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Development of 3-arylquinolines as antineoplastic agents that trigger PAR-4 secretion and tumor cell apopotosis

Various cancer cells often develop resistance to chemotherapy and radiation therapy, leading ultimately to the death of the patients. Therapy resistant cancer cells are susceptible, however, to apoptosis by the pro-apoptotic tumor suppressor Prostate Apoptosis Response-4 (Par-4). Par-4 is secreted by normal cells and selectively induces apoptosis in cancer cells by binding specifically to a cell-surface receptor, Glucose regulated protein-78 (GRP78) that is found only on the surface of cancer cells. Because the baseline levels of Par-4 secreted by normal cells are generally inadequate to cause apoptosis in cancer cells, secretagogues that bolster the release of Par-4 constitute an important therapeutic advance. We report a discovery and structure activity study on 3-arylquinolines or "arylquins" that induce normal cells to produce robust secretion of Par-4 protein that targets cancer cells in a paracrine manner. We identified 3-arylquinoline derivative, designated as Arylquin 1, as a potent Par-4 secretagogue that inhibits the proliferation of various cancer cells *in vitro* at nanomolar levels and *in vivo* in mice. Arylquin 1 induced a dose-dependent apoptosis in cancer cells without affecting normal cells. Using a biotinylated analog, we identified vimentin, a cytoskeletal intermediate filament protein, as its principal target. Arylquin 1 binds vimentin and displaces the Par-4 protein that acts as a tumor suppressor and kills cancer cells while leaving normal cells unharmed. Because, vimentin is also a key component of the epithelial mesenchymal transition (EMT) necessary for metastasis in diverse cancers, the identification of vimentin as the target for arylquins is consistent with arylquins functioning as antineoplastic agents.

Biography

Vitaliy Sviripa obtained his PhD from Institute of Organic Chemistry, Kyiv, Ukraine and completed Postdoctoral studies at the University of Kentucky (USA) in D S Watt's laboratory. He was promoted to Research Assistant Professor at the University of Kentucky, College of Pharmacy in 2017. He has published more than 30 papers in peer-reviewed journals and he is co-inventor on numerous patents. His research interests are focused on the design, synthesis and optimization of small-molecule probes with particular emphasis on the developing antineoplastic agents that affect novel biological targets.

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