Team reports diamond ring architecture of a protein complex

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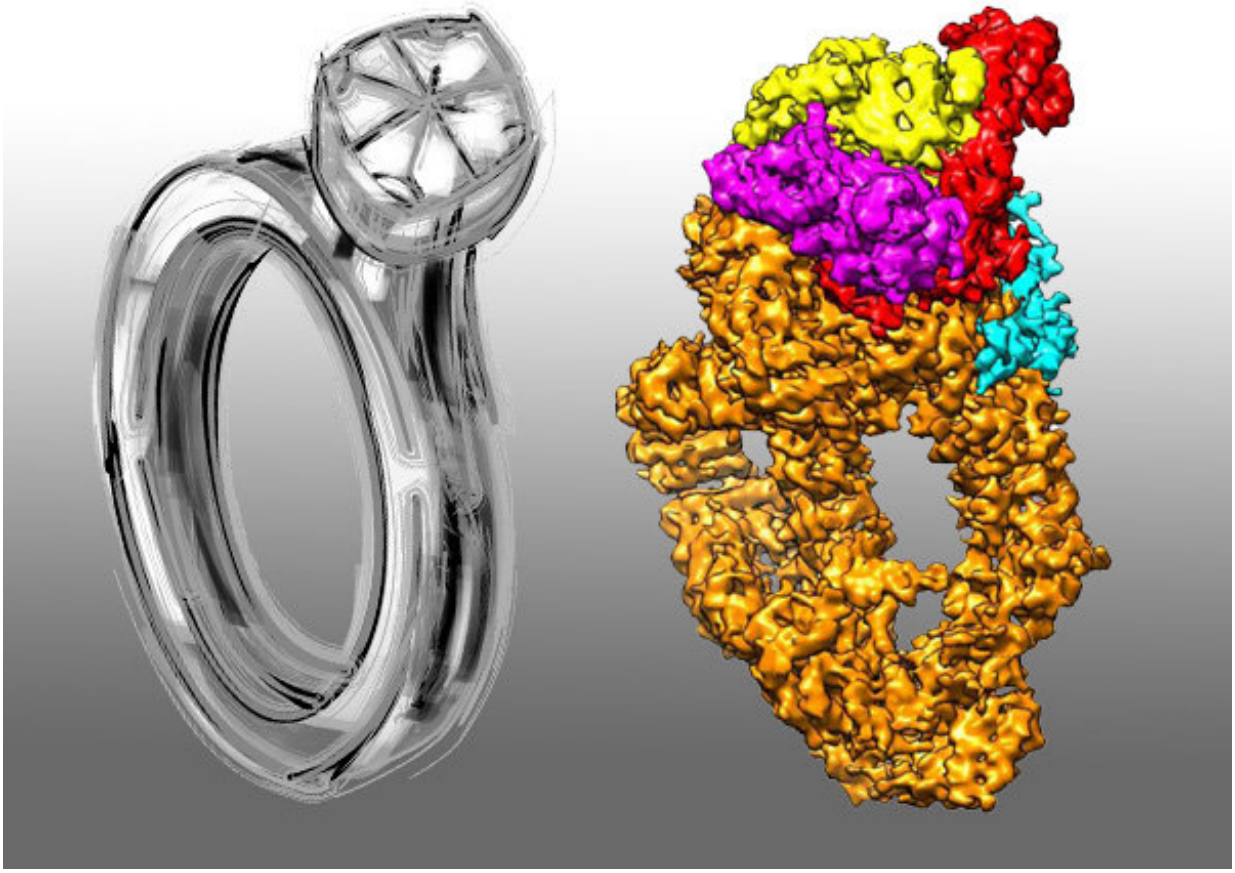

The NuA4 cryo-EM structure is akin to a diamond ring. Credit: USTC

NuA4/Tip60, a complex with diamond ring architecture, is required for

regulatory and repairing processes. Prof. CAI Gang and Prof. Jacques Côté's team reports the 4.7 Å structure of the yeast NuA4/TIP60 complex, which elucidates the detailed architecture and molecular interactions between NuA4 subunits. Related study is published online in *Nature Communications* on March 19th.

NuA4/Tip60 is a complex that catalyzes substrates critical for gene regulation, DNA repair and cell cycle progression. Yet its compositional complexity and conformational flexibility have long impeded researchers from exploring it with high precision. Via cryo-electron microscopy (cryo-EM), CAI Gang's team has provided a high-resolution view of this complex in sub-nanometer scale, and reports on NuA4/Tip60 assemblies for the first time.

Tra1/TRRAP and Eaf1 serve as a scaffold for NuA4/TIP60 assembly. Although Tra1/TRRAP lacks kinase catalytic activity, it adopts active conformation of the catalytic domain in NuA4/TIP60 assembly. Besides providing more insights about scaffolding and regulatory mechanisms of Tra1/TRRAP, the structure elucidates more details about NuA4/TIP60 subunits.

Unexpectedly, the structure also shows human TRRAP mutations are largely centered on the Tra1/TRRAP interaction surfaces mediating NuA4/TIP60 assembly. Since Tra1/TRRAP contains hotspots for tumor generation, this observation suggests anti-cancer possibilities of targeting the scaffolding function of TRRAP. In addition, since Tip60 is significantly down-regulated in many cancers (i.e. breast and prostate), specific inhibitors of Tip60 could provide a major breakthrough in cancer treatment.

In the future, CAI Gang will focus on obtaining structure of the holoenzyme and determining the substrate specificity and catalytic mechanism of NuA4/Tip60. These could greatly facilitate the

development of specific TIP60 inhibitors and potent chemotherapeutic drugs, aiming at treating more people suffering from cancer.

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