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Self-Powered Electrically Controlled Drug Release Systems Based on Nanogenerator

Weikang Luo, Ruizeng Luo, Jingjing Liu, Zhou Li, and Yang Wang**

Precision medicine requires precise regulation of drugs in terms of time, space, and dosage. Exogenous control systems, such as electrical responsiveness, have made great progress. However, wearable or implantable controlled drug release devices still face major challenges due to limitations including limited battery life, large size, and fixed power supply. To overcome these limitations, the fabrication of autonomous devices is available to endure extended periods without reliance on external power sources. As a promising strategy, nanogenerators (NGs) turn body mechanical energy into electricity, powering long-term drug release. In this review, the current status of drug delivery systems (DDS) is briefly outlined and the importance of self-driven controlled drug release systems is emphasized. The main types and operational mechanisms of various nanogenerators are introduced. This review also focuses on summarizing the latest progress of self-powered controlled drug release systems based on nanogenerators (NG-based CDRs). Additionally, their applications in the field of drug release are introduced in detail. Finally, the existing challenges and future trends of self-powered NG-based CDRs are discussed from the perspectives of clinical needs and practical translation.

1. Introduction

Endogenous sustained-release preparations or technologies are usually developed based on the average pharmacokinetics parameters observed in healthy individuals. These technologies solve the problems of poor selectivity, weak targeted release ability, and high effective drug dose of traditional medications.[1] However, such formulations lack the ability to adapt in real-time to accommodate individual variations in drug pharmacokinetics under different pathological conditions. Therefore, the clinical treatment of disorders necessitates a system device capable of self-adjustment and on-demand drug release.[2]

With the consistent development of biological detection technology and the improvement of the medical level, individual differences in disease diagnosis and treatment have attracted wide attention. In 2011, the American medical community introduced the concept of precision medicine for the first time.[3] Precision medicine utilizes large-scale genome sequencing for disease prediction and implements highly accurate diagnosis and treatment, mainly for diseases with numerous affected populations.[4] In the era of multiomics big data, sequencing technologies have been widely used in the screening of disease-related biomarkers,[5] the study of drug effects,[6] and the development of targeted drugs under its guidance.[7] With the continuous deepening of research on targeted drugs for various diseases, various endogenous and exogenous controlled drug release technologies have emerged one after another. To cater to the general environment of smart medical care, self-powered, miniaturized, and wearable controlled drug release systems have received more attention. Self-powered controlled drug release systems based on nanogenerator (NG-based CDRs) have been the subject of extensive study.

In this review, we give a brief overview of drug delivery systems (DDS) and drug carriers, with a particular focus on targeted and controlled drug delivery. Subsequently, the operational principles of various types of NGs are introduced, along with a summary of representative ways or behaviors by which mechanical energy is generated within the human body. Furthermore, this review comprehensively summarizes the significant progress in the field of electronically controlled drug release based on NGs, drug release

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mechanisms, and medical applications. Finally, we discuss and envision the future challenges and trends in the field of NG-based CDRs.

2. Drug Delivery Systems (DDS)

2.1. Overview of DDS

On-demand drug release pertains to the dynamic manipulation of drug release kinetics and timing throughout the delivery process, with the intention to achieve appropriate drug release in target areas in response to disease-specific requirements.[8] DDS is a drug delivery strategy aimed at delivering the right amount of drugs to a predetermined site at the optimal time.[2a] This approach aims to improve drug bioavailability, reduce drug dosages and off-target effects at lower cost, thereby mitigating side effects and enhancing therapeutic efficacy.[9] The emergence of novel technologies and the integration of multiple disciplines have greatly propelled the development of new-type DDS.[10] Compared with traditional drug delivery methods such as oral administration and injection administration, the new DDS has significant advantages in many aspects: 1) Excellent physical and chemical properties, including self-stability, stability in a biological fluid environment, and raw material biocompatibility. 2) High drug release efficiency, including drug encapsulation efficiency, targeting specific disease areas, precise and controllable local drug release, convenient on-demand drug release, and personalized drug release. 3) The preparation is simpler, the operation is more convenient, the cost is more reasonable, and it has the potential for industrial transformation.

2.2. Vehicles for DDS

DDS usually uses different forms of carriers to make the drug reach the affected area through different drug delivery routes.[9d] Several commonly used drug delivery vehicles, such as hydrogels,[11] microneedles,[12] patch films,[13] and nanoparticles (NPs),[14] have been used to assist in enhancing the in vivo delivery of a variety of drugs. It is important to note that these carriers are not fixed and unchanging. Conversely, these forms can be combined in a mutually beneficial manner, including microneedle patches,[15] hydrogel patch films,[16] hydrogel patches containing nanoparticles,[17] and various other forms. This enables the comprehensive integration of various drug carrier attributes, thus better satisfying the demands of practical applications. The release forms of drugs from carriers primarily include diffusion, dissolution, permeation, and ion exchange.[2a,18]

2.2.1. Microneedles

Microneedles are an innovative physical transdermal technology that can penetrate the stratum corneum of the skin in a minimally invasive manner without causing bleeding or pain. Generally, microneedles are composed of multiple regularly arranged microneedle arrays and bases. Microneedle technology has developed rapidly in the past few years and has been widely used in drug delivery/release,[19] tissue engineering,[20] and biosensors.[21] On the basis of integrating Traditional Chinese Medicine (TCM) acupuncture-moxibustion, the technology also has the advantages of drug loading and transdermal delivery.[22] As a minimally invasive transdermal device, microneedle can be used as a substitute for traditional injection drug delivery, and has the following advantages: 1) High penetration rate. It is difficult for macromolecular drugs to penetrate the stratum corneum and be absorbed by the epidermis and dermis, while the length of microneedles is usually hundreds of μm, which can penetrate the stratum corneum of the skin, thereby improving the skin permeability of macromolecular drugs. 2) Adjustable parameters. Different materials can endow microneedles with different properties, such as conductive microneedles made of conductive materials, degradable microneedles made of degradable materials. In addition, the size and array of microneedles can be designed and adjusted according to application requirements, with the most suitable depth and rate control and optimize drug release.[23] 3) High safety.[24] Because the needle body of the microneedle is short, the needle tip can only reach the epidermis, avoiding contact with blood vessels and nerve endings, so it has a lower risk of infection and bleeding. 4) High compliance. Microneedle delivery is a non-invasive drug delivery technology. Compared with conventional drug delivery methods, such as intramuscular injection or intravenous injection, microneedles cause little pain to patients and allow self-administration.[25]

2.2.2. Hydrogels

Hydrogels are hydrophilic 3D network structures, formed from a single component or multiple components, containing a significant amount of water. One of the strengths of hydrogels is that their physicochemical properties can be adjusted widely, making them extremely useful in the field of drug delivery.[26] First, various drugs can be loaded and delivered by manipulating the internal grid's pore size, quantity, and spatial distribution. Second, precise control over the release of loaded drugs can be achieved by modulating the degradation, swelling behavior, and mechanical deformation of hydrogels.[27] These control strategies encompass both endogenous responses, such as pH, temperature, and local microenvironment,[28] as well as exogenous responses, including electric field stimulation, magnetic field response, and photothermal response.[29]

2.2.3. Patch Films

Patch films can be fabricated using both inorganic and soft materials,[30] enabling them to conform to diverse biological microenvironments and effectively match the physiological characteristics of various tissue sites. Additionally, patch films can be fabricated using materials that possess responsive properties, such as electro-responsiveness or thermo-responsiveness. This enables the attainment of responsive control over the patch, enhancing its overall functionality. Even more critically, the presence of internal space structures in the patch films can greatly increase the drug loading efficiency and regulate the drug release by modifying the film structure and composition.

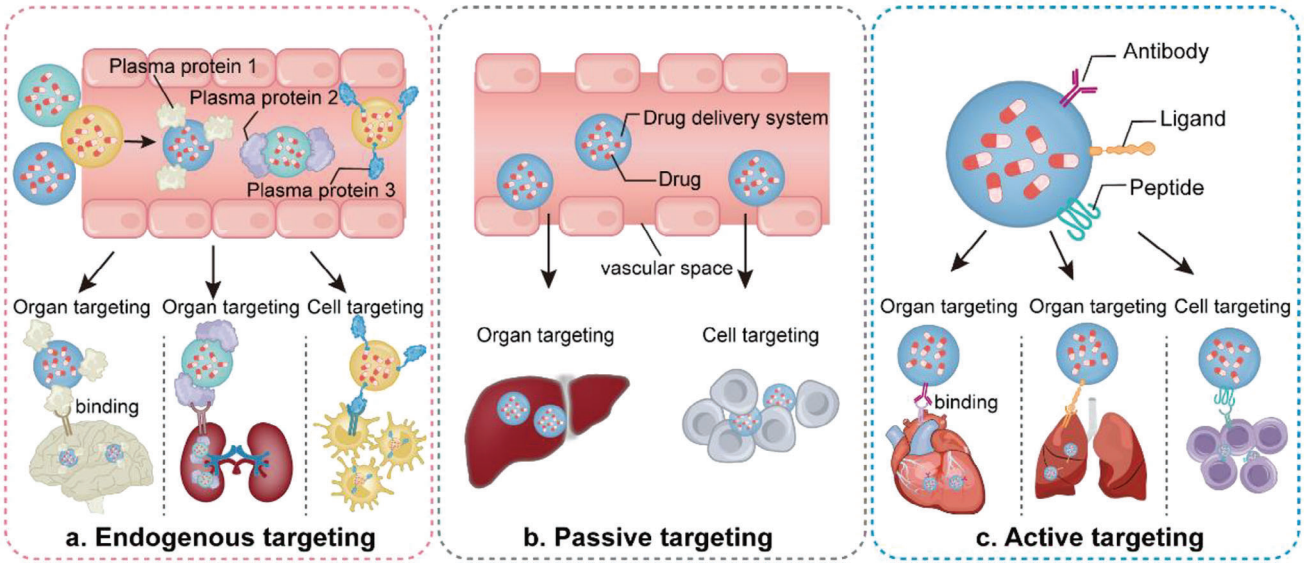

Figure 1. Three representative modes of TDSs. a) Endogenous targeting. Drug carriers deliver drugs to specific organs or cells by binding to endogenous targeting proteins. b) Passive targeting. Drug carriers cross the vascular space to reach the target organs or cells by EPR effects. c) Active targeting. Drug carriers with surface modification of targeting molecules carry drugs actively targeted to target organs or cells.

2.2.4. Nanoparticles

Nanoparticle drug carriers have partially achieved the transition from basic experiments to clinical trials. Up to now, the types of NPs have been divided into lipo-based NPs (liposome, lipid NP, emulsion), polymeric NPs (polymersome, dendrimer, polymer micelle, nanosphere), and Inorganic NPs (silica NP, quantum dot, iron oxide NP, Gold NP) into three categories.[14] Compared to the other types of drug carriers mentioned above, NPs have the following advantages. First, the drug delivered by nanoparticles can be directly delivered into the blood circulation through intravenous injection, avoiding the long-term circulation and metabolic effects of oral administration.[31] Second, the particle size, geometry, material composition and internal structure of NPs are designed to enhance the stability of carriers and overcome biological barriers to improve drug delivery capacity.[32] Increasingly fine engineered nanoparticles have considerably advanced the progress of precision drug delivery.

