Chapter 1

Introduction

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Cancer is the largest cause of mortality globally. Various efforts have been made over the last few decades to search therapeutics for effective cancer therapy. However, the drug's therapeutic effectiveness is hampered by its poor aqueous solubility, low penetration, and poor targeting potential. To overcome these challenges, nanomedicine have recently gained widespread popularity. Besides, tumor microenvironment (TME)-responsive nanomedicine has gained more traction in the past two decades for target specific delivery. The TME-responsive nanomedicine not only exploit the enhanced tumor permeation and retention (EPR) potential but also prolong systemic circulation, thereby improving translation of nanomedicine to tumor site for enhancing therapeutics availability at target site responsible for higher intracellular accumulation in cancer cells. It further offer target-specific release of therapeutic payload in response to the physiological stimuli unique to the tumor microenvironments further precising drug delivery and avoiding off target distribution [1].

The TME-responsive nanomedicine contains functional groups susceptible to distinct TME stimuli like acidic pH, enzymes, hypoxia, and ROS. Stimuli-responsive groups endow the nanomedicine with a prerequisite property for stimuli responsive release of therapeutics tailored to unique conditions of tumor microenvironment. The TME-responsive nanomedicine may exhibit special physicochemical properties such as size shrinkage/expansion capability, switching of surface charge, and exposure of hidden ligands on exposure to a particular tumor stimulus, which in turn results in further prolongation bioavailability, superior tumor accumulation, deeper penetration in the tumor site, maximum uptake by target cells and selective drug release at the target site [2].

Mainly three mechanisms are involved in providing on-demand drug release at the target site, i.e., a) bond cleavage, protonation, or conformational changes [3], b) disassembly

[4,5], and c) cap removal [6]. The TME-responsive nanomedicine makes use of polymers, either of natural origin or chemically engineered, that are sensitive to the tumor microenvironment and have the unique potential to effectively modify their microstructure in response to modest tumor microenvironmental changes [7,8]. These use of TME-responsive nanomedicine offer enhanced therapeutic effects and reduced side effects, therefore holds tremendous potential in providing site-specific delivery of therapeutic agents. Using biopolymers to develop unique nanocarriers ensures its biocompatibility, biodegradability, non-immunogenicity, safety, and reproducibility [9,10].

1.1 Biopolymers for the design of tumor microenvironment responsive systems

Biopolymers have been widely employed in the development of biocompatible, biodegradable nanomedicine. Different biopolymers and their derivatives have the potential for use in the development of tumor-microenvironment-responsive nanomedicine (discussed in detail in Chapter 2). These biopolymer-based nanomedicines increase drug accumulation and subsequent release on response to a specific tumor stimulus in target cells rather than normal cells, improving the clinical utility while reducing side or toxic effects in normal cells. **Figure 1.1** summarizes various stimuli-responsive strategies utilized by biopolymer-based TME-responsive nanomedicine to selectively deliver therapeutics to the targeted sites.

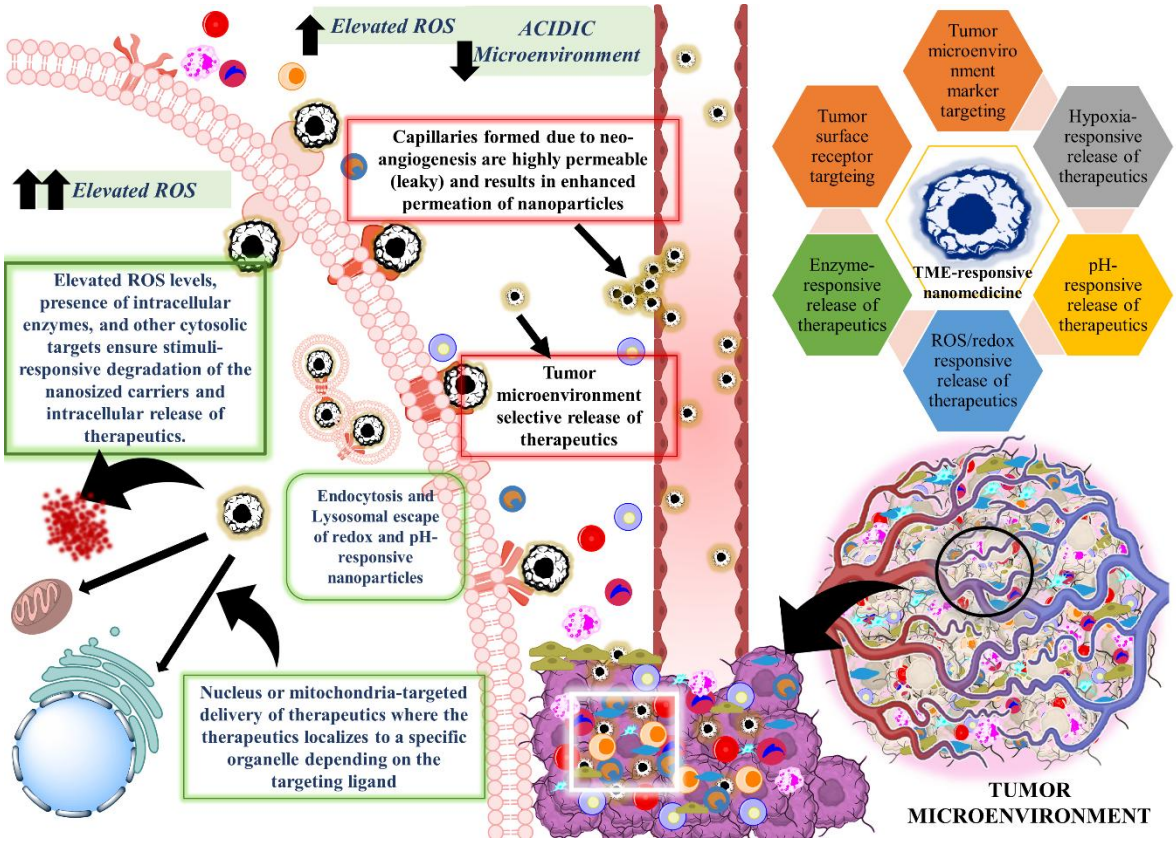

Figure 1.1 Graphical illustration of the precise therapeutic delivery mechanism of biopolymer-based nanomedicine tailored to exploit tumor microenvironment stimuli.