Calcium Bursts Kill Drug-Resistant Tumor Cells

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Multidrug resistance (MDR) – a process in which tumors become resistant to multiple medicines – is the main cause of failure of cancer chemotherapy. Tumor cells often acquire MDR by boosting their production of proteins that pump drugs out of the cell, rendering the chemotherapies ineffective. Now, researchers reporting in ACS' Nano Letters have developed nanoparticles that release bursts of calcium inside tumor cells, inhibiting drug pumps and reversing MDR.

A pump protein called P-glycoprotein (P-gp) often plays a key role in MDR. P-gp is in the cell membrane, where it uses energy in the form of adenosine triphosphate (ATP) to pump drugs out of tumor cells. Scientists have tried to block P-gp in various ways, such as with small-molecule inhibitors or by depleting ATP.

However, the strategies used so far can cause side effects, or they are unstable in the body. Some of the treatments can be difficult to prepare. Kaixiang Zhang, Zhenzhong Zhang, Jinjin Shi and colleagues wanted to block P-gp using a different approach. Previous research suggested that overloading tumor cells with calcium ions could both decrease production of P-gp and reduce ATP levels. But the team needed to find a way to deliver bursts of calcium, along with a chemotherapy drug, inside cancer cells.

The researchers made a "calcium ion nanogenerator" (TCaNG) by loading calcium phosphate nanoparticles with the chemotherapy drug doxorubicin and then coating them with molecules that would allow TCaNG to target and enter cancer cells. Once inside cells, TCaNGs entered an acidic compartment, where the TCaNGs disintegrated, releasing both doxorubicin and bursts of calcium ions.

When the team tested TCaNG on cancer cells in a petri dish in the lab, both ATP and P-gp production decreased, which allowed doxorubicin to kill the previously resistant tumor cells. When tested in tumor-bearing mice, TCaNG-treated mice showed significantly smaller tumors after 21 days of treatment than control mice, with no apparent side effects.

Read the original article on American Chemical Society (ACS).