2.3. Targeting Drug System (TDS)

While the judicious utilization of carriers can mitigate the toxic and adverse effects of drugs on normal tissues and enhance their efficacy to a certain degree, addressing these challenges remains challenging, particularly in the case of drugs with broad therapeutic actions. TDS offers a precise means of delivering drugs to the site of disease, effectively addressing the issue of specificity that is inherent in broad-spectrum drugs. TDS encompasses endogenous targeting, passive targeting, and active targeting modes.[33] Endogenous targeting is mainly carried out through the combination of drug carrier and plasma protein for drug delivery, that is, the surface modification of the carrier can selectively bind to the expected plasma protein (**Figure 1**a). Since this method is highly susceptible to the influence of the microenvironment in vivo, it is difficult to achieve precise recognition and accurate binding of the carriers and the target proteins. Passive targeting and active targeting, which rely on exogenous targeting strategies, are not affected by the tissue microenvironment. Passively targeted delivery systems usually implement drug delivery in the form of nanoparticles (carriers or drugs),[34] mainly utilizing the enhanced penetration and retention effect (EPR effect) to reach the target tissue through the vascular space (Figure 1b). This targeted delivery strategy can change the pharmacokinetics and pharmacodynamics of loaded active ingredients by optimizing parameters such as the shape, size, and surface charge to obtain the best targeted therapeutic effect. Active targeting refers to the specific recognition and binding of drugs to receptors present in large numbers on target organs or cells, so as achieving the purpose of disease treatment (Figure 1c).[9c,35] Compared with passive targeting, active targeting has higher and more controllable disease-specific targeting capabilities, reducing off-target effects and potential side effects on non-target organs. However, the disease-targeted TDS strategy faces challenges in achieving precise control over the spatial, temporal, and dosage aspects of drug distribution within the body. To overcome this difficulty, controlled drug release systems have been developed.

2.4. Controlled Drug Release Systems (CDRs)

CDRs, as the name suggests, can control the release of specific doses of drugs at specific times and locations through physical or chemical techniques, thereby provides a feasible solution for accurate and controllable local drug therapy.[36] CDRs can be divided into endogenous CDRs and exogenous CDRs according to their controlled release technology.

Table 1. The working mechanisms of CDRs.

Drug controlled-release modes	Internal stimulus	Working mechanisms	References
Endogenous drug controlled-release	pH-responsive	Protonated or deprotonated; Cleavage of acid-responsive bonds	[40]
	ROS-responsive	Cleavage of chemical bonds; Redox	
	GSH-responsive	Redox	
	Enzyme-responsive	Enzymatic activity	
Exogenous drug controlled-release	Light	Photofracture; Photoisomerism; Photo-induced rearrangement; Photocross-linking	[1,43–47]
	Acoustic waves	Cleavage of chemical bonds;	
	Magnetic field	Excited with alternating magnetic field to release heat	
	Electric fields	Opening/closing pores; Deformation/actuation; Skin permeabilization; Electromigration and electroosmosis	
	Temperature	Temperature stimulus	

Note: ROS, reactive oxygen species; GSH, glutathione.

2.4.1. Endogenous CDRs

In the state of disease, the microenvironment of the diseased tissue is often different from that of the surrounding normal tissue, such as the tumor microenvironment (TME) has the characteristics of low pH, high reactive oxygen species (ROS) level, hypoxia,[37] and inflammatory infiltration.[38] In addition, in normal tissues, there are many differences between the intracellular environment and the external environment, such as intracellular glutathione (GSH) levels are significantly higher than those in the extracellular environment.[39] The differences in the tissue microenvironment provide trackable targets for the development of controlled drug delivery systems. Therefore, endogenous CDRs are mainly developed based on the microenvironment-stimulus-responsive release patterns. At present, the main types of endogenous CDRs include pH-responsive, ROS-responsive, GSH-responsive, and enzyme-responsive, etc. (**Table 1**).[40] However, there are still many challenges when applying indicators of differences in the pathological microenvironment as stimulus response targets: 1) Individual differences lead to poor controllability of drug release.[41] 2) The release time and speed of the drug are easily affected by other components in the microenvironment. For example, after entering the blood, protein adsorption will occur on the surface of the CDRs, forming a protein corona, which acts as a barrier and reduces the responsiveness of the surface modification molecules.[42]

2.4.2. Exogenous CDRs

Exogenous stimulation, such as light,[43] sound waves,[1,44] magnetic fields,[45] electric fields,[46] and temperature,[47] can effectively solve the unpredictability of drug release caused by complex microenvironments and realize the in vivo precise control of drug release behavior (Table 1).[29d] This strategy can control the dose of drug release temporally and spatially by adjusting parameters such as on-time, intensity, and frequency of exogenous stimulation. Compared to other exogenous stimulation, electrical signals are more easily generated, acquired, and utilized.[48] The controlled release of various drugs in tissues or cells, such as the skin and bones, has been successfully achieved through electrical stimulation with the assistance of traditional power sources.[29c,d,49] Nonetheless, there are still challenges associated with electronically controlled drug release devices. These include the need for battery replacement, high cost of the control circuit required for drug release regulation, bulkiness and lack of portability, and potential safety hazards with long-term use.

3. Nanogenerators (NGs)

NGs were first proposed and fabricated by Wang et al. in 2006, can convert mechanical energy into electrical energy at the nanoscale.[50] Over the past few decades, NGs have found wide applications in various fields such as wearable smart devices, implantable medical devices, and alternative energy sources.[51] Compared with conventional exogenous power devices, NGs have several advantages of small size, low cost, adjustable shape, good biocompatibility, self-powered, and sustainable power supply. It is worth noting that NGs can collect small amounts of mechanical energy, which can be converted into electrical energy by human movement or physiological activities, such as respiratory movements,[52] heartbeats,[53] pulse jumps,[54] joint movement,[55] and muscle movement (**Figure 2**).[56] This ability to provide a stable and continuous power supply has greatly contributed to the advancement of portable medical devices. The design and fabrication of NGs exhibit high flexibility and adaptability, including adjustable shapes and sizes.[57] Combining different power generation mechanisms, material properties, and other factors, NGs that can withstand complex environments can be fabricated. These intrinsic properties endow NGs with great potential in diverse fields, including wearable devices, smart Internet of Things, mobile devices, and medical instruments. At present, NGs have been found to promote cell differentiation,[58] self-powered antibacterial,[59] and accelerate wound healing.[60] Therefore, miniaturized, flexible, wearable, and self-powered NGs provide a feasible strategy for self-powered drug controlled-release systems.

Currently, a variety of NGs have been developed and classified based on the polarization charge generation principles into three types: triboelectric nanogenerators (TENG), piezoelectric nanogenerators (PENG), and pyroelectric nanogenerators (PyENG) (**Figure 3**).[61]

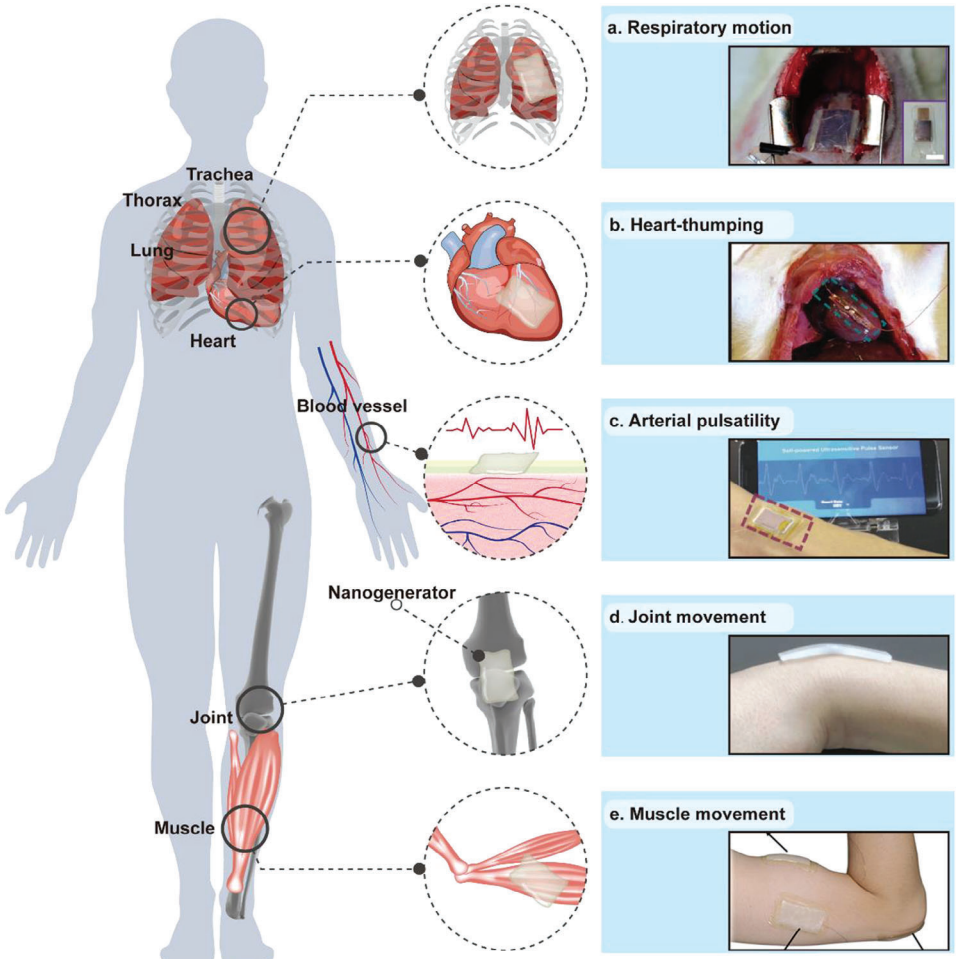

Figure 2. Mechanical energy generation ways in the human body. a) Respiratory motion. Digital image of a TENG implanted inside the abdominal cavity of a Sprague Dawley rat (Inset is the image of the TENG device). Scale bar = 1 cm. Reproduced with permission.[52b] Copyright 2018, American Chemical Society. b) Heart-thumping. A single-wire generator was attached to a Sprague Dawley rat' heart. Reproduced with permission.[53a] Copyright 2010, WILEY-VCH. c) Arterial pulsatility. A self-powered ultrasensitive pulse sensor was placed on the radial artery of a healthy volunteer. Reproduced with permission.[54a] Copyright 2017, WILEY-VCH. d) Joint movement. A multi-mode stretchable and wearable-TENG attached to the wrist joint of a healthy volunteer. Reproduced with permission.[55b] Copyright 2021, Elsevier. e) Muscle movement. A picture of a skin-mounted TENG-based active sensor monitoring muscle strength. Reproduced with permission.[56a] Copyright 2021, American Chemical Society.

