Molecular mechanisms underlying the liver injury induced by ulipristal acetate treatment

Ulipristal acetate (UA) belongs to the class of drugs of selective progesterone receptor modulators (SPRM) and is used in emergency contraception, as well as in the treatment of uterine fibroids. UA exerts an inhibitory (antagonistic) or stimulating (agonistic) effect in tissue via the nuclear progesterone receptor (PGR), by regulating its dependent signaling pathways. Studies have shown that UA can also be a glucocorticoid receptor (GR), and androgen receptor (AR) antagonist, but the affinity for these receptors is much lower than for the PGR receptor. In clinical trials, patients treated with UA were observed to have a reduction in the size of uterine fibroids, reduced bleeding, and a significant improvement in the quality of life. These studies showed no significant side effects, therefore UA was approved as for use in the management of uterine fibroids. However, since its approval, some patients treated with UA have been diagnosed with severe liver injury. Despite these studies, the causes of the drug-induced liver injury in patients taking UA and its mechanism of action in the liver remain unclear to this day. Therefore, the main goal of this project is to investigate the molecular mechanisms underlying the liver injury induced by ulipristal acetate treatment.

The project will be carried out using two research models – a mouse model and a coculture of human hepatocytes and Kupffer cells. Our preliminary data from mice experiment revealed that 12.5% (5 out of 40) mice treated with UA exhibited the significant weight loss, enlargement of liver and spleen as well as decreased albumin and increased serum bilirubin concentrations. Furthermore, we also identified morphological abnormalities in the liver, which were classified as intracellular cholestasis with hepatocyte necrosis. For a more thorough assessment of UA impact on the liver, we will perform additional histopathological analysis of livers by performing specialized tissue staining and examine serum concentrations of specific inflammatory biomarkers. In the next step, we will assess whether UA has an agonistic/antagonistic effect on PR, GR and AR receptors in the liver and which signaling pathways are dysregulated by UA in drug-induced liver injury. Next, in cell culture, we will evaluate the effect of different doses of UA on hepatocyte and Kupffer cells viability and apoptosis. Obtained results will be further confirmed in functional studies using hepatocyte and Kupffer cells culture to precisely characterize the signaling pathways potentially involved in the development of liver pathology.

A precise characterization of the signaling pathways involved in the UA-induced liver injury will be a very important step for the development of better and safer SPRMs treatment strategies in the future. This proposed project will also reveal the mechanistic interplay between the UA and downstream regulators of the pathophysiological mechanisms in the liver. This may be helpful in identifying potentially liver injury-susceptible patient groups and in improving the UA treatment strategy. Results obtained from this project will be published in open access high-impact factor translational medicine scientific journals as well as presented at international conferences.