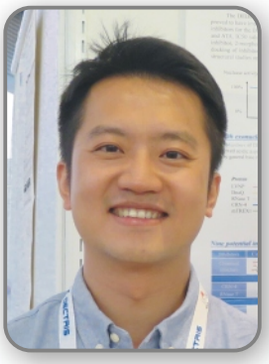

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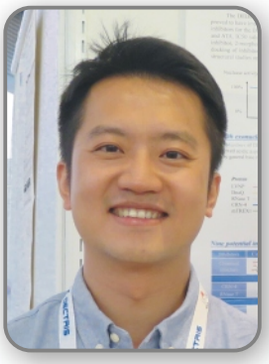
研究興趣

本實驗室使用 X-ray Crystallography 為核心技術來探討蛋白質三維結構與其生理功能的關聯性，研究標的為參與在基因組穩定性維持 (genome integrity maintenance) 或核酸介導免疫反應 (nucleic acid mediated immune response) 所需之核酸結合蛋白質或多蛋白質複合體，搭配細胞內外的生化實驗分析，即可詳盡了解目標蛋白質的分子層級作用機制。此外，我們的研究還可用來釐清目標蛋白質相關遺傳性疾病的成因與應用於結構基礎藥物設計 (Structure-based drug design) 上。

我們的研究標的之一為DEDDh核酸外切酶家族 (也稱為核酸外切酶DnaQ家族)，它由成千上萬個成員所組成，廣泛存在於各種原核與真核生物內，並參與在多種的RNA或DNA代謝處理相關的途徑之中。所有家族成員均帶有一個包含雙金屬離子的高保留性活性位點，以及高度分化的受質結合位。大多數DEDDh核酸外切酶的獨特細胞功能和底物偏好性都可能與其獨特的受質結合位有關，其相關性也需要進一步的研究。

TREX1和TREX2是哺乳動物細胞中的兩個典型的DEDDh核酸外切酶。這兩個成員皆與核酸介導的免疫反應有關。TREX1存在於細胞質，負責降解由DNA複製過程或內源性逆轉錄病毒 (endogenous retrovirus) 所產生的內源性ssDNA，dsDNA或RNA-DNA雜合體。TREX1的基因突變與許多自體免疫性疾病有關，例如阿爾卡迪症候群 (Aicardi-Goutières syndrome)和系統性紅斑狼瘡 (Systemic Lupus Erythematosus)。TREX2對於基因組完整性維持及腫瘤抑制至關重要，功能失常的TREX2會導致染色體的自發斷裂，細胞複製的減少以及對藥物或UV誘導的皮膚致癌作用的敏感性增加。此外，TREX2在皮膚細胞中的過量表達會導致細胞凋亡，因而影響皮膚免疫反應而導致牛皮癬表型的發生。因此，TREX2的抑制劑或許可以成為一種治療牛皮癬的藥物。我們想要研究並了解TREX1和TREX2在各種核酸加工中的分子機制，來揭示突變與相關遺傳疾病的關聯性。我們的另一個研究方向為了解TREX1和TREX2如何與其他蛋白質一起合作並處理各式不同的核酸分子。

有趣的是，部分的DEDDh核酸外切酶為病毒感染和複製所必須，包括SARS冠狀病毒 (SARS Coronavirus) 的Nsp14、拉薩熱病毒 (Lassa fever virus) 的NP核酸外切酶，以及被HIV劫持以消化病毒轉錄物的人類TREX1，這些DEDDh核酸外切酶是抗病毒藥物的理想靶標。因此，我們也想利用結構基礎藥物設計來找出病毒DEDDh核酸外切酶的抑製劑，並將這些抑製劑應用於抗病毒治療上。



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Research Interests

We are structural biology research group and determine bio-macromolecule structures by X-ray crystallography, SAXS or Cryo-EM. We aim to reveal the biological functions and working mechanisms of nucleic acid binding proteins or multi-protein complexes involved in genome integrity maintenance and nucleic acid mediated immune response. In addition, our study can used to understand the causes of genetic diseases and be applied in structure-based drug design.

The DEDDh exonuclease family (also named DnaQ-family of exonucleases) is one of our research targets, which constitutes thousands of members that play essential roles in RNA or DNA processing in prokaryotes and eukaryotes. All of the DEDDh exonucleases bear a conserved two-metal ion contained active site but diversified substrate binding site. The distinctive cellular functions and substrate preference of most DEDDh exonucleases can be link to their distinctive substrate binding sites and need further studies.

TREX1 and TREX2 are two DEDDh exonucleases of mammalian cells and associated with nucleic acid mediated immune responses. TREX1 is a cytosolic exonuclease responsible for degrade endogenous ssDNA, dsDNA or RNA-DNA hybrid generated from DNA replication and endogenous retrovirus. Mutations in the gene encoding TREX1 are associated with many autoimmune diseases, such as Aicardi-Goutières syndrome (AGS) and Systemic Lupus Erythematosus (SLE). TREX2 is participates in various genomic integrity-maintaining pathways. Dysfunctional TREX2 leads to spontaneous broken chromosomes, reduced cell proliferation, and susceptibility to drug- or UV-induced skin carcinogenesis, highlighting the role of TREX2 in DNA replication and the importance of tumor suppression. In addition, overexpression of TREX2 in skin cells leads to the development of psoriasis phenotype by altering the apoptosis and influencing skin immune responses. Therefore, inhibitors or drugs that target TREX2 pathways may be useful in treating psoriasis. We are interesting in the molecular mechanisms of TREX1 and TREX2 in various nucleic acid processing pathways and want to reveal the linkage between mutations and diseases. How TREX1 and TREX2 work with interacting partners in the nucleic acid metabolism pathways is the other question we want to address.

Interestingly, some of the DEDDh exonucleases are essential for viral infection and replication, including Nsp14 of SARS Coronavirus, NP exonuclease of Lassa fever virus, and human TREX1 that is hijacked by HIV to digest viral nonproductive transcripts. These DEDDh exonucleases are poetical target for anti-viral therapy. Therefore, we aim to discover the inhibitors of viral DEDDh exonucleases by structure-based drug discovery and applied these inhibitors in anti-viral therapy.