Development of novel anticancer compounds targeting mitochondrial protein homeostasis

Walid A. Houry[1,2]

[1]Department of Biochemistry, University of Toronto, Toronto, Ontario M5G 1M1, Canada

[2]Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

ABSTRACT

The mitochondrial ClpP protease is responsible for mitochondrial protein quality control through specific degradation of proteins involved in several metabolic processes. ClpP overexpression is also required in many cancer cells to eliminate ROS-damaged proteins and to sustain oncogenesis. Targeting ClpP to dysregulate its function using small molecule agonists is a novel strategy in cancer therapy. Here, I describe novel anticancer compounds that we synthesized and characterized using biochemical, biophysical, and cellular studies. Using X-ray crystallography, we found that these compounds have enhanced binding affinities due to their greater shape and charge complementarity with the surface hydrophobic pockets of ClpP. N-terminome profiling of cancer cells upon treatment with one of these compounds revealed the global proteomic changes that arise and identified the structural motifs preferred for protein cleavage by compound-activated ClpP. Together, our studies provide the structural and molecular bases by which dysregulated ClpP affects cancer cell viability and proliferation.