3.1. TENG

The operation principle of TENG is the coupling of the triboelectric effect and the electrostatic induction effect. When two dissimilar materials come into contact, the difference in electron affinity of materials results in the generation of opposite charges. Upon the separation of the interface between the materials due to an external force, a potential difference arises between the positive and negative charges.[62] Consequently, when the two materials are linked via a circuit or an external load, the potential difference propels electron flow between the layers, generating an alternating current. It facilitates the conversion of mechanical energy into electrical energy. TENGs can be categorized into four types depending on their operational modes: vertical contact-separation mode, lateral sliding mode, single-electrode mode, and freestanding triboelectric-layer mode (**Figure** 3a).[63]

3.1.1. Vertical Contact-Separation Mode

The vertical contact-separation mode of TENGs offers several advantages, including a simple fabrication process, convenient encapsulation, and high instantaneous power output.[64] This mode was the first to be proposed and extensively studied in 2012.[65] In this mode, the TENG is formed by overlapping two different dielectric materials with metallic electrode layers on their dorsal surfaces. Under the influence of external mechanical force, the contact surfaces of the two materials acquire opposite charges. With the removal of the external force, the contact surface is separated and the electric potential difference is generated on the metal electrode on the back side of the two materials by electrostatic induction. After connecting the load, the free electrons are driven to balance the potential difference, generating an electric current. Under the periodic action of external forces, the surfaces of the two materials can periodically contact and separate,

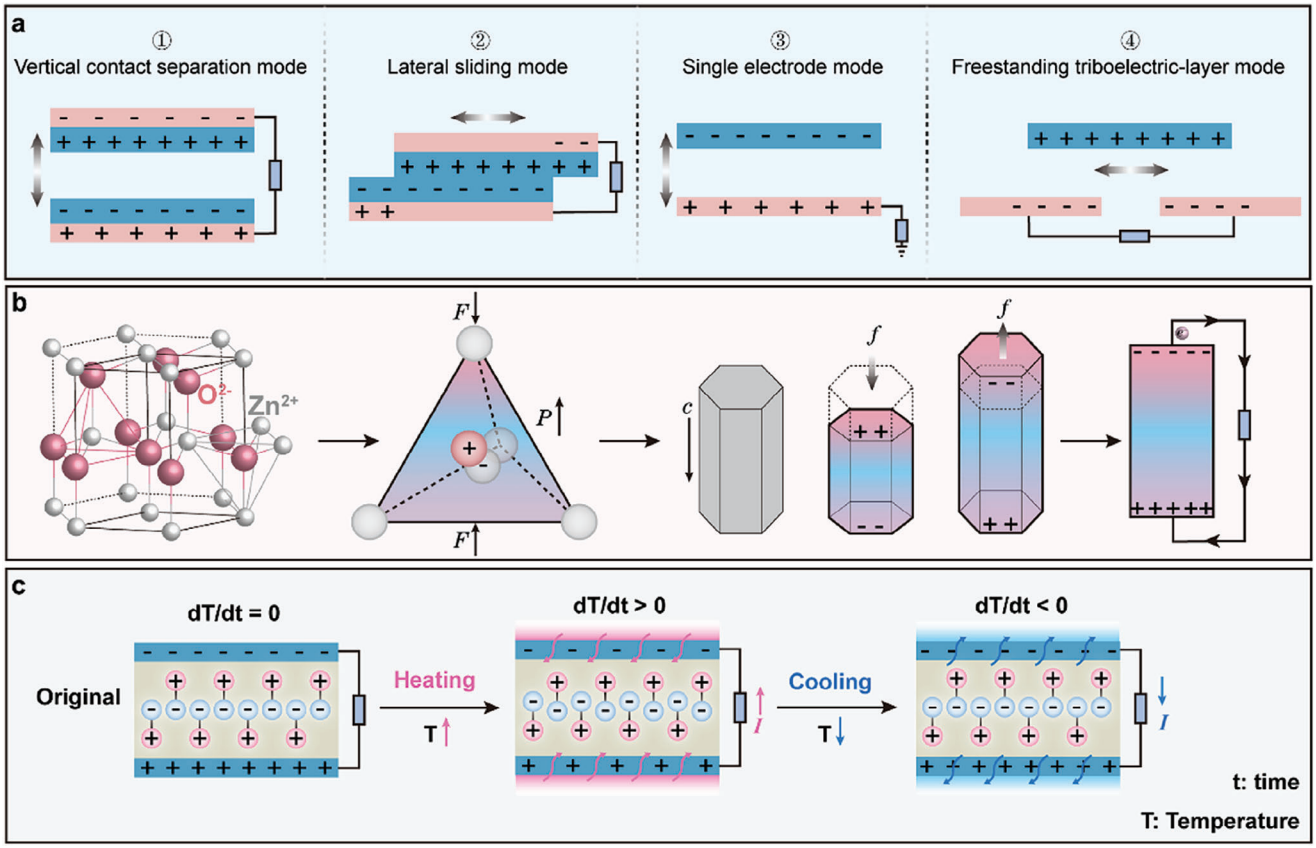

Figure 3. The classification and working principles of NGs. a) Four fundamental working modes of the TENG. b) Working modes of the PENG based on the ZnO nanowire. c) Working principles of the PyENG.

resulting in a changing potential drop or alternating current between the two electrodes (Figure 3a).

3.1.2. Lateral Sliding Mode

The principle of converting mechanical energy into electrical energy in the lateral sliding mode bears a resemblance to the vertical contact-separation mode.[66] Still, the key distinction lies in the horizontal sliding separation that occurs between the two contact surfaces in the lateral sliding mode. With the relative sliding between two contact surfaces, a potential difference between the electrodes at the rear of the materials. The reciprocating sliding motion driven by mechanical forces results in the generation of a continuous and periodic current. This mode facilitates a relatively more complete transfer of charges, thereby potentially generating higher voltage and current output (Figure 3a).[67]

3.1.3. Single-Electrode Mode

The single-electrode mode of TENGs is developed based on vertical contact-separation mode and lateral sliding mode, which comprises only a movable free object and a grounding electrode layer. Periodic changes in the contact area between a freely moving object and a grounded electrode layer can cause periodic charge transfer. The electrode on the back of the contact surface generates a potential difference by electrostatic induction, which drives the flow of electrons in the external circuit (Figure 3a).[68] This configuration has high flexibility and effectively expands the application scenarios of the above two modes.[69] Due to the effect of electrostatic shielding, the electron transfer efficiency in this mode is low, which is usually solved by array arrangement and spacing expansion.

3.1.4. Freestanding Triboelectric-Layer Mode

The freestanding triboelectric-layer mode of a TENG comprises a freestanding triboelectric-layer and multiple different electrode layers on the same plane. The contact or separation of an independent triboelectric-layer from another triboelectric-layer results in an asymmetric electric field within the electrode surface, which drives electrons to flow in an external load to generate alternating current (Figure 3a).[70] Reserving a specific gap between the freestanding triboelectric-layer and the opposing triboelectric-layers enhances the operational lifespan of the generator. In addition, freestanding triboelectric-layer mode without the effect of electrostatic shielding has a higher electron transfer efficiency than single-electrode mode.

3.2. PENG

PENG is a self-powered technology based on the piezoelectric effect, which can convert external pressure into electrical energy.[71] It typically comprises three components: a piezoelectric material, an external circuit, and flexible substrates.[61a] The piezoelectric material deforms under force, which will lead to changes in the arrangement of internal cations and anions, thereby causing an electric dipole moment.[72] The most typical example of this phenomenon is the zinc oxide (ZnO) structure with a wurtzite lattice (Figure 3b).[73] In the internal structure of the material, the positive charge center of Zn^{2+} and the negative charge center of O^{2-} coincide, with a regular tetrahedral coordination structure. As an external force is applied to a vertex of the tetrahedron, the center of positive and negative charges inside the ZnO shifts, and the formation of an electric dipole moment causes a potential difference at the axis end. When an external load is connected, electrons move in a direction to balance this potential difference. Therefore, if the piezoelectric material is subjected to periodic external pressure, it will generate a periodic pulse current.

3.3. PyENG

PyENG is one type of temperature-responsive NGs, mainly composed of two metal electrodes, materials with pyroelectric effects and connecting wires. The pyroelectric effect refers to the phenomenon in which certain materials induce spontaneous polarization changes with temperature fluctuations.[74] In thermal equilibrium (constant temperature), PyENG does not generate any current. As temperature rises, the oscillations of the electric dipole intensify, leading to the weakening of the internal polarization, which in turn drives the movement of electrons in the external load. Conversely, as the temperature drops, the internal polarization increases and the electrons in the external load move to a new electrostatic equilibrium. Finally, through continuous temperature fluctuations, PyENG can establish periodic currents in external circuits (Figure 3c).[75] This self-powered technology, which can convert thermal energy into electrical energy, is widely used in many fields. Notably, PyENG is difficult to obtain continuous power due to the small temperature range of the human body, consequently limiting its potential application in biology and medicine.

4. Applications of NGs in Controlled Drug Release

4.1. Timeline of the Development of NG-Based CDRs

At present, NG-based electrical controlled drug release systems have been widely used in implanted or wearable controlled drug release devices and used for the treatment of various diseases.[76] By selecting the appropriate release mechanism, optimizing structural design, replacing appropriate materials, etc., the NG-based CDRs shows excellent control of drug release capabilities in terms of time, space, dose, and other aspects.

As early as 2016, the first self-powered CDRs based on TENG has been applied for transdermal insulin delivery (**Figure 4**a).[77] This system incorporated a novel liquid volume sensor and a flexible energy collector based on a similar frictional mechanism. Drug dosage detection and control were achieved by pressure regulation. In conjunction with a microneedle array, the patch successfully reduced blood glucose levels in a diabetic rat model by gently tapping the skin (power was ≈33 μW).

Subsequently, Wang et al. verified the effect of TENG on implanted CDRs in pig eyes. The rotational speed controllable turntable can drive the electrochemical pressure pump to release the drug so that the drug release rate is precisely controlled by the rotational speed of the TENG (Figure 4a).[78] Under the control of TENG, the drug delivery rate of this system can reach up to 40 μL min^{-1}. However, this semi-implantable CDR system has large equipment and complicated operation, which is difficult to realize clinical transformation. The development of fully implantable NGs -based CDRs is imminent.

