A tailored DNA nanoplatform for synergistic RNAi-/chemotherapy of multidrug-resistant tumors

With the support of the National Natural Science Foundation of China and the Chinese Academy of Sciences, the research team led by Prof. Ding BaoQuan (丁宝全) at the CAS Key Laboratory of Nanosystem and Hierarchical Fabrication, National Center for Nanoscience and Technology, recently reported DNA origami as the nanocarrier for synergistic RNAi-/chemotherapy of multidrug-resistant tumors, which was published in *Angew Chem Int Ed* (2018, 57: 15486—15490) as a hot paper.

Multidrug resistance (MDR) is a major obstacle in the clinical treatment of cancer during the chemotherapy process. To reach considerable therapeutic effects, much higher doses and different combinations of chemotherapeutics must be administered. At a certain point, this approach is tantamount to drinking poison to quench thirst. To solve this problem, much attention has been given to the detailed biological mechanisms of multidrug resistance. Various reports have shown that P-glycoprotein (Pgp) and survivin are two important therapeutic targets through RNAi technology in the multidrug-resistant tumors. Under this situation, it calls for great efforts to develop multifunctional drug carriers to deliver RNA interference (RNAi) and chemotherapeutic drugs for synergistic therapy.

DNA nanostructures with excellent biocompatibility are employed in the construction of drug delivery systems. Ding group's previous finding showed that self-assembled DNA origami can efficiently load various drugs such as doxorubicin (DOX) (*J Am Chem Soc*, 2012, 134: 13396—13403). Due to its unique addressability, DNA origami with controllable size and shape can be tailored to precisely assemble linear nucleic acid drugs. With these outstanding properties, multifunctional DNA origami is a promising candidate to deliver RNAi and chemotherapeutic drugs into target cells.

In their recent work, they reported a facile strategy to construct a versatile chemically well-defined DNA nanostructure as a co-delivery vector of RNAi and chemotherapeutic drugs to combat multidrug-resistant tumor (MCF-7R) *in vitro* and *in vivo*. In the tailored nanocarrier, two linear small hairpin RNA (shRNA) transcription templates targeting MDR-associated genes (Pgp and survivin) are precisely organized in DOX pre-loaded DNA origami. With the incorporation of active targeting and controlled-release elements, these multifunctional DNA nanocarriers can successfully enter the target MCF-7R cells and synergistically inhibit tumor growth without apparent systemic toxicity. This tailored DNA nanoplatform, which combines RNAi therapy and chemotherapy, provides a new strategy for the treatment of MDR tumors.

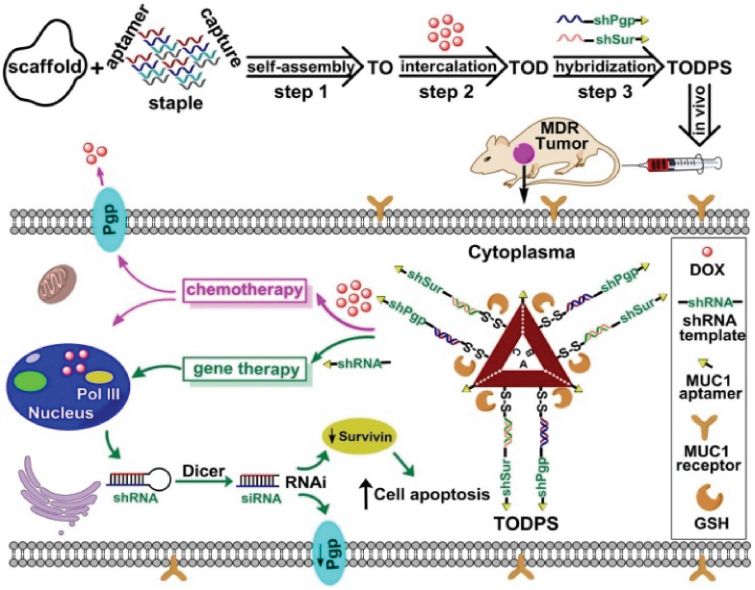

Figure DNA origami-based nanoplatform for synergistic cancer therapy involving RNAi therapy and chemotherapy of a multidrug-resistant tumor.