Poster Presentation

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Structural studies on 14-3-3ζ: Compounds that target the dimer interface

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14-3-3 proteins are a highly conserved family of dimeric phospho-serine binding proteins that modulate the functions of key cellular proteins involved in signaling. 14-3-3ζ plays a prominent role in signaling pathways leading to inhibition of apoptosis, sequestration of tumor suppressor proteins and activation of signalling pathways that promote growth. 14-3-3ζ expression is up-regulated in many human cancers and associated with enhanced survival of cancer cells. The significant association of 14-3-3ζ over expression with disease recurrence and chemo-resistance makes this protein an attractive candidate for anti-cancer therapy. The anti-apoptotic activity of 14-3-3ζ is entirely dependent on the dimeric state of the protein. Our studies have shown that 14-3-3ζ activity is regulated by sphingosine and other lipid analogs that render 14-3-3 phosphorylatable, disrupting its dimeric state thereby leading to apoptosis [1]. Structural studies and mutagenesis on 14-3-3ζ confirm that the dimeric state of 14-3-3ζ is stabilized by salt bridges that form across the dimer interface. Based on this we have carried out an in silico screen of a virtual library of drug-like small molecules to identify compounds that bind to the dimer interface of 14-3-3ζ. Candidate small molecules have been assessed for their ability to render 14-3-3ζ phosphorylatable in vitro and consequently we have identified a family of small molecules with 14-3-3ζ dimer-destabilizing properties. These small molecules induce apoptosis in leukemic cells by activating apoptotic mediators known to be regulated by dimeric 14-3-3. We have recently solved the crystal structure of 14-3-3ζ with one of our hit compounds bound at the dimer interface. Our results suggest that relatively small perturbations at the dimer interface, can destabilize the salt bridges that hold 14-3-3 dimers together, thus providing a novel approach to targeting 14-3-3 proteins for therapeutic benefit.

[1] *Woodcock, J.M., Ma, Y., Coolen, C.,et al., Cellular Signalling, 2010, 22, 1291-129.*

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