Zhao et al. reported the first TENG-based self-powered fully implantable CDRs for disease therapy until 2019 (Figure 4a).[79] This study developed an implantable magnet triboelectric nanogenerator (MTENG) that can convert the mechanical energy generated by motion into an efficient and stable electric field. The device can locally control the release of doxorubicin (DOX) entrapped in red blood cells, enabling effective tumor treatment at low DOX doses, reducing the systemic toxic side effects associated with oral or injected tumor drugs. These characteristics are conducive to the long-term administration and management of cancer patients. Since then, TENG-based and PENG-based CDRs have been used in the treatment of skin diseases,[80] providing a new structural design for self-driven CDRs. In addition, TENG-based CDRs were also confirmed to control the release of nitric oxide (NO) in the brain, proposing a new controlled-release scheme for intracerebral gas therapy.[81]

It is worth noting that CDRs should also incorporate the concept of modulating pharmacokinetics and pharmacodynamics, which is different from directly controlling drug release. The new concept of self-powered electrical adjuvants to improve drug pharmacodynamics was first proposed to expand the breadth of NGs-based controlled drug release research.[60b] The feasibility of electric adjuvants in enhancing pharmacokinetics was validated in the treatment of skin wounds with EGF and photosensitizer enhancement photodynamic therapy for tumor.[60b,82]

A search was conducted in the Web of Science database (Web of Science Core Collection, MEDLINE, Derwent Innovations Index, ProQuest™ Dissertations & Theses Citation Index, SciELO Citation Index, and KCI-Korean Journal Database) to retrieve relevant studies on the application of electrical stimulation in CDRs since 2000. Interestingly, a larger number of relevant articles were published each year (Figure 4b, left). This may be related to the continuous innovation of carrier materials, drug delivery forms, and the prolonged advancement of drug pharmacodynamics and multidisciplinary integration. Due to the large size, high price, and potential biosafety problems of traditional electrical stimulation equipment, the clinical transformation and adoption of CDRs based on traditional electrical stimulation are limited to some extent. With the rapid advancements in NG technology, NG-based self-powered CDRs have garnered significant interest among researchers.[83] Presently, research on NG-based CDRs is still in its nascent stages, and the number of related articles is relatively limited. However, the overall trajectory is posi-

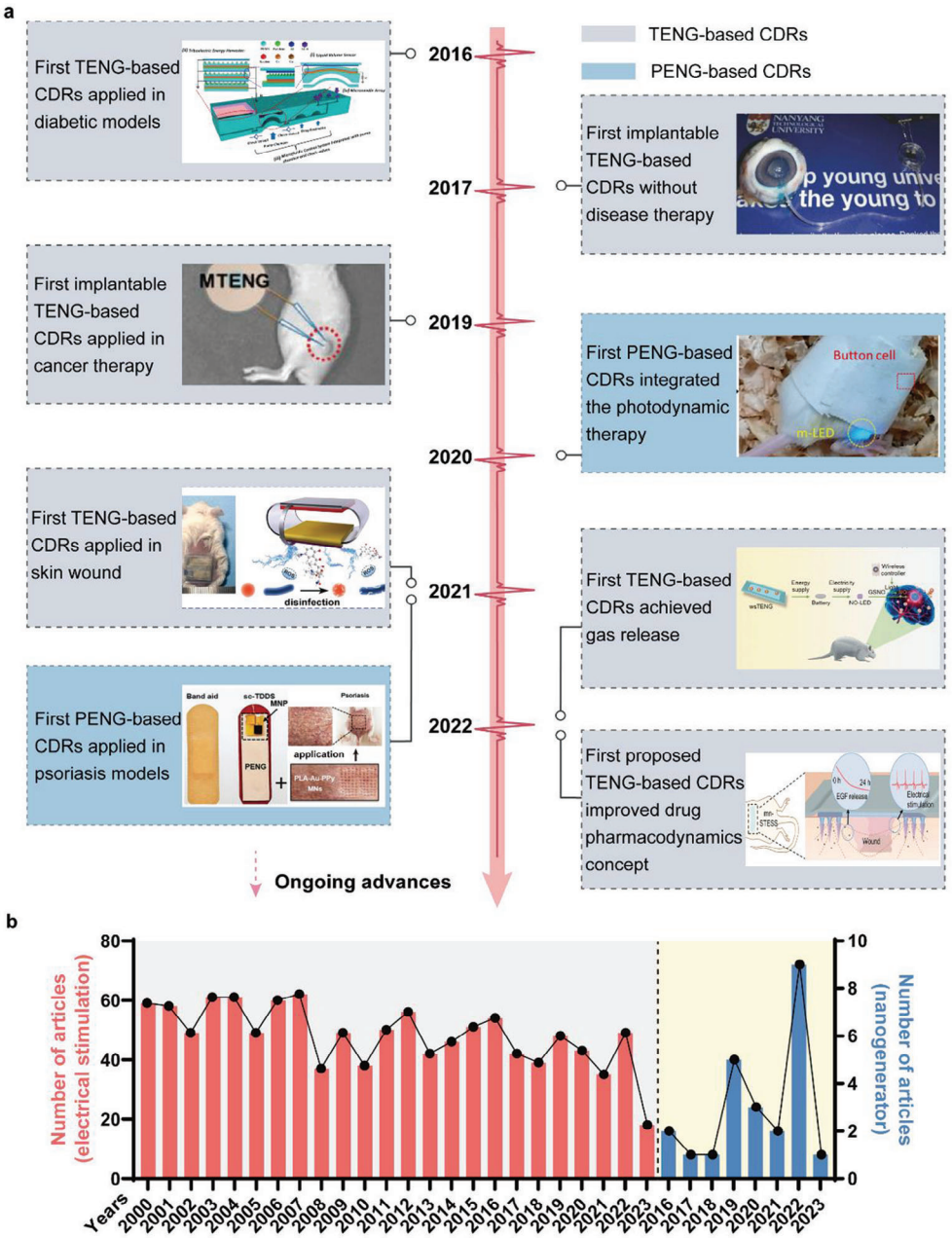

Figure 4. Evolution of NG-based CDRs. a) Timeline of key developments in the study of NG-based CDRs. The focus is on integrated systems that utilize different types of NGs and enable drug release for various diseases. Reproduced with permission.[60b] Copyright 2022, Springer Nature. Reproduced with permission.[77] Copyright 2016, Elsevier. Reproduced with permission.[78] Copyright 2017, WILEY-VCH. Reproduced with permission.[79] Copyright 2019, WILEY-VCH. Reproduced with permission.[80a] Copyright 2021, Elsevier. Reproduced with permission.[80b] Copyright 2021, Wiley-VCH. Reproduced with permission.[81] Copyright 2022, Wiley-VCH. Reproduced with permission.[82] Copyright 2020, American Chemical Society. b) Number of research articles with the electrical stimulation-based CDRs (left) and the NG-based CDRs (right) was conducted in the Web of Science database. Search strategy: drug controlled release (TS) AND electrical stimulation (TS). Article type: article. Preprint Citation Database is not included. The deadline is June 30, 2023.

tive, as depicted in Figure 4b (right). Compared to the traditional electrostimulation devices, NG-based CDRs possess various advantages, including small size, lower costs, and high biocompatibility. On the basis of these properties, there will be a future demand for this type of DDS to cater to the practical needs of the majority of patients. Consequently, it can be anticipated that there will be a sustained increase in research activities within this field.

4.2. Controlled Drug Release Manners and Applications

There are four main mechanisms for electrically controlled drug release based on NGs: electroporation, iontophoresis, electrochemistry, and electrocatalysis.[84] Here, we will introduce the mechanisms of electronically controlled drug release and its applications in NG-based CDRs in detail (**Table 2**).

Table 2. The summarization for the controlled drug release modes based on NGs.

NG-based CDRs modes	Disease/ tissue	Cell	Cargos	Working modes	Materials of NGs	Drug vehicles	Electrical output	References
Electroporation (TENG)	NA	MiaPaCa-2, k562	siRNA	Contact-separation	PMMA, Sponge, Al and Cu, PTFE and Cu	NA	115 V 15 μA	[112]
Electroporation (TENG)	Subcutaneous tumor in mice, Situ tumor of rabbit	Hepal6	APA	Contact-separation	PDMS, PTFE, Magnet, Cu, Al	Red blood cells	90 V 0.85 μA	[113]
Electroporation (TENG)	Subcutaneous tumor in mice	Hela	DOX	Contact-separation	PDMS, PTFE, Magnet, Cu, Ti	Red blood cells	70 V 0.55 μA	[79]
Electroporation (TENG)	NA	MCF-7, rBMSC	FITC-dextran, DOX	Contact-separation	Kapton, Sponge, Cu, FEP	NA	220 V NA	[89]
Electroporation (TENG)	NA	Hela	FITC-dextran	Free-standing	PVC, Nylon, Cu	NA	≈4000 V ≈100 μA	[114]
Electroporation (TENG)	Mice skin	MCF-7, HeLa, rBMSC	Propidiumiodide, FITC-Dextran, siRNA	Free-standing, Contact-separation	Cu, PTFE, Acrylic	NA	20 V 4 μA	[88]
Iontophoresis (TENG)	NA	Hep G2	Dex	Contact-separation	Al, PDMS, XG3-TMAT30-STMP hydrogel	Hydrogel	0.9–1.3 V NA	[97]
Iontophoresis (TENG)	NA	NA	SA, MB, R6G, FSA	Contact-separation	FEP, Copper, Sponge, Acrylic sheet	PDMS well	647.6 V 165.6 μA	[96]
Iontophoresis (TENG)	Wound	NIH-3T3		Contact-separation	Ag, PTEF, LDH@Al	Film patch	39 V 2 μA	[80a]
Iontophoresis (TENG)	Porcine cadaver skin	NA	R6G, MB	Contact-separation	PTFE, Kapton, PET, Al	Hydrogel	≈1200 V ≈20 μA	[95b]
Iontophoresis (TENG)	Porcine cadaver skin	NA	Dex-P	Free-standing	Cu rotator, PTFE, Cu stator	PPy film	>100 V NA	[95a]
Iontophoresis (TENG)	Porcine cadaver skin	NA	Hydrolyzed sodium hyaluronate	Contact-separation	SDNA, Polymer, Counter electrode	Microneedle	150 V 70 μA	[115]
Electrochemistry (TENG)	Porcine eyes	NA	Fluorescent microparticles	Free-standing	Cu rotator, PTFE, Cu stator	PDMS drug reservoir	15 V ≈1500 μA	[78]
Electrochemistry (PENG)	Psoriasis mouse models	NA	Dex	Piezoelectric effect	PET, Ag, PVDF, Cu, Kapton	Microneedle	≈100 V 2 μA	[80b]
Electrocatalysis (TENG)	Subcutaneous tumor in mice	4T1	DOX	Contact-separation	Cu, PTFE, Kapton	Nanocages	40 V 0.35 μA	[103a]
Electrocatalysis (TENG)	Subcutaneous tumor in mice	L929, 4T1	DOX	Contact-separation	Al, TiO_2+PDMS, Nitrile	Nanofibrous patch	84 V 0.38 μA	[103b]
Electrocatalysis (TENG)	Subcutaneous tumor in mice	4T1	Carbon nanotube	Free-standing	Cu, PTFE, Acrylic	Hydrogel	33 V 1 μA	[102]

Note: NG-based CDRs, controlled drug release systems based on nanogenerator; NA, not available; rBMSC: rat bone mesenchymal stem cell; APA, Apatinib; DOX, Doxorubicin; FITC, Fluorescein Isothiocyanate; R6G, Rhodamine 6G; SA, Salicylic acid; MB, Methylene blue; FSA, Fluorescein sodium; Dex-P, Dexamethasone Sodium Phosphate; TENG, triboelectric nanogenerator; PENG, piezoelectric nanogenerator; PMMA, poly-(methyl methacrylate); PTFE, poly-(tetrafluoroethylene); PDMS, polydimethylsiloxane; FEP, fluorinated ethylene propylene; PVC, poly(vinyl chloride); SDNA, salmon deoxyribonucleic acid; PET, polyethylene terephthalate; PVDF, poly(vinylidene fluoride).

