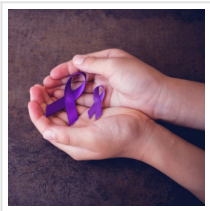
Researchers Develop Acid-Sensitive Nanoparticles as New Treatment for Pancreatic Cancer



2021-03-24

The research team led by Prof. YANG Lihua from Hefei National Laboratory for Physical Sciences at the Microscale, School of Chemistry and Materials Science of the University of Science and Technology of China (USTC) of the Chinese Academy of Sciences proposed nanomicelles composed solely of macromolecules as a new approach for treating pancreatic tumor. The study was published in ACS Applied Materials & Interfaces.

Host dense peptides (HDP) is a part of the innate immunity of eukaryotic organism. It helps the host fence back attack by microbes through disrupting cellular membrane integrity. Inspired by HDP, membrane-disruptive macromolecules are designed with two most HDP's common structural characteristics (cationic and amphipathic) to realize similar membrane-disrupting function so that drug-resistant cancer cells can be efficiently eliminate. The onset of drug resistance is delayed after repeat treatment, suggesting the potential for addressing the cancer resistance issue.

Despite these advantages, membrane-disruptive macromolecules normally cannot distinguish cancerous from normal cells. How to make membrane-disruptive macromolecules preferentially active to cancerous cells over normal cells is a significant challenge.

In this study, the researchers used an acid-sensitive, membrane-disruptive micelle (M-14K) as the model for such nanoparticles.

This long-circulating nanoparticle showed acid-activated cytotoxicity indiscriminately to both cancerous and fibroblast cells, which is realized by acid-activatable disruption of cellular membrane integrity. The ability of such nanoparticles to penetrate the stromal barrier and eliminate the sheltered cancer cells was verified both in vitro using three-dimensional (3D) cell spheroids and in vivo using mouse models bearing BxPC-3 tumors.

Notably, through animal experiments, the researchers found that the expression of extracellular matrix components was significantly suppressed, the tumor tissue was transformed into a less dense structure, and stroma was remodeled, without promoting tumor metastasis.

Using acid-responsive nanoparticles composed solely of membrane-disruptive macromolecules, stroma remodeling and cancerous cells elimination can be realized simultaneously. This approach may open a new avenue for the development of efficacious drugs inhibiting pancreatic tumor growth and metastasis.

What makes pancreatic tumor hard to cure is the dense stromal barriers sheltering cancerous cells. The penetration of drugs is hindered. To promote the infiltration of therapeutics, an adjuvant is used prior to gemcitabine to remodel the stroma. Nevertheless, this widely studied strategy may raise the risk of tumor metastasis and tumor cells' resistance to drugs.