LABORATORY OF

CELL DIFFERENTIATION

Chemical biology, hematopoietic and neural cell differentiation, signalling pathways, zebrafish

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The main interest of the laboratory lies in the study of the molecular mechanism of cell fate determination. We have established systems to get insight into the self-renewal and differentiation of haematopoietic and neural stem cells.

Neural stem cells (NSCs) are defined by their dual ability to self-renew through mitotic cell division or differentiate into the varied neural cell types. DISP3/PTCHD2 is a sterol-sensing domain-containing protein, which is highly expressed in neural tissues. We demonstrated that NSC differentiation triggered significant reduction in DISP3 expression in the resulting astrocytes, neurons and oligodendrocytes. Moreover, when DISP3 expression was disrupted, the NSC "stemness" was suppressed, leading to a larger population of cells undergoing spontaneous neuronal differentiation. Conversely, overexpression of DISP3 resulted in increased NSC proliferation and impaired cell differentiation (Konirova et al. 2017).

In brain cancer treatment, radiotherapy plays a significant role; however, the use of this therapy is often accompanied by neurocognitive decline that is, at least partially, a consequence of radiation-induced damage to NSC populations. Our new findings describe features that define the response of neural stem cells to ionizing radiation. We investigated the effects of irradiation on NSCs isolated from the mouse brain. We show that most cells do not undergo apoptosis after irradiation but rather cease proliferation and start a differentiation programme (Konirova et al. 2019).

Our studies on vertebrate haematopoietic development have been extended by establishing *ex vivo* cultures of zebrafish haematopoietic cells. Recently, we have produced several recombinant zebrafish growth factors (Epo, Gcsfa/b, Tpo, IL34, Mcsfa/b and SCFa/b) that allow us to establish, for the first time, zebrafish haematopoietic clonal assays in semisolid media. Our findings bring information on how haematopoietic cytokines had evolved following the diversification of teleosts and mammals from a common ancestor (Oltova et al. 2018).

Moreover, these tools enabled us to reveal the clonogenic and proliferation capacity of bi-potent thrombo/erythropoietic progenitors with respect to their mammalian haematopoietic counterparts. Despite obvious phenotypic differences between fish and mammalian thrombocytes and erythrocytes, our results strongly demonstrate the evolutionary conservation of the basic processes and molecular mechanisms of erythro/thrombopoiesis in the vertebrates.

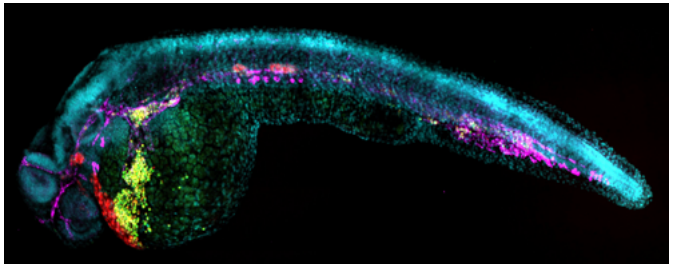

Figure 1. Whole-mount multiplexed RNA fluorescence in situ hybridization of 30 hpf zebrafish embryo. RNA was stained using hybridization chain reaction technology (Molecular Instruments). Zebrafish erythrocytes were detected using gata1a (green) and klf17 (red) probes, endothelial cells were stained using etv2 probe (magenta), and nuclei were visualized using DAPI (cyan).

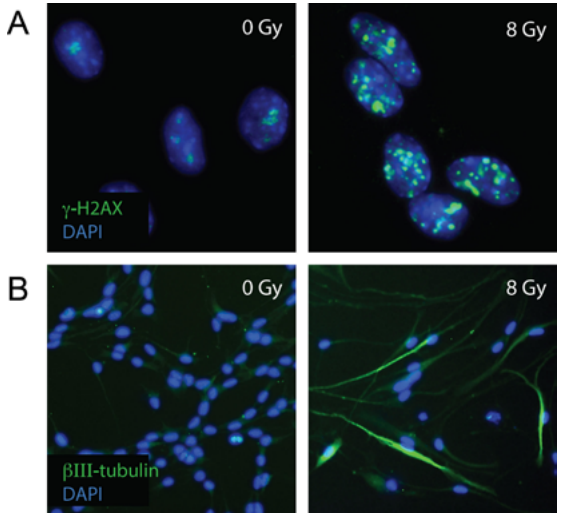

Figure 2. The response of neural stem cells to ionizing radiation. (A) DNA damage response is induced by irradiation. Neural stem cells after irradiation stained with γH2AX antibody (green) and DAPI (blue). (B) Radiation promotes NSC differentiation. Neural stem cells after irradiation stained with βIII-tubulin antibody (green) and DAPI (blue).

Selected publications:

1. Konířová J, Oltová J, Corlett A, Kopycińska J, Kolář M, Bartůněk P, Zíková M* (2017) Modulated DISP3/PTCHD2 expression influences neural stem cell fate decisions. *Sci Rep*, **7**:41597.
2. Škuta C, Popr M, Muller T, Jindřich J, Kahle M, Sedlák D, Svozil D, Bartůněk P* (2017) Probes & Drugs portal: an interactive, open data resource for chemical biology. *Nat Methods*, **14**:759–760.
3. Králová J*, Kolář M, Kahle M, Truksa J, Lettlová S, Balušíková K, Bartůněk P (2017) Glycol porphyrin derivatives and temoporfin elicit resistance to photodynamic therapy by different mechanisms. *Sci Rep*, **7**:44497.
4. Králová J*, Jurášek M, Krčová L, Dolenský B, Novotný I, Dušek M, Rottnerová Z, Kahle M, Drašar P, Bartůněk P, Král V (2018) Heterocyclic sterol probes for live monitoring of sterol trafficking and lysosomal storage disorders. *Sci Rep*, **8**:14428.
5. Konířová J, Cupal L, Jarošová Š, Michaelidesová A, Vachelová J, Davídková M, Bartůněk P, Zíková M* (2019) Differentiation induction as a response to irradiation in neural stem cells in vitro. *Cancers (Basel)*, **11:**913.
6. Oltova J, Svoboda O, Bartunek P. Front Cell Dev Biol. 2018 Dec 20;6:174. doi: 10.3389/fcell.2018.00174. eCollection 2018. Review

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