Triggering Mechanisms of Thermosensitive Nanoparticles Under Hyperthermia Condition

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ABSTRACT: Nanoparticle-based hyperthermia is an effective therapeutic approach that allows time- and site-specific treatment with minimized off-site effects. The recent advances in materials science have led to design a diversity of thermosensitive nanostructures that exhibit different mechanisms of thermal response to the external stimuli. This article aims to provide an extensive review of the various triggering mechanisms in the nanostructures used as adjuvants to hyperthermia modalities. Understanding the differences between various mechanisms of thermal response in these nanostructures could help researchers in the selection of appropriate materials for each experimental and clinical condition as well as to address the current shortcomings of these mechanisms with improved material design.
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INTRODUCTION

Nanoparticle-based drug delivery is an innovative method that has been employed to achieve reduced systemic toxicity, improved drug retention in circulation, and increased intratumoral drug accumulation via the enhanced permeability and retention effect.[1] However, the structure heterogeneity of tumor vasculature inflicts an irregular drug extravasation within the infected region.[2,3] Moreover, because of the complexity of interstitial tumor matrix as well as the limited interstitial fluid flow, diffusion of nanoparticles in the extravascular extracellular space remains challenging.[4] The intratumoral nanoparticle accumulation could be enhanced by employing mild hyperthermia as an adjunctive therapy to increase the perfusion and permeability in tumor vasculature.[3,5] Furthermore, increased permeability of cell membrane, inhibition of DNA repair, and higher rates of cytotoxic chemical reactions at elevated temperatures could lead to an enhanced cytotoxicity of antineoplastic agents under hyperthermia condition.[6,7]

The efficacy of nanoparticle-based hyperthermia could be further improved using thermosensitive nanocarriers of chemotherapeutic agents.[8] The thermosensitive nanocarriers must ideally preserve their cargo at physiological temperature and quickly release it into a locally heated tumor to counteract rapid clearance by bloodstream.[9] These carriers can be fabricated using a diversity of organic and inorganic compounds including biocompatible polymers,[10–12] lipids,[13–15] and self-assembling amphiphilic micelles.[16–18] The thermosensitive nanostructures may also be made using metallic,[19–23] or carbon-based compounds[24–26] that directly act as therapeutic adjuvants, rather than carrying other therapeutics, through enhancing the heat deposition rate within the infected region. Thermal sensitivity is often determined by a sharp nonlinear alteration in at least one characteristic of these materials during the temperature change. The onset and ending temperatures, rate, and intensity of this property change could significantly influence the efficacy of thermosensitive nanostructures under hyperthermia condition.

This review is an attempt to provide a comprehensive review of the most widely observed triggering mechanisms of thermosensitive nanoparticles and outline their substantial features and shortcomings. Several mechanisms of thermal sensitivity such as coil–globule, gel–liquid, and micellization transitions are generally applied for thermal-triggered drug release, whereas enhanced heat generation under hyperthermia modalities is often obtained by employing materials with superparamagnetic behavior, or photo-absorbing ability. Recently, fabrication of hybrid nanostructures has allowed simultaneous application of both drug- and heat-triggering mechanisms for a faster drug delivery and improved hyperthermia condition. It is noteworthy that a number of other mechanisms have recently shown potential for application in nanoparticle-based hyperthermia systems. For instance, a thermal-triggered drug release could be obtained by encapsulation of chemotherapeutics inside the core–shell nanostructures comprising porous drug reservoirs and low melting point polymer shells.[27] However, the focus of this review is only on the mechanisms the efficacy of which has successfully been established through extensive *in vitro* and *in vivo* studies. Understanding the substantial parameters that influence these triggering mechanisms could aid researchers in the selection of appropriate thermosensitive nanostructures and thermal modalities according to their own experimental and clinical condition.

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COIL–GLOBULE PHASE TRANSITION

Coil–globule phase transition of the thermosensitive polymers has recently found increasing interest for effective release of therapeutics under hyperthermia condition. The unique characteristic of thermosensitive polymers is their discontinuous water-solubility change at a specific temperature referred to as the critical solution temperature (CST). In the concentration–temperature phase diagrams, CST is a temperature where both coil-shaped soluble polymer chains and insoluble polymer globules are present in the aqueous medium.[28–31]

Critical solution temperature could generally be categorized into lower critical solution temperature (LCST) and upper critical solution temperature (UCST). LCST is considered as the minimum temperature in the concentration–temperature phase diagram where the phase separation occurs in the polymer solutions.[32,33] UCST by contrast is the maximum temperature in the phase diagram where the polymer solution changes from phase-separated to a single-phased solution.[32,34] Phase separation because of the temperature changes is often accompanied by a discontinuous volumetric collapse of the polymer network in aqueous solution. Therefore, the phase transition at elevated temperatures results in negative and positive temperature-dependent volumetric changes in LCST and UCST polymers, respectively. The volumetric ratio between the swollen and collapsed states is often less than 10-fold.[35]

