Katedry Genetiky, Molekulárnej biológie a Biochémie
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Vás pozývajú na 49. prednášku v rámci Kuželových seminárov:

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CELLULAR AND MOUSE MODELS OF DEREGULATED SIGNALING PATHWAYS IN HEMATOPOIESIS

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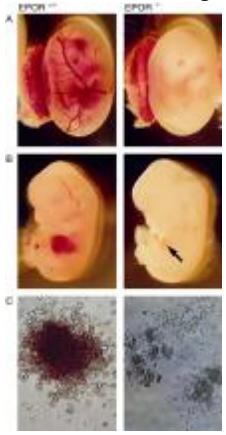

Figure. Analysis of erythropoiesis in erythropoietin receptor deficient (*EPOR* $^{-/-}$) and wild-type embryos. (*A*) E12 embryos inside the yolk sac and (*B*) after removal of the yolk sac, showing severe anemia - lack of circulating red blood cells - in the mutant. The liver size of the mutant embryos was dramatically reduced (arrow) but contained committed erythroid progenitors. *In vitro* cultures (α-methylcellulose with serum and pokeweed mitogen-stimulated murine spleen cell conditioned medium, recombinant murine stem cell factor and recombinant murine thrombopoietin) allowed a partial rescue of terminal differentiation of the mutant erythroid progenitors (*C*). Adapted from Prchal JT, Divoky V: Lessons to a better understanding of hypoxia sensing. New York, Kluwer/Plenum Academic, 2001.

Hematopoiesis is a process by which a hematopoietic stem cell differentiates into multiple cell types. Multiple growth factors, receptors and transcription factors affecting this process are primary regulators of survival, proliferation and differentiation of hematopoietic progenitors. Many of the genes encoding these signaling molecules are mutated in leukemia. We focus our research on two key signaling molecules implicated in leukemogenesis: transcription factor MLL (Mixed Lineage Leukemia) and tyrosine kinase Bcr/Abl. MLL protein is a transcription factor with histone methyltransferase activity that can be activated into an oncoprotein by diverse mutations in human acute leukemias. The high diversity of MLL mutations and fusion proteins, as a consequence of chromosomal translocations with a variety of partner genes suggests multiple molecular mechanisms for leukemogenic conversion of MLL and cellular transformation. We use double-replacement gene targeting in mouse embryonic stem cells to replace a mouse MLL gene with its inducible oncogenic form - a MLL-ENL fusion gene, which is one of the most common fusions in MLL - associated leukemias. This animal model should be useful for studies of the early events in leukemogenic transformation.

The second area of our interest is the molecular pathophysiology of congenital disorders of erythropoiesis. After initial studies involving erythropoietin signaling pathway (Figure) and hypoxia inducible factor-1 (HIF-1) regulation of erythropoesis, we recently focus on pathophysiology of disorders of iron metabolism. We revealed a new mechanism of severe hypochromic microcytic anemia caused by a homozygous mutation in the divalent metal transporter 1 (*DMT1 1285G>C*) gene. Using a model system we showed that both the expression and the iron transport function of DMT1 protein are disrupted. The functional study of the human DMT1 defect brings novel insights into a role of DMT1 in iron metabolism diseases.

Selected papers:

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Ricci C, Scappini B, **Divoky V**, Gatto S, Onida F, Kantarjian HM, Beran M (2002): Mutation in the ATP-binding pocket of the abl kinase domain in an STI571 resistant BCR/ABL-positive cell line. **Cancer Res** 62(21):5995-8.

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Priwitzerova M, Pospisilova D, Prchal JT, Indrak K, Hlobilkova A, Mihal V, Ponka P, **Divoky V**: Severe hypochromic microcytic anemia caused by a congenital defect of the iron transport pathway in erythroid cells. **Blood**. 2004;103(10):3991-2.

Mims MP, Guan Y, Pospisilova D, Priwitzerova M, Indrak K, Ponka P, **Divoky V**, Prchal JT:Identification of a human mutation of DMT1 in a patient with microcytic anemia and iron overload. **Blood**. 2005;105(3):1337-42.