

Inhibiting Human Copper Transfer and Tumor Growth

Copper is a trace element that is required by almost all forms of life. Acting as cofactors for various key metabolism enzymes, copper takes part in many vital biological processes. Previous studies have found the concentration of copper is significantly higher in tumor cells than in normal cells. In addition, copper can promote angiogenesis by activating VEGF and FGF signaling. A recent paper in *Nature* revealed that copper is essential for oncogenic BRAF signaling and tumorigenesis. These studies suggest copper metabolism could be a promising target to treat cancer.

At present, the only way to regulate intracellular copper level is to use chelating agents such as Tetrathiomolybdate (TTM). Through chelating copper ions, TTM reduce the concentration of cellular copper and has been used to treat diseases caused by excess copper, such as Wilson's disease. TTM can also inhibit angiogenesis and show anti-cancer activities. Unfortunately, most chelating agents, including TTM, show very poor selectivity among cations, and therefore exhibit severe side-effects in clinical use.

Combining computational and experimental approaches, Prof. JIANG Hualiang's group from the CAS Shanghai Institute of Materia Medica, Prof. HE Chuan's group from Chicago University and Prof. CHEN Jing's group from Emory University jointly identified a series of compounds that could regulate cellular copper signaling by targeting copper trafficking protein Atox1 and hCCS. Structural based virtual (*in silico*) screening was firstly used to identify small molecules that target the copper transfer interface

of Atox1 and hCCS. Subsequent biochemical experiment validated that several compounds could bind to Atox1 and CCS. Among them, DCAC_50 and DCAC_2 showed the highest binding affinity. In addition, mutagenesis studies confirmed the binding mode predicted by *in silico* modeling. Cellular assays showed that these compounds exhibit dose-dependent inhibitory activities on the proliferation of cancer cells, through increasing cellular ROS level and inhibiting ATP synthesis. Most importantly, one of these compounds, DCAC_50, also showed prominent anti-tumor activities on animal models without toxicities.

"The challenge in drug design is hitting one of these copper-dependent processes without messing with housekeeping functions that normal cells depend upon. DC_AC50 appears to block the function of copper metallochaperone proteins without interacting directly with their cargo, copper ions. As the first member of a new class of inhibitors, it provides a new way to interrogate the physiology of copper trafficking disorders and possibly intervene," commented Thomas O'Halloran from Northwestern University, who has studied tetrathiomolybdate.

This study was published online by *Nature Chemistry* on November 9, 2015. DCAC_50 has also obtained an international patent and is now under pre-clinical evaluation.

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