Calcium peroxide nanoparticles for ion interference therapy

With the support by the National Science Fund for Distinguished Young Scholars and the National Natural Science Foundation of China, the research team led by Prof. Bu WenBo (步文博) at the Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, proposed the "Ion Interference Therapy (IIT)" to combat tumor, which was published in *Chem* (2019, 5(8): 2171—2182).

In clinical tumor treatment, patients who undergo radiotherapy or chemotherapy are always accompanied by the process of tumor calcification, which can contribute to tumor death. This phenomenon is initiated by the accumulation of localized calcium ions and progressed by the calcium salt deposition in local tissues. With the in-depth study, it is found that the biological effect of radio/drug treatment is commonly related to the generation of free radicals. On this basis, Bu's group interconnected the two parts, free radicals generation and intracellular Ca accumulation/overload, to make tumors becoming calcified over time for better treatment feedback. In fact, Ca^{2+} is one kind of the second messengers in intracellular signal transmission, whose fluctuations in local concentration can control vital physiological processes through the activation of specific targets (proteins, nucleic acids, etc.). However, abnormal accumulation of calcium in the cytoplasm leads to cell calcium overload, and persistent calcium overload further stimulates NADPH oxidase activity that is responsible for reactive oxygen species (ROS) generation, finally inducing cell death. This provides theoretical support for efficient tumor treatment based on calcium overload.

Therefore, they prepared sodium hyaluronate modified, pH-sensitive calcium peroxide nanoparticles (SH-CaO_2 NPs) to demonstrate the new role of calcium in tumor therapy. In the acidic tumor microenvironment, the modified layer is firstly degraded by hyaluronidase, and then the exposed CaO_2 NPs are decomposed into free Ca^{2+} and H_2O_2, leading to intracellular calcium overload and free radicals accumulation together. For tumor cells, the down-regulated catalase (CAT) makes them unable to clear the accumulated H_2O_2 in time, causing cells to become more vulnerable and easily driven into oxidative stress. This increased oxidative stress alters the calcium channels and can result in abnormal retention of the generated Ca^{2+} in cells. The full process would irreversibly change the calcium signals from "regulating" to "destroying", this process can be defined as "calcicoptosis". Since Ca^{2+} are essential in various types of cells, tumor type and oxygen partial pressure do not limit the killing effect. Moreover, NPs were also observed to be capable of initiating cell calcification during the therapeutic process. Finally, they presented great tumor suppression effect in the orthotopic mice model. This "Ion Interference Therapy" strategy will promote us to utilize the biological effects of ions for efficient diseases treatment.

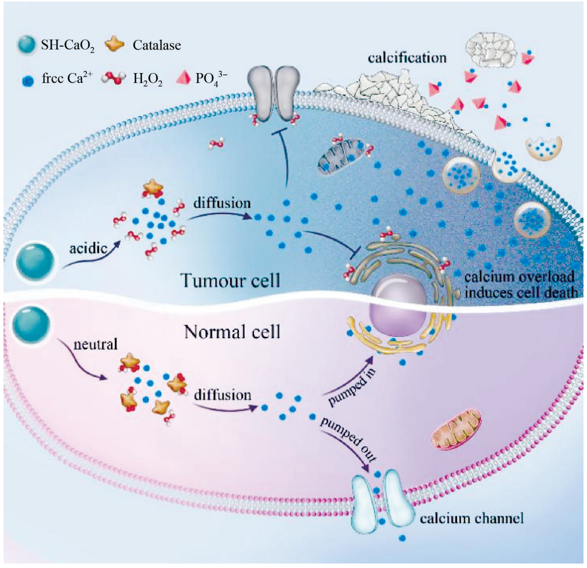

Figure Schematic representation of the functional pattern of SH-CaO_2 NPs.

With regards to the future, they insist that the *in-site* degraded products of nanomaterials, including metal ions, anions, small molecules and clusters, can really make a difference for tumor treatment with their unique biological effects and interactions with tumor microenvironments. Digging out the new role of Ca^{2+} is just a beginning. With the in-depth understanding of their invisible effects to tumors and in turn taking advantage of them, the idea of "Ion Interference Therapy" will potentially open a new opportunity for the development of antitumor strategies.