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New stress-tolerant super enzyme found in Taiwan springs

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Singapore: A research team from Institute of Biological Chemistry of Academia Sinica, led by associate research fellow Dr Chung-I Chang and distinguished research fellow Dr Shih-Hsiung Wu, resolved the structure of a LonC protease from Meiothermus taiwanensis, a domestic bacterium from hot springs of Wu-rai, Taiwan.

Structural analysis of this Lon-like protease showed an architectural feature consisting of a hollowing chamber and substrate recognition domains constituted of six flexible tentacles. This study reveals the structure of active site inside the hollowing chamber and its interaction mechanism with three inhibitors. The findings, which may shed light on new drugs design, were published in an article titled 'Structures of an ATP-independent Lon-like protease and its complexes with covalent Inhibitors' in the August issues of the journal Acta Crystallographica Section D: Biological Crystallography and was also selected as the cover article of the issue.

Lon proteases are large protein complexes and are ubiquitously found in bacteria and the organelles of eukaryotes (for example, mitochondria). Lon proteases help bacteria to maintain normal functions under severe environments. Recently, it has been found that many pathogenic bacteria, including cancer cells, need Lon proteases to live inside of a human body. Therefore, Lon protease is a new possible target for anti-microbial or anti-cancer therapies.

The LonC protease from domestic hot-spring bacterium is a new type of Lon protease, which was found inside the hot-spring bacterium from Wu-rai. The proteins from hot-spring bacterium are stable in high temperature environment; therefore they may have a potential for industrial or pharmaceutical applications.

The team, including the first author Dr Jiahn-Haur Liao, determined the full-length structure of the Lon C protease by X-ray crystallography, and found major features of this protease, including a hollowing chamber and substrate recognition domains constituted of six flexible tentacles. Notably, the Lon C protease can be crystallized in full-length form and the crystals exhibit an excellent X-ray diffraction quality. Moreover, as these crystals are still proteolytically active, the research team was able to exploit this property and successfully loaded three different inhibitors into the active site inside the hollowing chamber and determined the complex structures to visualize the binding of each of the compounds to the active site.

"The structure of the Lon protease is so unstable that no enzymatically active Lon protease bound to inhibitors could be crystallized over the past thirty years," Dr. Chang said. "We are happy to be the first team to resolve these complexed structures of Lon isolated from indigenous Taiwanese hot spring bacterium.

This study demonstrates that the crystals of the Lon C protease from indigenous Taiwanese thermophilic bacterium are suitable for inhibitor soaking and consequently structure-based drug design. Importantly, one of the inhibitors whose binding mode was determined is Velcade (bortezomib), a clinically used anti-cancer drug; the result will thus be valuable for design of more specific drugs of this kind with less side effects.