Popular –scientific abstract

Despite the progress in understanding the molecular basis of liver and pancreas tumorigenesis and the implementing the new treatment strategies, no improvement in survival rates of patients with liver or pancreas cancers was achieved. Thus, search for an alternative approach, such as chemoprevention along with the new treatment modalities is still feasible and necessary. Liver and pancreas cancers are among the leading cause of cancer-related deaths worldwide. These cancers are refractory to nearly all currently available therapies and lack of initial symptoms makes impossible their early diagnostics. In the pathogenesis of these cancers chronic inflammation plays important role. In the case of liver cancer inflammation results from the chronic HBV/HCV infection. Inflammation activates multiple signaling pathways eventually leading to increased cancer cells proliferation and avoidance of programmed cell death.

NF-κB signaling pathway, regulator of cell survival, immunity and inflammation, is one of the most important pathways that are activated during inflammation related carcinogenesis. Transcription factor NF-κB controls the expression of genes encoding, among the others, cyclooxygenase-2 (COX-2), which is the target of several anti-inflammatory drugs. It was also shown that in the inhibition of inflammation the induction of enzymes and cytoprotective proteins controlled by Nrf2 pathway is equally important as NF-κB. Interesting links have been found between these two pathways. In this regard, glycogen synthase kinase-3β (GSK-3β) can phosphorylate Nrf2 on tyrosine 568, resulting in activation of this factor. The same enzyme has been reported to be necessary for the full transcriptional activity of NF-κB, demonstrating that GSK-3β selectively supports the expression of a subset of genes activated by NF-κB-dependent proliferative signals. These discoveries might have implications for future NF-κB-based therapies and Nrf2-focused chemopreventive strategies, although the very complex crosstalk, probably tumor and cell-type specific, between these transcription factors, might strongly influence the outcome of the prophylactic/therapeutic interventions.

The aim of this project is verifying the hypothesis that targeting the selected elements of these pathways, such as GSK-3β, by new synthetic analogues of naturally occurring triterpenoids may results in enhancement of their potential chemopreventive and/or chemotherapeutic activities. In addition, their conjugates with nonsteroidal anti-inflammatory drugs (NSAIDs) will be also assessed.

Triterpenoids are common components of several plants and show a broad spectrum of biological activities. One of them, pentacyclic oleanolic acid (OA), in experimental models showed not only anti-inflammatory, and anti-mutagenic activities, but also by increasing the activation of Nrf2 hepatoprotective activity. Moreover, OA and other triterpenoids inhibited the NF-κB activation and activity of COX-2. Recent data indicate that OA induces the programmed death of pancreatic cancer cells and modulates the levels of Nrf2 and NF-κB in the liver cancer cells. Synthetic analogues of triterpenoids usually possess better pharmacological and physicochemical properties. Moreover, their bioavailability is higher than bioavailability of the parent compound. Some of synthetic analogues of triterpenoids were shown to be extremely potent inducers of phase 2 enzymes/cytoprotecive proteins controlled by Nrf2 which are at the same time anti-inflammatory agents.

In this project the synthesis of a series of new derivatives of OA and their conjugates with NSAIDs (aspirin, ibuprofen, ketoprofen, indomethacin and diclofenac) is predicted. NSAIDs, inhibitors of COX-2 (coxibs), were the first chemopreventive drugs registered by the US FDA for prevention of colon cancer. Cancer chemoprevention or reversal of carcinogenesis in the premalignant phase is defined as the use of natural or synthetic chemicals to suppress, delay, or prevent the cancer induction. Such approach requires long term of drug administration. There are the data, which identifies new molecular targets triggered by aspirin in the colon and supports the use of non-toxic low dose of aspirin in long-term treatments as a prophylactic approach against colon carcinogenesis. Unfortunately, long term clinical trials showed several undesired cardiovascular side-effects of coxibs treatment. Such unfavorable effects might be overcome by conjugation of drug molecules with compounds inducing cytoprotective proteins. We propose that such effect may be achieved by conjugation with new OA derivatives, which will be synthesized within the project. This assumption will be verified by evaluation of their effects on key elements of Nrf2 and NF-κB signaling pathways, including GSK-3β in liver and pancreas cancer cells in vitro.

The effectiveness of the proposed new chemopreventive/chemotherapeutic strategy will be evaluated *in vivo* in mice transfected with liver and pancreas cancer cells with luciferase reporter gene allowing the cancer development detection.

Overall, the realization of the project will allow to select the new, more efficient modulators of the analyzed signaling pathways in liver and pancreas cancer cells and to propose the mechanism(s) of their activity, which might be useful in designing new preventive and/or therapeutic strategies. The results of the project realization will provide data justifying their further pre-clinical investigation and in a long perspective clinical trials. The enlargement of our knowledge of the interaction between Nfr2 and NF-κB signaling pathways in response to small-molecule modulators is an equally important aspect of the proposed studies.