4.2.1. Electroporation

When a high-intensity electric field is applied to cells, the resulting electrical pulses can penetrate the cell membrane, leading to the formation of micropores with varying diameters on the membrane. This technique is known as electroporation, which is a physical method that does not involve the use of chemical reagents. The process of cell electroporation involves three steps: membrane charging, pore nucleation, and pore evolution.[85] Initially, during membrane charging, the non-conductive cell membrane functions as a capacitor between the cell cytoplasm and the physiological solution. Once the potential difference reaches

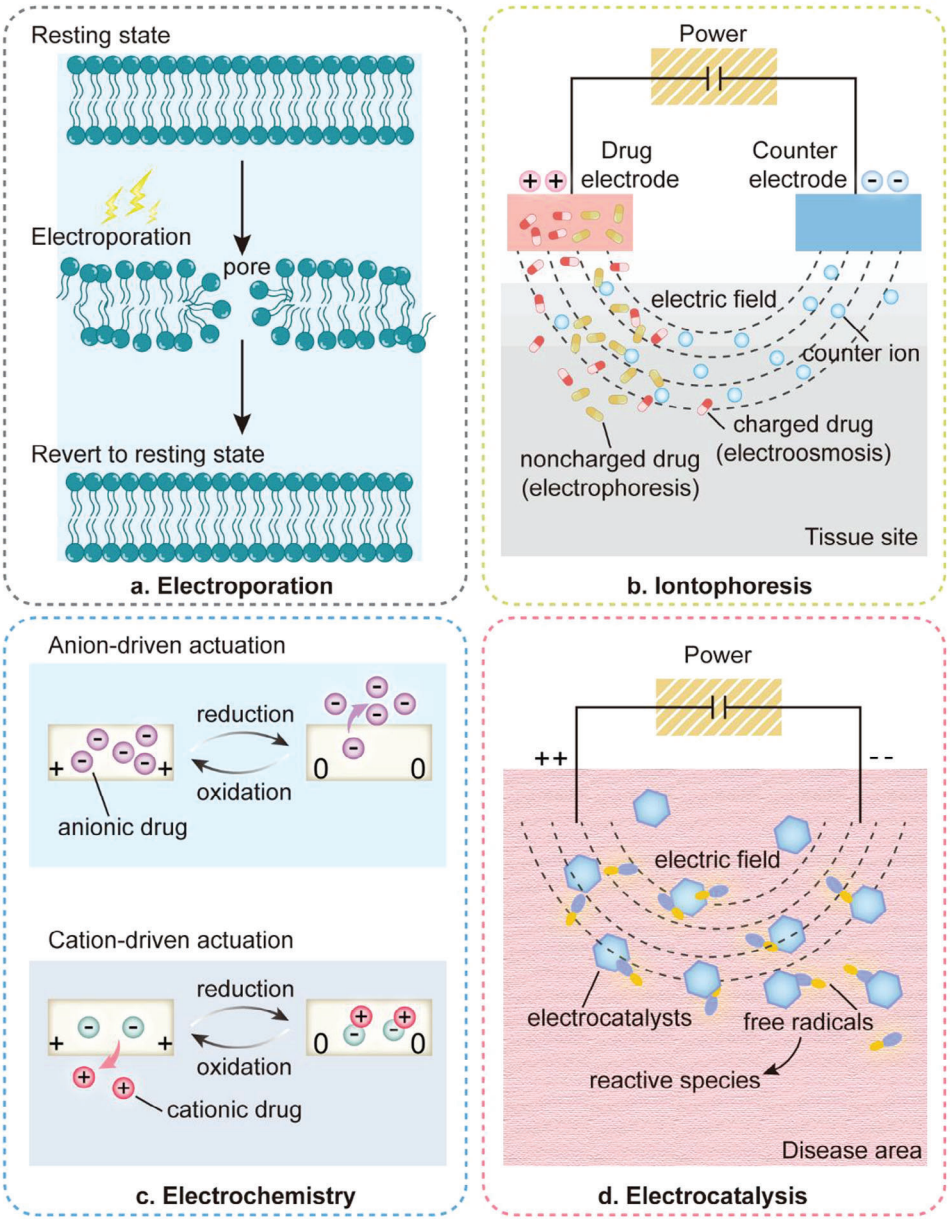

Figure 5. Four drug-controlled release manners. a) Electroporation. b) Iontophoresis. Two modes: electrophoresis and electroosmosis. c) Electrochemistry. d) Electrocatalysis.

a specific threshold, the majority of the cell membrane's surface undergoes the formation of nanoscale pores. This phenomenon facilitates the entrance of diverse substances into the cell, thus exerting certain effects.[86] Lastly, following the electric pulse, the nanoscale pores possess the capability to spontaneously close, serving as a protective measure for the cell. Form this, the micropores created by electroporation provide a fast channel for exogenous molecules (e.g., drugs and genes) into the cells; moreover, these micropores are reversible, which can effectively maintain normal cell viability while achieving controlled release (**Figure 5**a). The density and size of nanopores can be manipulated by modulating parameters such as the amplitude, duration, orientation, and shape of the electronic input signal.[48b,85] However, conventional electroporation technology suffers from shortcomings, such as high-voltage power supply equipment is bulky, expensive, and severe cell damage, which affects the normal efficacy of drugs.[87] Different from traditional electroporation equipment, the electrical parameters of nanogenerators represented by TENG present the characteristics of high voltage, low current, and short pulses, which can ensure the survival efficiency of cells without affecting the drug release efficiency.[88]

Currently, electroporation technology is the most widely adopted approach in NG-based CDRs and has been successfully utilized to deliver and release various drugs in different diseases or cell models (Table 2).

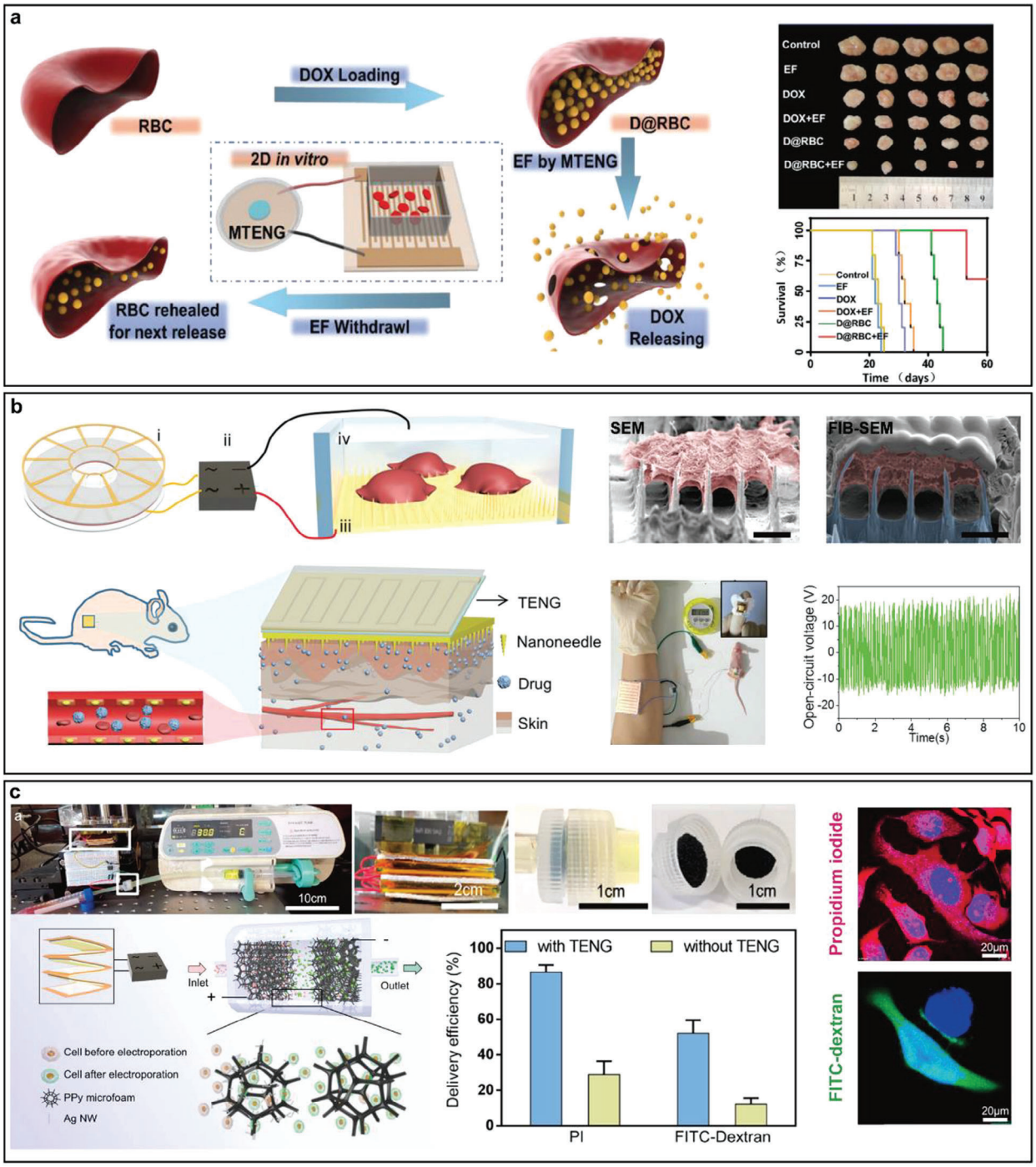

Figure 6. Controlled drug release by electroporation. a) TENG-based CDRs achieved controlled DOX release in vivo via electroporation. Reproduced with permission.[79] Copyright 2019, WILEY-VCH. b) TENG-based CDRs achieved transdermal delivery of dextran via electroporation. Reproduced with permission.[88] Copyright 2019, WILEY-VCH. c) TENG-based CDRs achieved controlled molecules release in vitro by means of high-flux electroporation. Reproduced with permission.[89] Copyright 2020, American Chemical Society.

In the first TENG-based self-powered fully implantable CDRs,[79] the magnet effectively facilitated repeated contact and separation cycles between the friction layers, ensuring a consistent and efficient power output in TENG (**Figure 6**a). Even when the device was encapsulated and implanted, it was able to maintain its pre-encapsulation levels of 70 V for open-circuit voltage and 0.55 μA for short-circuit current. Applying the electric field generated by this self-powered device significantly enhanced the release of DOX loaded in red blood cells via electroporation. This effectively guaranteed that DOX could rapidly

achieve therapeutic drug concentrations in the diseased area, thereby resulting in an effective treatment for tumors at a low-dose DOX. The self-powered electroporation mode not only reduces the systemic toxic side effects associated with high-dose oral or injected drugs but also provides a switchable and controllable release pattern. The device is expected to achieve the long-term administration and management of cancer patients in the future.

Although the output of TENG has the characteristics of high voltage when using the flat electrode of the traditional electroporation device, its local electric field strength is difficult to meet the requirements of cell membrane perforation. With the aim of this problem, Liu et al. developed a CDR device that integrates a silicon microneedle array with a TENG (Figure 6b) .[88] The silicon microneedle array with optimal heights, diameters, and spacing was screened and fabricated using photolithography and metal-assisted chemical etching techniques (Top diameter = 100 nm; Bottom diameter = 700 nm; Height = 7 μm; Inter-needle spacing = 4 μm). In the presence of a 20 V applied voltage on MCF-7 cells, the tips of the microneedle generated a localized electric field of ≈2800 V cm^{-1}, effectively reducing the negative impact of electric fields on neighboring normal cells. Additionally, compared to no microneedle array or TENG pulses, the TENG-integrated silicon microneedle array significantly enhanced the permeation efficiency of impermeable small molecules (propidium iodide), large molecules (dextran-FITC, 10 and 70 kDa), and siRNA within MCF-7 breast cancer cells, HeLa cells, and difficult-to-transfect bone marrow mesenchymal stem cells. Electroporation via the TENG-integrated silicon microneedle array increased drug release efficiency by more than fourfold compared to passive mechanical penetration alone. Furthermore, cell viability exceeded 94% following electroporation with the device, indicating no adverse effect on cell viability. Controlled release and enhanced subcutaneous permeation efficiency of dextran-FITC on mouse skin were successfully achieved through finger rubbing-driven TENG.

