Abstract (English)

Tumor suppressors genes are capable of repressing the growth of neoplastic cells; therefore, their inactivation is an important hallmark of cancer. The novel tumor suppressor Serine beta-lactamase-like protein (LACTB), highly expressed in normal tissues but often downregulated in cancer cells, is a ubiquitously expressed mitochondrial protein with an active serine catalytic site and unknown substrates.

In this project we show that LACTB possesses autoproteolytic activity which, in cancer cells, is enhanced by the MRPS34 (Mitochondrial Ribosomal Protein S34) protein thus leading to post-translational downregulation of LACTB. This process can be partially reverted by “A4” chemical compound that has the ability to reactivate LACTB. Our results reveal a novel and previously unknown regulatory mechanism by which cancer cells downregulate a potent tumor suppressor and offer promising new avenues for its therapeutic reactivation and cancer treatment.

We further elucidate the biology of LACTB through uncovering binding partners and additional substrate candidates of LACTB and uncover the requirements for salts and ions in LACTB’s filament formation and enzymatic activity.

Furthermore, we unveiled the mechanistic circuitries of LACTB-induced cell death, revealing that LACTB can induce caspase-independent cell death, mainly through increasing Reactive Oxygen Species (ROS) in cancer cells. LACTB was also identified as a tumor suppressor in ovarian cancer setting, where its expression leads to inhibition of Slug transcription factor and consequently the inhibition of the process of Epithelial-Mesenchymal Transition (EMT).