

Design of novel nanomedicines to regulate the redox equilibrium for therapeutics of oxidative stress-related diseases (Thiết kế hạt Nano-Y được điều hoà cân bằng oxi hoá khử trong điều trị các bệnh liên quan đến stress)

Excessive generation of reactive oxygen species (ROS) is strongly related to gastrointestinal (GI) disorders including ulcerative colitis (UC) and colon cancer. Although oral administration is preferable for patients, the use of low-molecular-weight (LMW) drugs is limited due to low stability, non-specific distribution in GI tract, and causing undesired adverse effects. Nanomedicine has recently developed as promising drug carriers; however, these nanocarriers themselves often cause toxic adverse effects. Here, we developed a novel redox nanoparticle (RNP⁰) prepared by self-assembly of an amphiphilic block copolymer possessing stable nitroxide radical TEMPO, an ROS scavenger (Fig.1), as a nanotherapeutics for treatment of GI disorders. In an experiment using zebrafish embryo, we evaluated the toxicity of RNP⁰ and compared to LMW TEMPOL and control polymeric nanoparticle without ROS scavenging character. In fact, all zebrafish died after treatment with TEMPOL or control polymeric nanoparticle, while no zebrafish death was observed by treatment with RNP⁰ under same concentrations, indicating an extremely low toxicity of RNP⁰. It is important to note that almost all mitochondria were damaged for the LMW TEMPOL treatment, while no damage was observed for RNP⁰ treatment, indicating a protection of healthy mitochondria is one of important mechanism for our nanoparticle antioxidant.

When we evaluated the accumulation of nanoparticles in colon, a considerable high accumulation of RNP⁰ in colon was observed, as compared to TEMPOL and polystyrene latex particles, even though the same size (40 nm) due to high stability of RNP⁰ in GI tract. Interestingly, we found that orally administered RNP⁰ tended to accumulate in inflamed colon and cancer but not in healthy cells, resulting in an effective ROS scavenging in colonic mucosa of dextran sodium sulfate (DSS)-treated mice, suppressing the inflammation in colon.

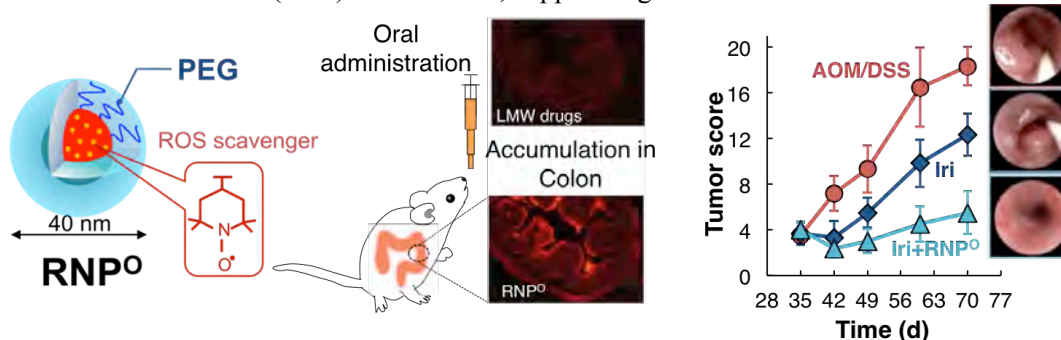


Figure 1: Redox nanoparticle (RNP⁰) and oral administration for GI disorders

We also confirmed the efficacy of RNP⁰ on colon cancer model mice induced by azoxymethane (AOM) and DSS. The mice given 5 mg/mL RNP⁰ for a month had significantly reduced tumor scores compared to AOM/DSS-treated mice. Because overproduced ROS in tumor microenvironment induce drug resistance of cancer cells, when anticancer drug Irinotecan (Iri) was administered in combination with free drinking RNP⁰, a remarkable suppression of tumor growth was observed in mice treated with combination compared to mice treated with Iri alone (Fig. 1). The Iri-induced adverse effects, such as diarrhea and GI toxicity, were remarkably reduced in RNP⁰-treated mice. These results indicate that oral administration of RNP⁰ not only significantly enhances the anticancer efficacy of Iri against colon cancer development, but also effectively suppresses the severe adverse effects of Iri. In another study, combinative therapy of RNP⁰ and Doxorubicine was also investigated in colon cancer model mice. In summary, oral administration of RNP⁰ is a promising and safe nanomedicine for treating not only GI disorders but also other ROS-related diseases.