Traditional electroporation has drawbacks such as low cellular throughput and high cellular damage, which severely restrict its potential for clinical applications. To achieve self-powered and high-throughput drug delivery/release, Liu et al. developed a TENG-based self-powered PPy foam system with high-throughput electroporation for drug control release (Figure 6c).[89] Surface modification of 1D silver nanowires (Ag NWs) on PPy electrodes further reduced the applied voltage and significantly enhanced the local electric field, thereby preventing abnormal damage to surrounding cells caused by high voltage. When employing this integrated system for intracellular delivery of various sized biomolecules, the highest delivery efficiency reached 86%, while maintaining cell viability above 88%. In this self-powered electroporation system, the cell throughput reached up to 10^5 cells min^{-1}. Emergency rescue during acute medical conditions may be one of the significant potential future applications for the system.

4.2.2. Iontophoresis

Iontophoresis is a physical process in which ions diffuse in a medium driven by an electric field force. This method of actively transporting substances can promote the release and diffusion of charged drugs.[90] CDRs based on the iontophoresis mechanism generally consist of three components: an anode, a cathode, and a power supply device. Under the electric current drive, drug permeability is enhanced through two kinetic mechanisms, namely, electrophoresis and electroosmosis (Figure 5b).[91] Electrophoresis occurs as a result of the repulsive force between drugs and electrodes, allowing drugs, especially small charged molecules, to directly permeate into cells through the biological membrane. Moreover, electroosmosis refers to the directed movement of solvents caused by the electric migration of ions under the influence of an externally applied electric field. Large molecules or neutral drugs typically traverse the biological barrier to by means of electroosmosis.[92] Nowadays, this technology has been widely employed for drug delivery and release in various tissues and organs, including the eyes,[93] gastrointestinal tract,[92a] and mucosa.[94] The emergence of self-powered technology has broadened the application range of iontophoresis, and NGs-based CDRs have been rapidly developed and applied to various disease models in recent years (Table 2).[95]

Ouyang et al. reported a TENG-based on-demand CDRs,[95a] which consists of drug patch electrodes, ion permeation patch electrodes, a power management module (PMM), and a rotating TENG (**Figure 7**a). In the ion permeation patch, a highly conductive and biocompatible PPy material was utilized as the drug carrier. A drug reservoir was then synthesized to store negatively charged drugs through an electrochemical formal. When the TENG was driven by motors, the output voltage can reach 250 V. Even instead of manual rotation, also could achieve more than 100 V output voltage. During a manual rotation of the TENG for 1.5 min (30–40 rpm), the drug release amount was ≈3 μg cm^{-2}. Importantly, drug release ceased when the TENG was not in operation, ensuring control over drug release during transdermal administration. Furthermore, by real-time control of the TENG charging time or adjustment of the PMM resistance, it was possible to achieve controllable changes in the drug release rate (ranging from 0.05 to 0.25 μg cm^{-2} min^{-1}). Compared to the conventional way, a higher drug release rate was observed in the TENG-based CDRs group (≈50% increase). This strategy sheds new light on the use of TENG-assisted CDRs in various administration routes.

In order to achieve a self-powered power supply and closed-loop feedback control for the controlled release system, Wu et al. developed a self-powered wearable iontophoretic CDRs based on conductive hydrogels in 2019 (Figure 7b).[95b] The system comprised a TENG and a drug patch with parallel electrodes utilizing Poloxamer 407 hydrogel. The flexible conductive hydrogel not only facilitated the iontophoretic release of ion-based medications but also exhibited excellent skin adhesion. In the concept validation of the insole TENG for treating ankle joint pain, hydrogel drug patches could adhere to the pain site of the ankle joint. As the insole TENG was compressed during walking and generated electricity, the electric current could be transmitted to the hydrogel drug patches, facilitating the release of medication through iontophoresis. Throughout this process, the device exhibited an open-circuit voltage of up to 1200 V and a short-circuit current of ≈20 μA. This study significantly contributes to the exploration of closed-loop sensing and self-powered transdermal drug delivery.

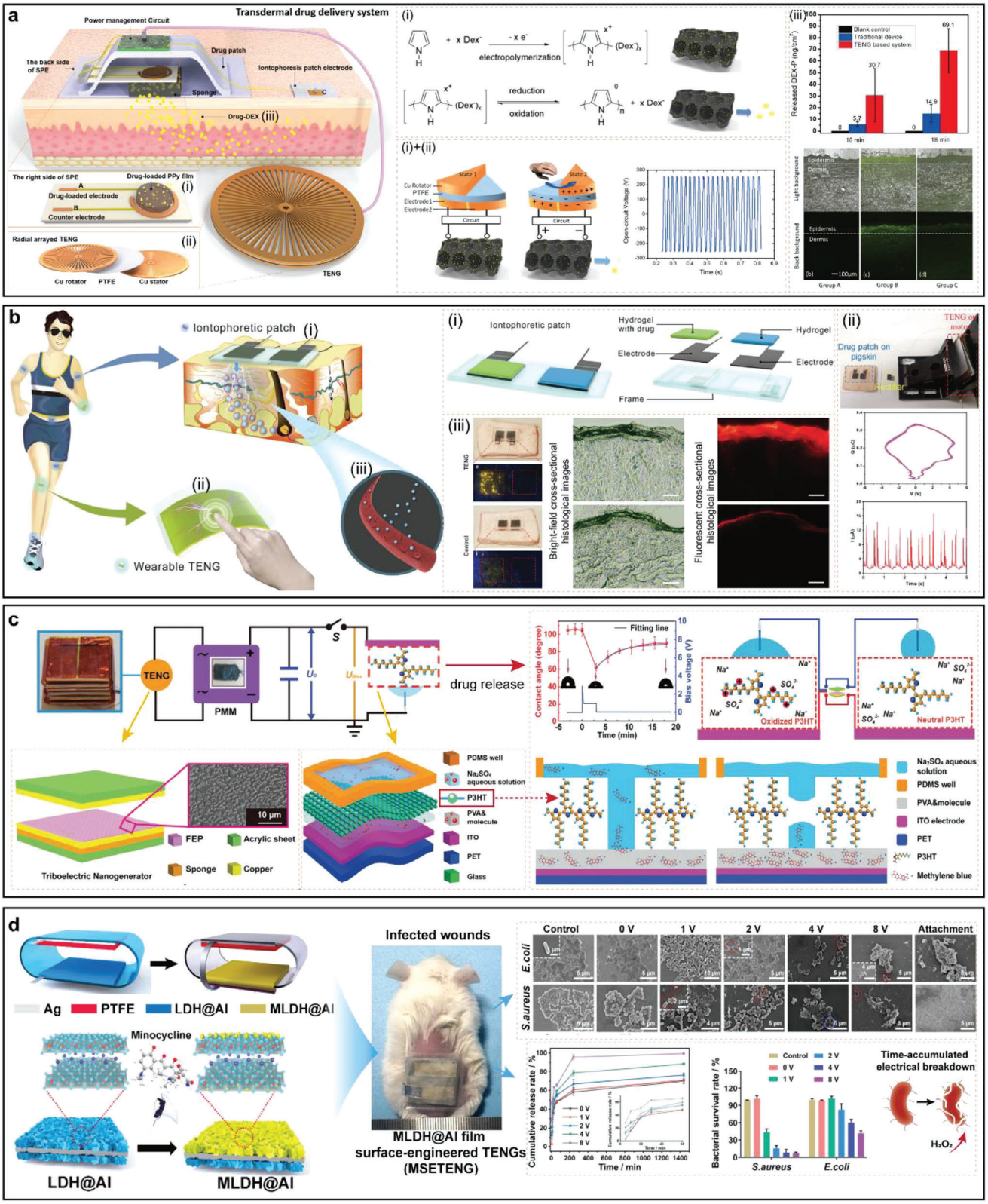

Figure 7. Controlled drug release by iontophoresis. a) TENG-based CDRs realized Dex transport in porcine carcass skin in vitro by iontophoresis. Reproduced with permission.[95a] Copyright 2019, Elsevier. b) TENG-based CDRs introduced simulated drugs into porcine cadaver skin in vitro by iontophoresis. Reproduced with permission.[95b] Copyright 2019, WILEY-VCH. c) TENG-based CDRs enabled the controlled release of various small molecules in vitro through iontophoresis. Reproduced with permission.[96] Copyright 2020, WILEY-VCH. d) TENG-based CDRs provided controlled minocycline release through iontophoresis to promote infectious wounds healing. Reproduced with permission.[80a] Copyright 2021, Elsevier.

Drugs encompass not only ionic drugs but also various neutral small molecule drugs and macromolecules. To achieve the controlled release of small molecule drugs, Liu et al. designed a flexible drug release device (FDRD) based on TENG (Figure 7c).[96] The device consisted of three components: TENG, PMM, and FDRD. First, the surface charge density was further enhanced by polarizing the fluorinated ethylene propylene (FEP) film. Making increased open-circuit voltage of TENG from 277.1 to 647.6 V, short circuit current increased from 53 to 165.6 μA. Second, the FDRD incorporated a poly (3-hexylthiophene) (P3HT) membrane to regulate the release behavior of small molecules. Specifically, the switchable wetting property of P3HT in Na_2SO_4 aqueous solution was manipulated by controlling the bias voltage, enabling precise control over the release of small molecules (methylene blue, sodium fluorescein, and rhodamine 6G). Through a series of three repetitions of activating the FDRD switch, precise control over the release concentration of the salicylic acid was achieved, ultimately reaching a concentration of 1.4 μg mL^{-1}.

PMM is commonly employed in the development of NGs to stabilize the output voltage of alternating current (AC). However, this practice simultaneously contributes to the complexity of the equipment. To enable the direct utilization of AC output, Du et al. designed an integrated, non-rectifying, and flexible TENG patch (SETENG) (Figure 7c).[80a] At 50 N pressure, the SETENG had an output voltage of 39 V and an output current of 2 μA. The patch utilized Mg-Al layered double hydroxides surface-engineered electrodes as smart drug containers and friction layers. Minocycline was encapsulated in the drug library by adsorption with a loading efficiency of ≈82.12 μg cm^{-2}. Then, when the TENG was driven to generate an electric field, minocycline could be released through iontophoresis. More critically, the electric field could cause a time-accumulated breakdown of the cell membranes via electrical shock, which helps the drug enter the cell after release and exert a more effective therapeutic effect. SETENG had been shown to have significant antimicrobial action in skin infectious wound diseases. Similar to the study, to simplify the synthesis of the device, Zhang et al. successfully synthesized a conductive hydrogel and utilized it as a bioelectrode for TENG.[97] The hydrogel, denoted as XG-TMAT-STMP, was prepared through the cross-linking of three compounds: electroactive aniline tetramer (AT)-grafted mushroom hyperbranched polysaccharide (TM3a), xanthan gum (XG), and sodium trimetaphosphate (STMP). XG-TMAT-STMP hydrogel exhibited excellent electrical conductivity and stretchability, as evidenced by its low strain coefficient (= 1.13) and wide strain range (10% < ϵ < 50%). Employing XG-TMAT-STMP as a triboelectric material, NG-based CDRs was successfully fabricated, capable of generating an output voltage of 0.9–1.3 V. This CDRs effectively realized the controlled release of ciprofloxacin and dexamethasone by iontophoresis. In future practical applications, these flexible patches are more suitable for use in mobile joints, enabling continuously generating electrical output through joint movement to achieve continuous drug release.

