

Influence of ionizing radiation on early human brain development*

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The development of the nervous system is extremely susceptible to perturbations. Only slight changes in the tightly orchestrated follow-up of developmental events can lead to dramatic malformations such as spina bifida, mental retardation, reduced IQ, impairment in hearing, autism, stuttering, attention deficits, deficits in affect, aggressiveness, depression and other neurologic diseases. Neurodevelopmental toxicants such as alcohol, mercury and lead have now been well established [1]. Less well established is the impact of low dose environmental pollutants. However, increasing evidence points to a direct correlation of low dose exposure during early development and impairment of neural development, and possibly neurodegenerative diseases [1, 2].

Animal models only insufficiently model human neurodevelopment. Outcome of developmental neurotoxicity (DNT) such as reduced IQ or stuttering are challenging to model in animal models. Embryonic stem cells (ESCs) have been shown to faithfully recapitulate neural development in vitro [3], and are as such ideal to model toxicity to the developing human nervous system.

We have developed a neurodevelopmental model based on human embryonic stem cells (hESCs) in which hESCs are differentiated in a 3-dimensional (3-D) neurosphere model (Fig 1).

This model has been characterized in depth. It recapitulates crucial stages of central nervous system development, and we could demonstrate DNT of methylmercury and of low dose, chronic exposure to chemically inert nanoparticles [4].

This system has now been transferred to the University of Applied Sciences of Albstadt-Sigmaringen and is used within a BMBF-funded project* to investigate the impact of sparsely ionizing X-rays and densely ionizing carbon ions on early human brain development. In parallel, we have established human induced pluripotent stem cells (hiPSCs) and are differentiating the cells in our neurodevelopmental system to assess whether we can detect differences in differentiation capabilities.

Preliminary data obtained for hESCs irradiated with carbon ions (25mm spread-out Bragg peak, LET=75 keV/μm) at GSI indicate that ionizing radiation has a detrimental impact on the ability of neuroepithelial cells to form neurospheres. Neurospheres were smaller and less abundant, indicating toxicity (Table 1). Gene expression was also changed for crucial neurodevelopmental markers.

Future experiments will focus on sparsely ionizing X-rays. Therefore, neural progenitor cells will be exposed to both acute and continuous low-dose radiation. Changes in Gene expression will be assessed and electrical activity of neuronal cells will be measured. These experiments will allow elucidating the effects of ionizing radiation on early

neural development in more detail and point towards possible impact of exposure during early human development.

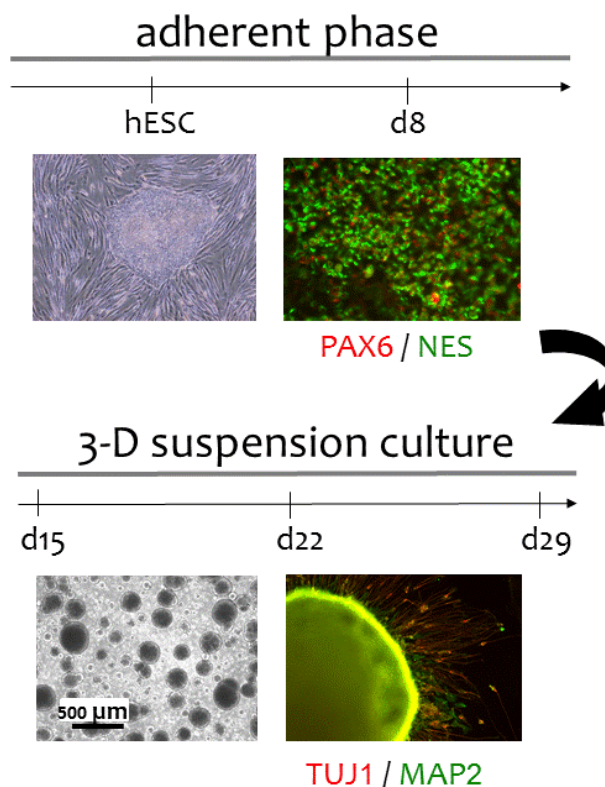


Figure 1: Neurodevelopmental model from hESCs. hESCs (first panel) were differentiated for 11 days in adherence to an almost pure population of PAX6⁺ central nervous system precursor cells (second panel). On day 11 cells were transferred to suspension cultures where the cells form neurospheres (third panel) and differentiate further to mature neurons (right panel).

Dose	Mean diameter	Standard deviation	Range
0 Gray (n = 17)	413,9 nm	139,7 nm	181-642 nm
1 Gray (n = 23)	282,6 nm	96,8 nm	114-536 nm

Table 1: Reduced neurosphere size after irradiation with 1 Gy carbon ions.

References

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