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**ABSTRACT**: Tumor heterogeneity is considered as one of main obstacles to limit the clinical application of stimuli-responsive nanocarriers. Multidrug resistance (MDR) is also a major challenge in cancer chemotherapy. Here, we developed a tumor redox heterogeneity-responsive prodrug with self-induced reactive oxygen species (ROS) amplification property for facilitating rapid drug release and overcoming MDR and lung metastasis. The prodrug can self-assemble into polymer micelles (PMs) with high drug loading content (~30%), good physiological stability, prolonged systemic circulation and enhanced tumor distribution. Moreover, the prodrug PMs can stimulate tumor-specific ROS signal amplification, which provided a replenishment of consumed ROS necessary for rapid and complete drug release. The elevated ROS could not only evoke the mitochondria-dependent apoptosis by caspase-9/3 activation, but also inhibit inherent and acquired drug resistance by altering expression of Bcl-2 protein family and by reducing mitochondria membrane potential ($\Delta\Psi m$) and ATP