4.2.3. Electrochemistry

The electrochemical control of drug release is a method that utilizes electrochemical principles to regulate the release of drugs. This strategy physically or chemically binds the drugs to the polymer-carriers and releases the drug embedded in the polymer through an electrochemical reaction (Figure 5c).[98] Drugs usually approach cells via iontophoresis (electroosmosis or electrophoresis), and exert their effects.[80b] Additionally, the release rate, timing, and location of the drug can be further adjusted by adjusting parameters like voltage or current, enabling on-demand release.[99] Regrettably, the implementation of this method is very much dependent on an external power source, such as a battery or a power adapter. Nanogenerators perfectly replace traditional power sources with the advantages of being small, portable, and self-powered (Table 2).[78,80b]

The penetration efficiency of transdermal drug delivery is hindered by the thickening of the stratum corneum in certain diseases such as psoriasis, leading to poor clinical effectiveness. To address this issue, Yang et al. chose to use polypyrrole (PPy) as a conductive material to fabricate a microneedle array, and integrated it with a PENG to develop a self-powered and force-controlled transdermal drug delivery system (sc-TDDS) (**Figure 8**).[80b] As a minimally invasive way, microneedles as drug carriers can autonomously deliver drugs directly to the epidermis or dermis,[100] effectively overcoming the problem of cuticle thickening. When driving PENG through motion (hand clapping), the open-circuit voltage and short-circuit current could reach 50 V and 1 μA, respectively, and could remain stable. With continuous electrical energy supplied by PENG, the PPy main chain acquired electrons. It caused the de-doping of the negatively charged drug anions, such as Dex, thereby achieving effective drug release. Each pulse stimulation of the sc-TDDS subcutaneously released ≈8.5 ng of Dex. When this device was used to deliver Dex for mouse psoriasis-like skin disease therapy, skin recovery to a normal state was observed after 5 days. The therapeutic effect was significantly superior to the conventional application of the Dex solution. This strategy offers a promising controllable on-demand drug release platform for TDDs.

4.2.4. Electrocatalysis

Electrocatalysis is a kind of catalysis that transfers charges on the electrode-electrolyte interface and accelerates chemical reactions. Changing the electrode potential on the electrode, the structure of the electric double layer at the electrode/solution interface, the free energy of reactants/products, and the adsorption energy and equilibrium coverage of certain adsorbed ions will all affect the efficiency of electrocatalysis. Delivery of prodrugs to disease sites and in situ generation of therapeutic drugs using electrocatalysis is one of the current strategies to address the poor stability of drugs.[101] Electrocatalysis, as a switching strategy for controlled drug release, usually has no effects on the diffusion and action of drugs. A high concentration of the drug is released in the target organ and then approaches the target cell in a free diffusion manner to exert its drug effect.[102] Electrocatalytically controlled drug release generally depends on external power sources (Figure 5d). Facing the limitations of traditional power supply devices, power supply devices based on self-powered technology are undoubtedly a suitable solution.[102,103]

Due to the highly hypoxic tumor microenvironment, the targeted clearance of tumor cells using highly reactive free

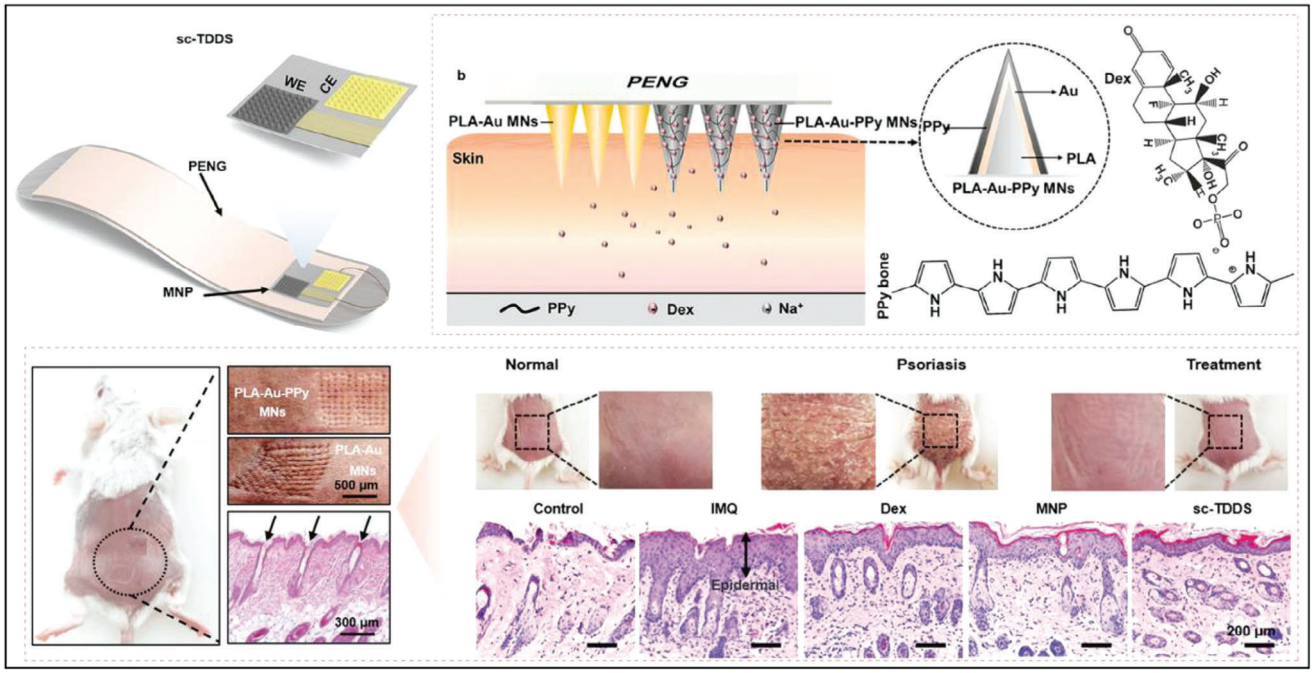

Figure 8. Controlled drug release by electrochemistry. PENG-based CDRs controlled Dex release through electrochemistry for psoriasis therapy. Reproduced with permission.[80b] Copyright 2021, Wiley-VCH.

radicals, such as hydroxyl radicals and singlet oxygen, has emerged as a critical approach in both clinical treatment and fundamental research.[104] Among the various strategies explored, nanomaterials with catalytic activity have garnered extensive attention for tumor therapy.[105] However, improving the catalytic activities in the local tumor region remains a major challenge and has become a focal point of current research. A range of cancer treatment systems, which harness NGs to boost the activity of nanocatalysts, have been developed. In 2022, Yao et al. elaborated a novel approach by preparing a 1D π–π conjugated iron porphyrin-based covalent organic framework-carbon nanotube (COF-CNT) composite.[102] COF-CNT was then integrated into a conductive hydrogel consisting of poly(2,3-dihydrothieno-1,4-dioxin):poly(styrene sulfonate) (PEDOT:PSS) to create a PC hydrogel (**Figure 9**a). This hydrogel formulation not only enhanced the internal conductivity but also exhibited excellent injectability. A simple wearable TENG was employed for self-powering with an open-circuit voltage of 33 V and a short-circuit current of 1 μA during finger friction. Following injection into the subcutaneous tumor, the open-circuit voltage was stable at ≈30 V, which resulted in a four-fold increase in catalytic activity compared to no voltage. Based on this theory, the team has also developed other self-powered catalytic systems, such as nanogenerators integrated with spherical nanocage and nanofilms (Figure 9b,c).[103] In these investigations, nanocarriers enabled the DOX loading. When TENG generated electrical stimulation, it not only enhanced the peroxidase-like activity but also facilitated the efficient controlled release of loaded drugs. Overall, the integration of TENG with nanocatalytic materials demonstrated a remarkable enhancement in the anti-tumor effectiveness of drugs. This innovative approach holds immense potential for long-term self-sustained or implantable tumor catalytic therapy.

4.2.5. Electrical Adjuvants

In addition to directly regulating the release of drug molecules, self-powered electrical stimulation also serves as an electrical adjuvant. This can be categorized into two types: 1) Promoting the generation of active ingredients. The self-generated electric field speeds up the conversion of prodrugs into active substances, thereby indirectly exerting therapeutic effects and enhancing efficacy against diseases. 2) Enhancing drug pharmacodynamics. During drug release, the electric field can regulate or mitigate factors that influence drug release behavior, thus aiding in enhancing drug efficacy following drug release.

Assisting Potentiating Photodynamic Therapy: Photodynamic therapy (PDT) has emerged as a prominent approach in cancer therapy, encompassing three pivotal components: photosensitizers, light sources, and oxygen molecules.[106] The procedure involves the prior administration of photosensitizers that display targeted selectivity toward tumor tissues, either through injection or oral intake. Subsequently, the tumor site is irradiated with light of a specific wavelength from an external light source. This facilitates the interaction between the photosensitizers and the local oxygen, resulting in the generation of toxic substances and ultimately tumor cell killing (**Figure 10**a). While external high-intensity light irradiation may enhance the penetration and treatment of deep-seated tumor tissues, it also raises potential safety concerns regarding potential damage to the surrounding normal tissues.[107] Therefore, low-intensity, long-duration, rhythmic light stimulation is considered a crucial factor in driving the future development of PDT.[108] Self-powered NGs fulfill these requirements and possess notable advantages, such as long-term energy supply, convenient portability, high voltage, and low current (Figure 10b). Based on this, Liu et al. have developed the

