Comparing Structures of Active Site and Allosteric cGAS Inhibitors

Hoan Tran
Bioinformatics Program, The University of Texas at El Paso, El Paso, TX

Cyclic GMP-AMP synthase (cGAS) is an enzyme that detects DNA in the cell's cytoplasm, the fluid-filled region outside the nucleus, and triggers inflammatory signaling. However, continual detection of a cell's own DNA can drive unwanted inflammation, making cGAS a potential treatment target. There are limitations: inhibiting an isolated enzyme does not guarantee an effect in living cells, and differences between human and mouse cGAS complicate testing in mouse models. As a stepping stone, this project will compare two synthetic inhibitors: G150, which binds the active site where cGAS catalyzes its reaction, and XL-3156, which also occupies a regulatory (allosteric) region. Human and mouse protein sequences, represented as strings of amino acid building blocks, were taken from UniProt and compared using EMBOSS Needle. Preliminary alignment showed roughly 55% sequence identity and differences at positions associated with inhibitor binding, and published structures of cGAS bound to each inhibitor were also available in the Protein Data Bank. Next, ChimeraX will be used to visualize contact regions of enzyme inhibition in three dimensions, and sequence alignment mapping provides a correspondence between positions in the two proteins. Combining this mapping with three-dimensional structures will help identify which differences occur near the inhibitors that may guide further investigation. These structural comparisons will be considered alongside published measurements from isolated enzymes and living cells, accounting for species and experimental conditions. The expected outcome is an annotated comparison of binding sites to guide inhibitor selection for further testing.