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Nanomedicine Therapeutics

Liu *et al. Nanomed Ther.* 2026;1:5 **DOI:**10.20517/nmt.2026.08

Engineering intracellular assembly for programming cell fate

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Citation: Liu L, Yi T. Engineering intracellular assembly for programming cell fate. *Nanomed Ther.* 2026;1:5. https://dx.doi.org/10.20517/nmt.2026.08

Received: 29 Jul 2026 **First Decision:** 14 Aug 2026 **Revised:** 21 Aug 2026 **Accepted:** 4 Sept 2026 **Published:** 15 Sep 2026

Academic Editor: Xiangyang Shi **Copy Editor:** Shu-Yuan Duan **Production Editor:** Shu-Yuan Duan

MAIN TEXT

From responsive nanomedicine to biological programming

In recent years, nanomedicine has emerged as a promising approach for improving the precision and efficacy of cancer treatment[1,2]. Advances in nanomaterial engineering have improved pharmacokinetics and tissue selectivity and have enabled stimulus-responsive systems that release therapeutic agents in response to pH, reactive oxygen species (ROS), enzymes, or other disease-associated signals[3,4]. These advances have improved the efficiency of drug delivery. Nevertheless, despite significant improvements in targeting efficiency and responsiveness, most nanomedicines still mainly release therapeutic agents upon detecting pathological signals, with limited ability to regulate dynamic biological processes. Growing evidence indicates that the pathogenesis of many diseases is not simply caused by the abnormal expression of a single molecule, but rather involves a series of highly coordinated intracellular molecular events that ultimately alter cell behavior[5,6]. Accordingly, future responsive nanomedicines should move beyond simply detecting disease-associated signals and instead be designed to integrate multiple biological signals and regulate cell behavior in a controlled manner.

In light of these challenges, programmable therapeutics based on responsive nanomedicine have been developed that respond to the tumor microenvironment, precisely control drug release, and engineer tumor metabolism, offering new opportunities for effective and precise cancer treatment[7-10]. Unlike conventional responsive systems that merely react to environmental stimuli, programmable therapeutic materials are designed to regulate cell behavior through a series of coordinated intracellular events, such as apoptosis, pyroptosis, ferroptosis, necroptosis and senescence, rather than simply releasing cytotoxic drugs in response to disease-related signals. Studies have shown that therapeutic efficacy depends not only on the dose of drug delivered to diseased tissues but also on how cellular responses are regulated after delivery[11-13]. Consequently, the focus of therapeutic intervention is gradually shifting from molecular targeting towards cell fate programming.

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Intracellular assembly as a biological programming strategy

The concept of intracellular assembly has evolved remarkably over the past decade. It was initially regarded as a strategy for constructing functional nanostructures within living cells[14,15]. By exploiting endogenous stimuli, researchers have developed diverse supramolecular systems that improve intracellular retention, amplify imaging signals, and enhance local therapeutic efficacy[16]. In most of these studies, however, intracellular assembly was primarily regarded as the final outcome of molecular activation, serving as a structural endpoint that improved the physicochemical properties of therapeutic systems, such as stability, intracellular retention and subcellular localization. Growing evidence suggests that its role extends far beyond structural construction. As a dynamic process, intracellular assembly continuously reshapes the intracellular microenvironment by influencing molecular diffusion, organelle function, and reorganizing intracellular signaling networks[17]. Consequently, assembled nanostructures should be viewed not merely as passive products of molecular recognition but as active regulators capable of directing subsequent cellular responses.

Building on this concept, intracellular assembly can be viewed as a programmable process that converts molecular recognition into coordinated cellular responses[18]. Rather than simply producing a final nanostructure after stimulation, assembly provides a dynamic intermediate stage in which structural changes guide subsequent biological events. The properties of assembled architectures, including their morphology, mechanical properties, localization, and temporal dynamics, collectively influence how intracellular pathways are activated and regulated. Thus, material structure is no longer merely the outcome of molecular design but becomes a means of regulating cellular behavior.

