Structural Study of Human ATM under Oxidation Stress by Cryo-EM

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Ataxia-telangiectasia mutated (ATM) kinase is a signaling protein responsible for activating the DNA double-stand breaks (DSBs) repair and oxidative stress. Functional loss mutations in ATM lead to Ataxia telangiectasia (AT), which is a multisystem disorder characterized by genome instability, cancer predisposition, progressive neurologic impairment and immune dysfunction. Oxidative stress comes from ROS produced by cellular respiration reactions which occurs every second in our bodies. Free radicals from ROS can damage components of cell even induce strand breaks in DNA. Once activated by oxidative stress in the cell, ATM forms a covalent dimer which phosphorylates numerous downstream substrates including the tumor suppressor p53 to initiate DNA repair and arrest cell cycle progression. Our current understanding of the fundamental mechanism of ATM function and molecular pathology of AT is limited by the lack of the high-resolution structure of the active form of enzyme.

Traditional structural methods have proven challenging for solving the structure of the intact ATM dimer, which has molecular weight of 700 kDa. The aim of this study is to determine the atomic structure of the oxidized ATM dimer and ATM/P53 complex by single-particle cryo-electron microscopy (cryo-EM) in order to allow for better understanding of its working mechanism under oxidative stress.

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