combination of both? A critical analysis. Indian J Psychiatry 2010; 52: 21-27.
3. CANNON TD. What is the role of theories in the study of schizophrenia? Schizophr Bull. 25; 35:563-567.
4. MA DK, BONAGUIDI MA, MING GL, SONG H. Adult neural stem cells in the mammalian central nervous system. Cell Res. 2009;19:672-682.
5. NISHIOKA N, ARNOLD SE. Evidence for oxidative DNA damage in the hippocampus of elderly patients with chronic schizophrenia. Am J Geriatr Psychiatry. 2004;12:167-175.
6. REIF A, SCHMITT A, FRITZEN S, LESCH KP. Neurogenesis and schizophrenia: dividing neurons in a divided mind? Eur Arch Psychiatry Clin Neurosci. 2007;257:290-299.
7. HEINE VM, MASLAM S, JOËLS M, LUCASSEN PJ. Increased P27KIP1 protein expression in the dentate gyrus of chronically stressed rats indicates G1 arrest involvement. Neuroscience. 2004;129:593-601.
8. Benes FM. Relationship of $GAD_{67}$ regulation to cell cycle and DANN repair in GABA neurons in the adult hippocampus. Cell Cycle 2010;9:1-3.
9. KATSEL P, DAVIS KL, LI C, TAN W, Greenstein E, Kleiner Hoffman LB, Haroutuian V. Abnormal indices of cell cycle activity in schizphrenia in association with oligodendrocytes. Neuropsychopharmacology 2008; 33: 2993-3009.
10. HAYES TE, VALTZ NL, MCKAY RD. Downregulation of CDC2 upon terminal differentiation of neurons. New Biol. 1991; 3:259-269.
11. MAĆKOWIAK M, KOLASIEWICZ W, MARKOWICZ-KULA K, WEDZONY K. Purvalanol A, inhibitor of cyclin-dependent kinases attenuates proliferation of cells in the dentate gyrus of the adult rat hippocampus Pharmacol Rep. 2005; 57:845-849.
12. MAO Y, GE X, FRANK CL, MADISON JM, KOEHLER AN, DOUD MK, TASSA C, BERRY EM, SODA T, SINGH KK, BIECHELE T, PETRYSHEN TL, MOON RT, HAGGARTY SJ, TSAI LH. Disrupted in schizophrenia 1 regulates neuronal progenitor proliferation via modulation of GSK3beta/beta-catenin signaling. Cell. 20;136:1017-1031.
13. BATH KG, LEE FS. Neurotrophic factor control of adult SVZ neurogenesis. Dev Neurobiol. 2010 Feb 22. [Epub ahead of print].
14. REIF A, FRITZEN S, FINGER M, STROBEL A, LAUER M, SCHMITT A, LESCH KP. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry. 2006; 11:514-22.
15. KEILHOFF G, BERNSTEIN HG, BECKER A, GRECKSCH G, WOLF G. Increased neurogenesis in a rat ketamine model of schizophrenia. Biol Psychiatry. 2004; 56: 317-322.
16. KEILHOFF G, GRECKSCH G, BERNSTEIN HG, ROSKODEN T, BECKER A. Risperidone and haloperidol promote survival of stem cells in the rat hippocampus. Eur Arch Psychiatr Clin Neurosci 2010; 260:151-162.
17. BERNSTEIN HG, STEINER J, BOGERTS B. Glial cells in schizophrenia: pathophysiological significance and possible consequences for therapy. Expert Rev Neurother. 2009; 9:1059-1071.
18. MERKWIRTH C, DARGAZANLI S, TATSUTA T, GEIMER S, LÖWER B, WUNDERLICH FT, VON KLEIST-RETZOW J-C, WESTERMANN B, LANGER T. Prohibitins control cell proliferation and apoptosis by regulating OPA1-dependent cristae morphogenesis in mitocheondria. Genes Dev. 2008;22, 476-488.
19. SMALLA KH, MIKHAYLOVA M, SAHIN J, BERNSTEIN HG, BOGERTS B, SCHMITT A, VAN DER SCHORS R, SMIT AB, LI KW, GUNDELFINGER ED, KREUTZ MR. A comparison of the synaptic proteome in human chronic schizophrenia and rat ketamine psychosis suggest that prohibitin is involved in the synaptic pathology of schizophrenia. Mol Psychiatry. 2008; 13:878-896.
20. WANG L, LOCKSTONE HE, GUEST PC, LEVIN Y, PALOTÁS A, PIETSCH S, SCHWARZ E, RAHMOUNE R, HARRIS LW, MA D, BAHN S. Expression profiling of fibroblasts identifies cell cycle abnormalities in schizophrenia. J Proteome Res. 2010; 9:521-527.