This emerging perspective is exemplified by the recent work of Zhang *et al.*, who demonstrated that intracellular assembly can be engineered as a programmable process to regulate cell fate[19]. Rather than using assembly merely to construct intracellular nanostructures, the authors designed a tandem-controlled strategy in which sequential biological events progressively transform molecular building blocks into functional supramolecular architectures. Through this cascade, intracellular assembly actively regulates cellular responses, ultimately leading to lysosomal disruption, pyroptosis, and antitumor immune activation.

The significance of this study extends beyond developing a new therapeutic nanomaterial, as it introduces a different approach to nanomedicine design. Conventional stimulus-responsive nanomedicines typically convert disease-associated signals into a defined therapeutic output, such as drug release[20]. In contrast, Zhang *et al.* established a sequential intracellular cascade in which each activation step drives the next transformation, allowing material assembly and cellular responses to occur in a coordinated manner[19]. In this strategy, tumor-associated signals initiate structural changes, and the resulting intracellular assemblies further reshape the cellular environment to regulate downstream biological processes. Therefore, assembly is no longer simply a consequence of molecular recognition but becomes an active link between material transformation and cell fate regulation. This approach provides a new framework for developing nanotherapeutics that can actively regulate cellular behavior rather than merely respond to pathological signals.

Engineering intracellular assembly cascades for programmable regulation of cell fate

The study by Zhang *et al.* provides an important example of how intracellular assembly can be developed from a structural phenomenon into a programmable biological process[19]. A key innovation of this work is the establishment of a tandem-controlled assembly cascade, in which multiple intracellular events are organized in a defined sequence rather than simply combined as independent stimuli. The authors designed a tandem-controlled intracellular assembly system that integrates tumor-associated extracellular activation with intracellular environmental cues, allowing the therapeutic function to emerge only after a series of sequential molecular transformations. This hierarchical design addresses a major limitation of conventional responsive nanomedicines, in which multiple signals often serve only as parallel filters to improve selectivity rather than control the order of biological events.

The importance of this sequential strategy is further supported by the intracellular behaviors of the system[19]. Following matrix metalloproteinase-2

(MMP-2)-mediated activation, the system undergoes a surface charge conversion that facilitates cellular uptake and enables subsequent intracellular activation[19]. Rather than directly triggering a therapeutic response after signal recognition, the first activation step creates the conditions required for the next transformation. This stepwise activation ensures that the therapeutic effect occurs only after all intracellular steps are complete. Such a strategy moves beyond conventional stimulus-responsive materials by allowing cellular responses to be controlled more precisely through sequential molecular events.

Beyond controlling activation, this study shows that the assembled structures themselves can regulate cellular responses. Intracellular reduction leads to supramolecular polymerization and the formation of nanofibers inside cells. The process begins outside the cell, where tumor-associated MMP-2 cleaves the anionic GLP-D_5 segment from the nanoparticles, thereby reversing their surface charge[19]. This charge conversion promotes cellular uptake and subsequent lysosomal enrichment. Once inside the lysosomes, GILT and glutathione (GSH) reduce the disulfide bonds, leaving the assembly-active component (F-C_6-NH_2), which then undergoes in situ self-assembly to form nanofibers inside cells. Thus, nanofiber formation is not a direct response to a single intracellular stimulus but the outcome of a linked sequence of molecular events, with each step preparing the system for the next. Importantly, the therapeutic effect does not rely on the release of a conventional cytotoxic drug but instead arises from the structural transformation of the assembled materials. Upon forming supramolecular structures, individual molecules acquire new biological functions and can actively influence cellular responses. Therefore, intracellular assembly is not simply the final product of molecular design but an active process that contributes to the therapeutic effect.

The biological effects of this intracellular assembly are closely linked to the physical and chemical properties of the resulting nanofibers. The original study showed that the nanofibers formed inside lysosomes have a high Young's modulus of 464 ± 75 MPa and are enriched in primary amines[19]. These properties may work together to destabilize the lysosomal membrane. The high stiffness of the nanofibers can generate mechanical stress at the membrane, while the abundant primary amines can buffer protons and contribute to a proton sponge effect. This can cause osmotic imbalance and increase membrane tension, further weakening the membrane and eventually leading to lysosomal rupture. Thus, lysosomal damage in this system is not simply a consequence of fiber rigidity but results from the combined mechanical and chemical effects of the assembled material. This finding highlights an important feature of intracellular assembly: structures formed inside cells can acquire physical and chemical properties that directly affect cellular behavior.

