MOLECULAR CYTOLOGY

Identification of molecular mechanisms associated with the induction of chosen angiogenic factors after the application of photodynamic therapy with hypericin in the cells of colorectal carcinoma.

supervisor: prof. RNDr. Peter Fedoročko, CSc. (peter.fedorocko@upjs.sk)
consultant: RNDr. Martin Majerník, PhD.
study form: full time

Annotation: The photodynamic therapy (PDT) represents the promising alternative to conventionally utilized therapeutic approaches such as chemotherapy and radiotherapy. It is based on the fact that most of photosensitizers are primarily accumulated in the tumor cells and the total toxicity on the organism is low. Besides many advantages, our results as well as the results presented by other authors point at the fact that PDT could represent an impulse for the development of pathological angiogenesis in affected cells. PDT itself in cells or tissues induces oxidative stress, which could be associated with hypoxia inducible factor (HIF-1) activation. In the context of mentioned, HIF-1 could fulfil the central role in the angiogenesis induction in affected cells. The aim of the dissertation thesis will be to analyze the connection of HIF-1 and other signaling pathways (MAPK, PI3K/AKT) in the induction of angiogenesis in the chosen colorectal carcinoma cell lines.

The main scope of employment will be:

- the cultivation of cancer cell lines
- the analysis of mRNA and protein levels taking the role of chosen growth factor regulation in cells affected by PDT with hypericin (HIF-1α, HIF-2α, p38, PI3K, AKT)
- the analysis of mRNA and protein levels of chosen growth factors (VEGF, FGF-2, PDGF-A, PD-ECGF) in cells affected by PDT with hypericin in the combination with chosen inhibitors of signaling pathways. This is associated with the identification of particular regulatory mechanisms co-responsible for the angiogenic stimulus
- *ex ovo* cultivation of *Coturnix japonica* embryos
- the application of tumour cells (affected and non-affected by chosen inhibitors of signaling pathways) on the chorioallantoic membrane of quil (*Coturnix japonica*) embryos associated with the temporal analysis of their angiogenic potential with the utilization of microscopic methods

References:

1. Majerník M. et al.: Novel insights into the effect of hyperforin and photodynamic therapy with hypericin on chosen angiogenic factors in colorectal micro-tumors created on chorioallantoic membrane. International Journal of Molecular Sciences, 2019, vol. 20, p. 1-24.
2. Bhuvaneswari R. et al.: Hypericin-mediated photodynamic therapy in combination with Avastin (bevacizumab) improves tumor response by downregulating angiogenic proteins. Photochemical and Photobiological Sciences, 2007, vol. 6, p.1234-1245.

3. Yee K.K.L. et al.: Anti-angiogenic effects of Hypericin-photodynamic therapy in combination with Celebrex in the treatment of human nasopharyngeal carcinoma. International Journal of Molecular Medicine, 2005, vol. 16, p. 993-1002.
4. Solban N. et al.: Mechanistic investigation and implication of photodynamic therapy induction of vascular endothelial growth factor in prostate cancer. Cancer Research, 2006, vol. 11, p. 5633-5640.
5. Solban N., Selbo K.P, Sinha K.A, Chang K.S, Hasan T. Mechanistic investigation and implication of photodynamic therapy induction of vascular endothelial growth factor in prostate cancer. Cancer Research, 2006, vol. 11, p. 5633-5640.

Nanoparticles in hypericin-mediated photodynamic therapy.

supervisor: doc. RNDr. Rastislav Jendželovský, PhD. (rastislav.jendzelovsky@upjs.sk)
study form: full time

Annotation: Nanoparticles are increasingly being studied for their interesting properties and potential exploitation in nano-oncology. The effectiveness of some anticancer drugs may be affected by decreased aqueous solubility, poor cell permeability, and high cell efflux. For this reason, various types of nano-drug carriers (e.g. liposomes, polymeric micelles, dendrimers, superparamagnetic iron oxide crystals and colloidal gold) have already been tested in practice to increase drug selectivity and thus minimize the side effects of anti-cancer drugs. A suitable subject in combination with nanoparticles appears to be hypericin, a natural photosensitizer, characterized by high production of oxygen radicals, but due to its hydrophobicity also reduced systemic availability. The aim of the dissertation thesis will be to find out whether the application of magnetic iron nanoparticles (Fe_3O_4; γ-Fe_2O_3; PLA) is safe for a healthy cell and how the use of nanotechnology can influence the amount of hypericin and the effect of photodynamic therapy in tumour cells and micro-tumours.

The main scope of employment will be:

- cultivation of cancer cell lines
- *ex ovo* cultivation of *Coturnix japonica* embryos
- preparation of solid micro-tumours on CAM
- analysis of the nanoparticle effect on chosen parameters of fibroblasts and CAM
- analysis of the nanoparticle effect on chosen parameters of cancer cells
- identification of nanoparticles ability to bind up in hypericin and influence hypericin transport into the cells
- analysis of hypericin content in cancer cell lines and cells and cells of micro-tumors using the methods of flow cytometry and confocal microscopy
- analysis of the combination therapy of nanoparticles and photoactivated hypericin on chosen parameters of cancer cells

References:

1. Sharma K. S. et al.: Photodynamic therapy with fullerenes in vivo: reality or a dream? Nanomedicine (Lond.), 2011, vol. 6, p. 1813-1825.
2. Huang Y-Y. et al.: Can nanotechnology potentiate photodynamic therapy? Nanotechnology Reviews, 2012, vol. 1, p. 111-146.

3. Gurunathan S. et al.: Nanoparticle-Mediated Combination Therapy: Two-in-One Approach for Cancer. International Journal of Molecular Sciences, 2018, vol. 19, 3264, p. 1-37.
4. Jendželovská Z. et al.: Hypericin in the light and in the dark: two sides of the same coin. Frontiers in Plant Science, 2016, vol. 7, p. 1-20.
5. Jendželovský R. et al.: Breast cancer resistance protein is the enemy of hypericin accumulation and toxicity of hypericin-mediated photodynamic therapy. Biomedicine and Pharmacotherapy, 2019, 109, p. 2173-2181.
6. Majerník M. et al.: Novel insights into the effect of hyperforin and photodynamic therapy with hypericin on chosen angiogenic factors in colorectal micro-tumors created on chorioallantoic membrane. International Journal of Molecular Sciences, 2019, vol. 20, 3004, p. 1-24.

Characterization of microenvironment in the subventricular zone of lateral ventricles of the brain in relation to postnatal neurogenesis.

supervisor: doc. RNDr. Juraj Ševc, PhD. (juraj.sevc@upjs.sk)
study form: full time
Annotation: The main goal of the dissertation thesis is to analyze selected morphogens and growth factors bound in the fractones and their effect on the activity of surrounding cells (B-, C-, A- and E- cells) in the ventricular and subventricular zone of lateral ventricles of rat brain during the ontogenesis. Comparison of content of morphogens and growth factors bound in the fractones of non-neurogenic postnatal spinal cord, should reveal the identity of morphogens and growth factors, which have substantial impact on postnatal neurogenesis in lateral ventricles of brain.