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Therapeutic impacts of enzyme-responsive smart nanobiosystems

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Summary

An important arena of the sophisticated nanosystems (NSs) is the combination of the responsive features of NSs with the biocatalytic properties of enzymes. The development of such smart drug delivery systems (DDSs) has seminal effectiveness in targeting, imaging, and monitoring of cancer. These NSs can exhibit site-specific delivery of the toxic cargo in response to the endogenous/exogenous stimuli. Enzyme responsive/targeted DDSs display enhanced accumulation of cargo molecules in the tumor microenvironment (TME) with a spatiotemporal controlled-release behavior. Based on the unique features of enzyme responsive/targeted DDSs, they offer incredible promise in overcoming some limitations of the currently used conventional DDSs. Taken all, targeting TME with the enzyme-responsive targeted DDSs may lead to versatile clinical outcomes in various malignancies.

Authors' Biosketch

Marziyeh Fathi is Assistant Professor of Organic Chemistry at the Research Center for Pharmaceutical Nanotechnology (RCPN). Her research is mainly focused on the development of advanced drug delivery systems as well as the synthesis of tissue engineering scaffolds using novel biopolymeric materials.

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Jaleh Barar (PharmD, PhD) is Professor of Drug Delivery and Targeting. She currently is the chair of the department of Pharmaceutics at the Faculty of Pharmacy, Tabriz university of Medical Sciences. Professor Barar's research is focused on various aspects of the pharmaceutical cell biology with the particular emphasis on the development of novel drug delivery and targeting strategies to combat cancer.

During the past decade, various advents in the nanoscaled drug delivery systems (DDSs), so-called multimodal nanosystems (NSs), have paved the path for the development of novel strategies for cancer diagnosis and treatment. These multifunctional NSs can incorporate simultaneously both therapeutic and imaging agents and deliver them to the target site with optimal efficiency and mitigated adverse effect.[1-4] The tailor-made surface modification and biofunctionalization allow a significant increase in the circulation time and hence efficient tumor-targeting and accumulation.[5-10] Stimuli-responsive NSs have been emerged as a promising alternative for conventional DDSs due to their responsive nature towards exogenous (e.g., temperature, magnetic field, ultrasound, and light) and endogenous (e.g., enzymes, pH, redox, and hypoxia) stimuli, which can even cross the biological barriers safely.[11-20]

Enzymes play a critical role in the development of many debilitating diseases and the imbalance in their expression/activity underpins the pathobiology of such ailments.[21] Furthermore, enzymes as biological triggers have several features, including (i) fast catalyzing chemical reactions under mild conditions with high efficiency, (ii) unique chemo/regio/enantioselectivity and specificity in detection of target molecules and substrates, and (iii) high relevance for different tissues and diseases. All these characteristics render the enzyme responsive nanomaterials as ideal smart biomacromolecules that can be used in an extensive array of biomedical applications.[5,7,22-25] Therefore, exploitation of enzyme-responsive DDSs can be an extremely valuable strategy as theranostics/diapeutics and can harness the biocatalytic

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property of enzyme and exceptional physicochemical properties of the nanocarrier. This strategy represents a wide range of advantages in targeting TME and diagnosing and controlling/curing cancer therapy, including (i) protection of drug molecules during circulation in the bloodstream, (ii) tumor-selective accumulation, (iii) controlled-release of anticancer drug(s), (iv) enhanced cellular uptake and intracellular delivery of drugs, and (v) improved pharmacokinetic (PK) and pharmacodynamic (PD) outcomes with much lower adverse reactions.[11,12] In fact, high affinity and exceptional selectivity of the enzymes towards their targets make them a suitable choice for specific, complicated, and biologically inspired chemical reactions.[5,26,27]

Different types of nanoscaled enzyme-responsive delivery systems have been constructed using polymers (e.g., micelles, hydrogels, dendrimers, and inorganic polymeric hybrids), lipids, liposomes, small organic molecules or inorganic/organic hybrid materials (Fig. 1). Enzyme-induced reactions can alter the physicochemical properties of constructed nanoparticles via cleavage of the covalent bond or some non-covalent interactions.[5,28,29] Several classes of enzymes including proteases, phospholipases, and oxidoreductases have been used in the development of enzyme-responsive controlled DDSs.[5]