The molecular consequences of lysosomal disruption were further investigated. The authors proved that lysosomal damage was associated with pyroptosis through the CatB-NLRP3-caspase-1-GSDMD pathway[19]. Importantly, this pathway was supported by both pharmacological and genetic experiments, rather than by pathway analysis alone. Inhibition of CatB or caspase-1 reduced the pyroptotic response, supporting their involvement in the downstream process. GSDMD knockout markedly attenuated the response, supporting that GSDMD-mediated membrane pore formation is an essential step in the observed cell death. The authors also performed control experiments to distinguish pyroptosis from other forms of regulated cell death, showing that necroptosis and ferroptosis were not major contributors under these conditions. Together, these results support a stepwise mechanism: intracellular nanofiber formation first damages lysosomes, which then activates the CatB-NLRP3-caspase-1-GSDMD pathway and ultimately leads to pyroptotic cell death. These findings provide important support for the proposed concept of cell fate programming. Unlike conventional nanomedicine strategies that mainly depend on drug release or nonspecific cytotoxicity, this approach controls cell fate through intracellular events triggered by material assembly. The final therapeutic outcome is therefore not determined by a single molecule, but by the combined effects of sequential structural and biological changes.

Overall, the work by Zhang *et al.* demonstrates that intracellular assembly can not only construct nanostructures but also regulate cell fate[19]. By combining sequential molecular activation with supramolecular assembly, the authors establish a direct connection between material transformation and biological

responses within cells. Unlike conventional nanotherapeutic approaches that mainly rely on drug release or signal-triggered activation, this strategy generates therapeutic effects through the structural transformation of the intracellular assembly. With this design, intracellular assembly becomes a new approach for directing cellular responses and improving therapeutic efficacy rather than simply serving as a carrier or delivery mechanism. This study therefore offers a new perspective on how engineered materials can interact with cells and control biological outcomes.

Future perspectives: towards programmable control of cell fate

The study by Zhang *et al.* provides a new perspective on how nanomaterials can interact with living systems[19]. By demonstrating that intracellular assembly can actively regulate cellular responses, this work expands the role of nanomedicine beyond simple delivery and stimulus-triggered activation. Rather than serving only as carriers for therapeutic molecules, future materials could be designed to undergo controlled transformations inside cells and directly influence biological processes. However, several challenges need to be addressed before engineered intracellular assembly can be widely applied. A major challenge is achieving precise control over when and where assembly occurs in complex biological environments. The extent and duration of assembly must be carefully controlled to achieve the desired therapeutic effects while avoiding unwanted cellular responses. In addition, most current systems respond to only a limited number of disease-related signals, whereas cellular behavior is governed by complex signaling networks. Therefore, future efforts should focus on developing assembly systems that can integrate multiple biological cues and dynamically respond to changes in the cellular environment.

Beyond cancer therapy, programmable intracellular assembly could also regulate biological processes that depend on precise intracellular organization. By controlling interactions among organelles, signaling pathways, and other cellular components, these strategies could help us better understand and treat complex diseases. However, achieving this goal will require a deeper understanding of how artificial assemblies interact with endogenous cellular mechanisms.

Ultimately, engineered intracellular assembly represents a new way to design therapeutic materials, in which material formation itself contributes to biological regulation. Future nanomedicine may focus not only on delivering molecules to specific locations but also on creating materials that can actively interact with cells and guide their responses. This concept could contribute to new strategies for precision therapy and the development of next-generation biomaterials.

DECLARATIONS

Authors' contributions

Conceived and wrote the manuscript: Liu L
Contributed to the discussion and revision of the final version: Yi T

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version GPT-5.6 Luna, released 2026-07-09) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

Financial support and sponsorship

This work was supported by the National Key R&D Program of China (No. 2023YFC3605700), the National Natural Science Foundation of China (No. 22371038; No. 22407023), the Fundamental Research Funds for the Central Universities (No. 2232026D26).

Conflicts of interest

Yi T is an Editorial Board Member of *Nanomedicine Therapeutics*. Yi T was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling, and decision-making. Liu L declares there are .no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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