Abstract

Proteomics as a modern comprehensive approach to the analysis of proteomes was applied in three projects aimed at diagnosis and therapy of cancer.

The aim of the first the project was to find a new diagnostic biomarker for ovarian cancer. Two different comparative proteomic approaches were used for comparative analysis of sera from patients diagnosed with ovarian cancer and from healthy age-matched women. We identified α-1-antitrypsin with increased concentration in patien sera, and apolipoprotein A4 and retinol-binding protein 4 (RBP4) with significantly decreased concentration in patients. The significantly decerased concentration of RBP4 in patients is a new observation. We propose that RBP4 is either decreased in ovarian cancer patients as a result of its reduced production by ovary or it may reflect less specific systemic changes, for instance early onset of cancer cachexia.

The second project was focused on gaining insight into the molecular mechanism of cytarabine resistance in mantle cell lymphoma (MCL). Proteomic and transcriptomic analyses of cytarabine-resistant cells revealed marked downregulation of deoxycytidine kinase (DCK) – a protein essential to intracellular activation of purine and pyrimidine nucleosides and their analogues including cytarabine. The cytarabine-resistant MCL cells exhibited cross-resistance to other nucleoside antimetabolites (gemcitabine, cladribine, fludarabine). We conclude that the downregulation of DCK is the molecular mechanism of acquired resistance to cytarabine, gemcitabine, fludarabine in the MCL cells. Our data suggest that nucleoside analogs should not be used in therapy of MCL patients, who relapse after failure of cytarabine-based therapies.

The objective of the third study was to identify the secondary molecular changes associated with resistance of MCL cells to cytokine TRAIL. Such changes could be exploited as a potential targets for selective elimination of such resistant cells. Using proteomic analysis we identified decreased expression of three enzymes involved in purine metabolism, namely nucleoside phosphorylase, adenine phosphoribosyltransferase and inosine-5'-monophosphate dehydrogenase in TRAIL-resistant MCL cells. Downregulation of these three enzymes may render TRAIL-resistant cells vulnerable to further disruption of purine nucleotide metabolism. This pathway thus represents a potential therapeutic target for selective elimination of such cells.