For instance, matrix metalloproteinases (MMPs), as a large family of zinc-containing endopeptidases, are overexpressed in many types of cancers and are involved in cancer initiation, progression, and metastasis via cleaving peptide substrates in the extracellular matrix (ECM).[30-32] This group of enzymes can be considered as a suitable candidate to improve the efficacy of the therapeutic agents. In this line, several MMP-responsive smart NSs have been engineered which have shown to improve drug specificity and efficacy in TME.[5,33,34] Besides, enzyme-responsive nanomaterials in conjugation with active targeting moieties such as antibodies (Abs), aptamers (Aps), and peptides can significantly increase drug accumulation at the target site via reducing unspecific uptake to non-targeted tissue, and site-specific controlled drug release.[35-44] Despite all the advantageous of enzyme-responsive DDSs, essential criteria for designing more effective delivery systems still pose a striking challenge, which needs to be considered for their clinical applications. In fact, before clinical applications of enzyme-responsive DDSs, a wide variety of issues need to be addressed, including (i) enzyme dysregulations in diseases, (ii) spatial and temporal patterns of enzyme activity, (iii) substrates overlap for closely related enzyme families, (iv) complexity in the large-scale production of the NSs (in terms of their physicochemical properties, e.g., size, stability, and surface charge), and (v) biocompatibility of nanoformulations and their long-term biological impacts.[29,45] Nonetheless, dual/multi-stimuli responsive DDSs have been designed to further enhance the targeting efficiency of the cancer therapy agent.[5,19,20] In short, aberrant enzymatic system of the TME could be considered as pivotal target, through which enzyme-responsive NSs can be triggered for on-demand drug release/activation. As a result, if successfully utilized, enzyme-responsive NSs would be a step forward in overcoming the limitations of conventional delivery strategies.

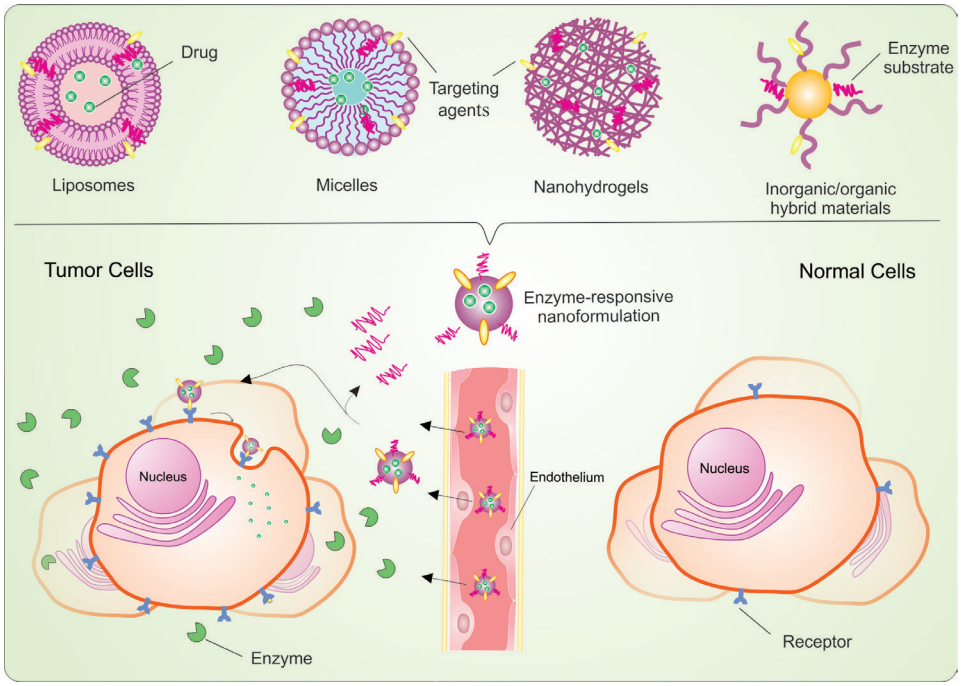

Fig. 1. Schematic representation of enzyme-responsive nanosystems using different nanomaterials. In the tumor microenvironment, enzymatic cleavage of the covalent bond or physical encapsulation leads to cargoes releasing from nanocarriers.

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Authors' contribution
MF, AS, and JB developed the idea, drafted the manuscript. JB finalized the submission.

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