Mechanisms of Coil–Globule Phase Transition

The coil–globule phase transition in thermosensitive polymers is governed by the balance between repulsive and attractive electrostatic forces that favor the polymer swelling and collapse behavior.[36] According to the mean field theory, discontinuity of the volumetric phase transition is controlled by the ionization degree as well as the persistence length of the polymer chains. In general, increased ionization or stiffness of the polymer chains leads to a discontinuous transition and higher volumetric changes. The volumetric changes above 10-fold could be resulted in the polymer network by increasing the swelling pressure via polymer ionization. Therefore, the polar solvents (e.g., aqueous solution) play an important role in obtaining a discontinuous volumetric transition in thermosensitive polymers. However, the organic solutions may also provide discontinuous volumetric phase transition when the polymer chains are highly ionized.[35] The electrostatic forces needed for the coil–globule phase transition in aqueous solutions of thermosensitive polymers are often produced by hydrophobic and cooperative hydrogen bonding interactions.[37–40] The other intermolecular forces such as Van der Waals and attractive ionic interactions are not considered as crucial forces in coil–globule phase transition of thermosensitive polymers.[37]

Hydrophobic Interaction

The presence of moderately hydrophobic groups (which allow partial dissolution in aqueous medium) such as methyl, ethyl, or propyl is a common characteristic of LCST polymers. At temperatures below LCST, water molecules near the hydrophobic polymer coil form highly ordered structures, called icebergs, via an exothermic and spontaneous hydrogen bonding process that decreases both enthalpy and entropy of the mixture. Although the energy of this hydrophobic interaction is about few kcal/mol, it could significantly stabilize the polymer configuration.[41] At temperatures above LCST, the water molecules leak out from the polymer because of the breakage of hydrogen bonds, resulting in coil–globule phase transition accompanied by precipitation of the polymer (Fig. 1).[42]

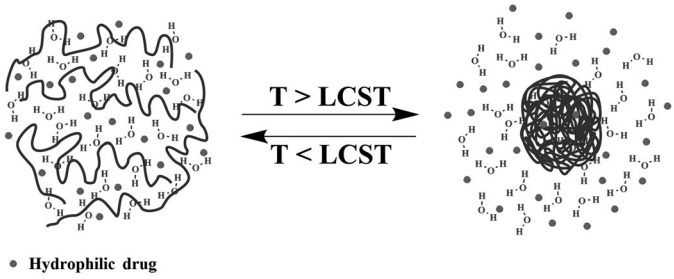

Figure 1. Schematic of coil–globule transition in LCST polymers because of the hydrophobic effect. The collapse of polymer chains provides a compressive force, leading to leakage of aqueous solution out of the globule structure.

From the thermodynamics perspective, the LCST and UCST phase transitions because of the hydrophobic interaction are controlled by entropy and enthalpy balances, respectively. At LCST, the entropic gain from the release of hydrogen-bonded aqueous molecules becomes higher than entropy loss because of polymer collapse, resulting in increased overall entropy.[13,41,43] Moreover, the entropic gain of the whole system becomes more significant compared with the enthalpic contribution of hydrogen bonds between aqueous molecules and the polymer chain.[13,43] UCST by contrast is a temperature at which the enthalpic effect because of the ordered state of aqueous molecules around the polymer chains becomes less than the entropy loss because of this phenomenon.[10,13]

Cooperative Hydrogen Bonding

A positive temperature-dependent volumetric phase transition (swelling in UCST system) via the cooperative hydrogen-bonding interaction is mostly observed in interpenetrating polymer networks (IPNs) comprising two independent networks intermingled but not chemically bonded to each other.[37,41] At temperatures below UCST, the formation of intermolecular hydrogen bonds between the interpenetrating chains results in the formation of continuous ladder-like complexes that probably cause water insolubility and volumetric shrinkage. However, the temperature rise presumably initiates the dissociation of the hydrogen bonds, allowing expansion of the polymer complex (Fig. 2).[44] Dissociation of the initial hydration bonds between the interpenetrating complex units also promotes the cooperative breakage of contiguous complexes (zipper effect), leading to free solubilization of the interpenetrating chains and a drastic volumetric expansion at higher temperatures.[44]

Coil-helix transition, which is mostly observed in random gel networks (e.g., gelatin), is another example of an intermolecular association by hydrogen bonding. In this mechanism, two or more polymer chains generate a helix conformation at low temperatures that forms physical junctions in the gel network. However, in spite of obtaining a positive temperature-dependent volumetric change in both IPNs and random gels, a sigmoidal transition above a specific transition temperature range is only observed in IPNs. On the contrary, the random gels undergo a relatively simple, exponential swelling during heating. The difference in the swelling mechanisms of IPNs