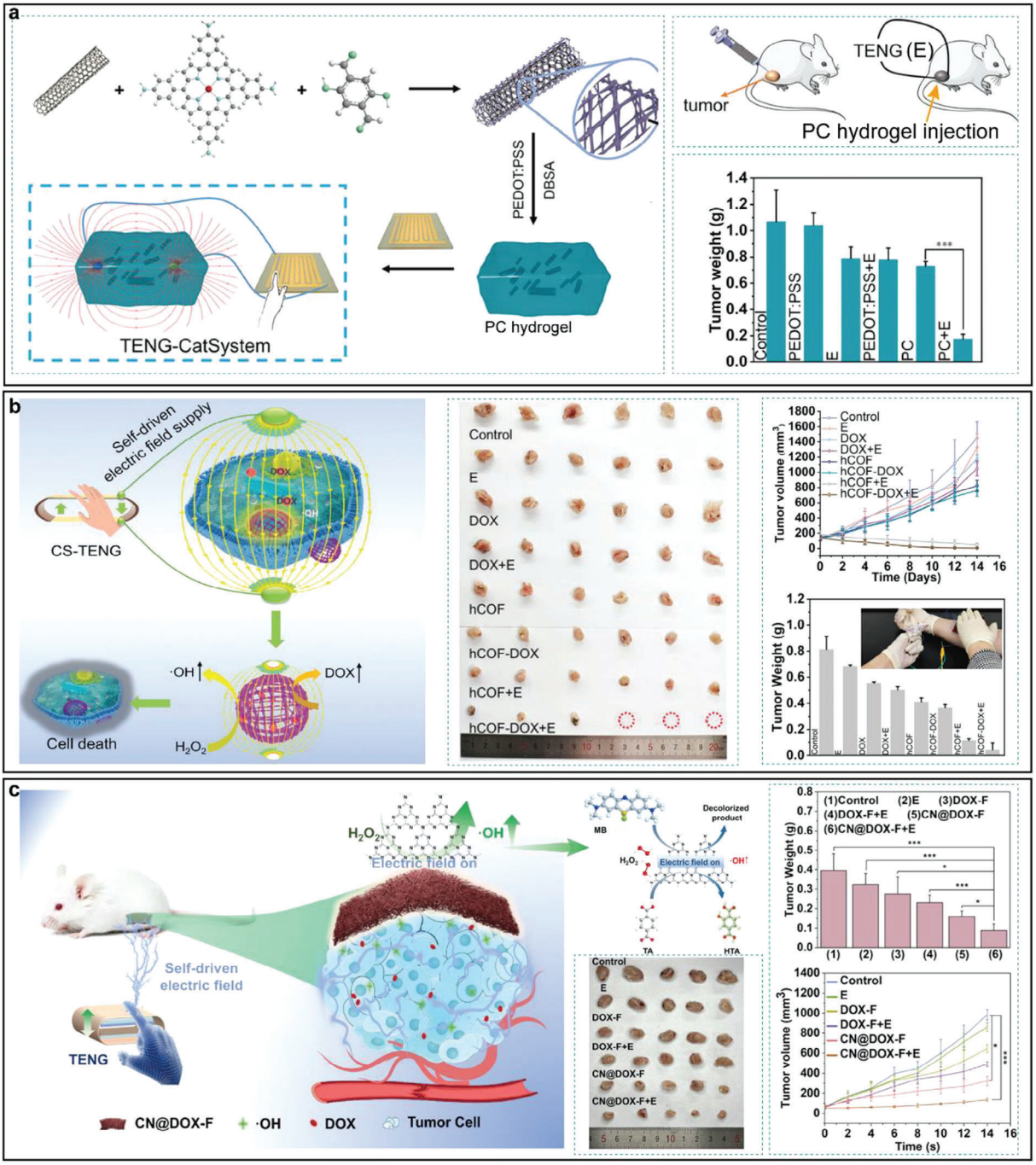

Figure 9. Controlled drug release by electrocatalysis. a) TENG-based CDRs improved the treatment of mouse models of breast cancer by electrocatalysis enhanced ROS production. Reproduced with permission.[102] Copyright 2022, Wiley-VCH. b) TENG-based CDRs improved the treatment of mouse models of breast cancer by synergistically enhancing ROS production and controlled DOX release through electrocatalysis. Reproduced with permission.[103a] Copyright 2022, Wiley-VCH. c) TENG-based CDRs improved the treatment of mouse models of breast cancer by synergistically enhancing ROS production and controlled DOX release through electrocatalysis. Reproduced with permission.[103b] Copyright 2023, American Chemical Society.

first automated force photodynamic therapy system based on PENG.[82] This system enabled long-term sustained power supply to implanted micro-LEDs through self-powered PENG, thus facilitating precise and efficient treatment with photosensitizers for an extended period. For the purpose of optimizing the output performance, the researchers devised a double layer PVDF membrane, leading to a significant improvement in short-circuit transferred charge by approximately two-fold (from 0.25 to 0.46 μC). Even during the motion of human joints, such as elbow or knee movements, the open-circuit voltage and short-circuit transferred charge of the PENG could consistently maintain values exceeding 200 V and 0.5 μC, respectively. Two switchable irradiation

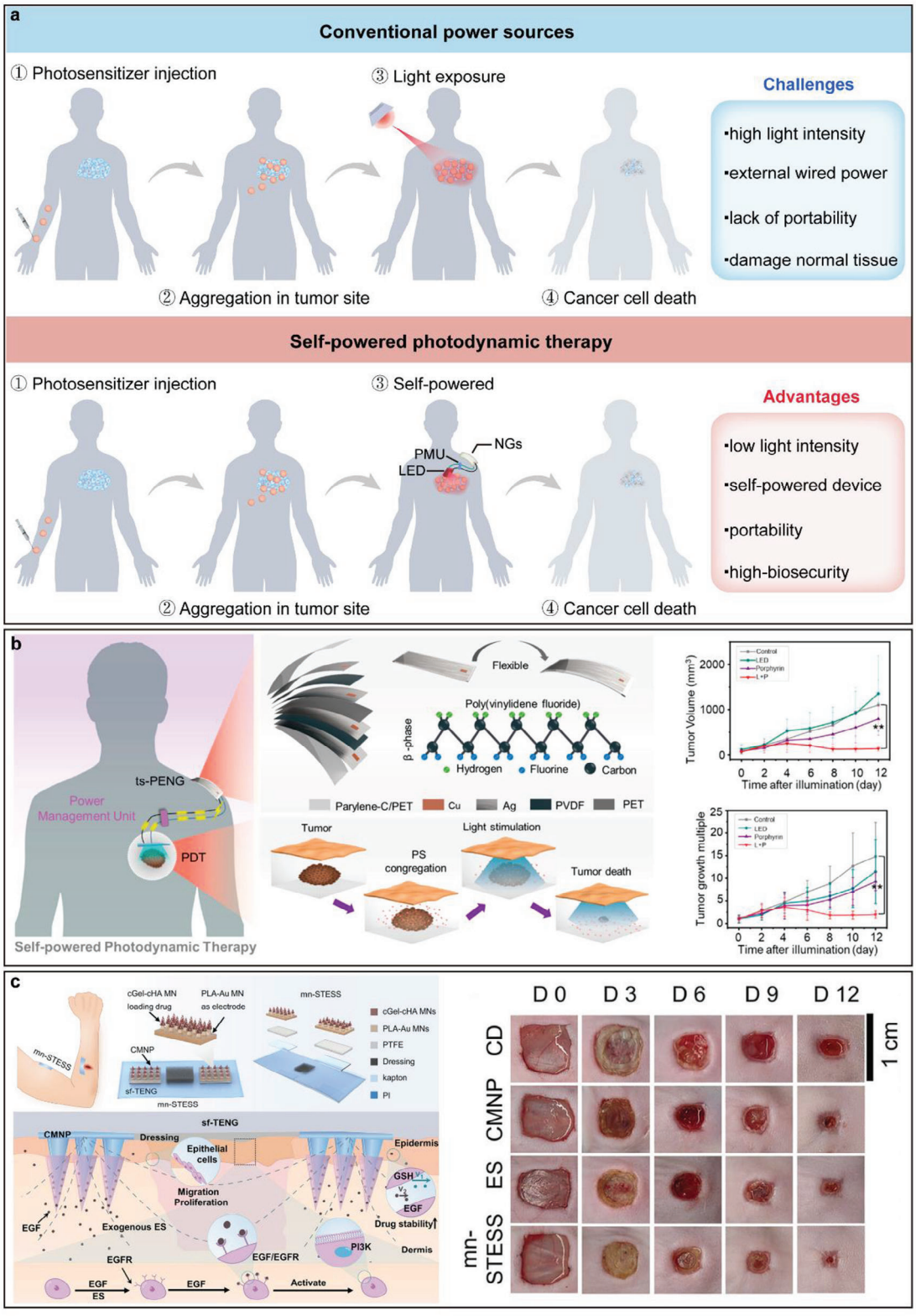

Figure 10. Self-powered electrical adjuvants. a) Contrast between conventional photodynamic therapy and self-powered photodynamic therapy. b) PENG-based CDRs provided long-term autonomous cancer therapy through enhanced photodynamic therapy. Reproduced with permission.[82] Copyright 2020, American Chemical Society. c) TENG-based CDRs accelerated wound healing by improving the pharmacodynamics of epidermal growth factor. Reproduced with permission.[60b] Copyright 2022, Springer Nature.

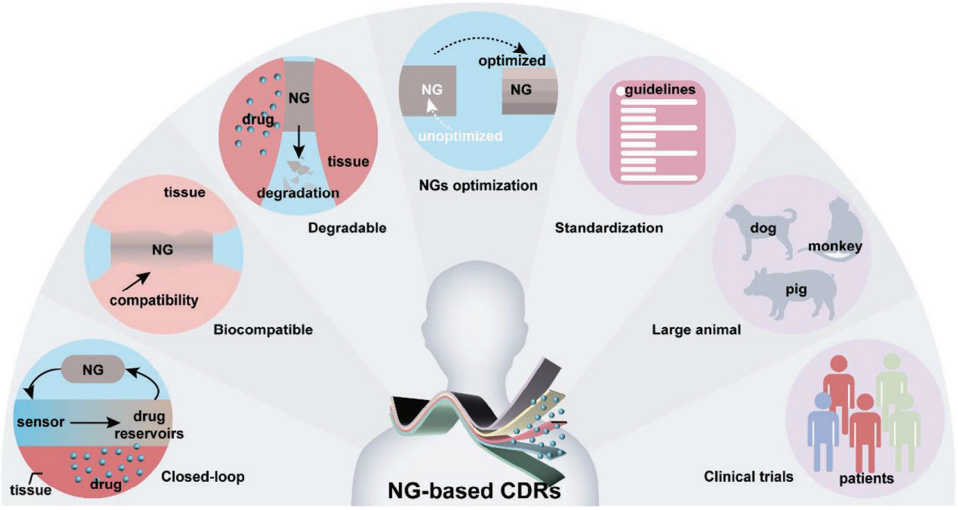

Figure 11. The future optimization directions of NG-based CDRs.

modes were also incorporated into the device to regulate the activity of photosensitizers, catering to the on-demand photodynamic therapy. This self-powered photodynamic platform offers an ideal, long-lasting, and precise-controllable model for cancer treatment, reduction of post-operative cancer recurrence, and the management of other chronic diseases.

Enhancing Drug Pharmacodynamics: Reducing negative factors on drug release aligns with intending to directly increase drug release. Electric fields can enhance drug efficacy through the influencing factors shielding following controlled drug release. According to this theory, a self-powered transdermal electrical stimulation system (known as mn-STESS), consisting of a sliding friction NG and a two-stage microneedle patch, was reported by Yang et al.[60b] They introduced a novel concept of self-powered electrical adjuvants at the same time (Figure 10c). Unlike directly controlled release systems, mn-STESS could improve drug permeability without modifying the release rate. Self-powered electric stimulation significantly potentiated the diffusion coefficient of GSH, increasing the distance between GSH and EGF, and subsequently attenuating the effect of GSH on EGF. In parallel, EGF receptor (EGFR) expression was significantly upregulated by the electrical field, thus compensating for the desensitization effect of EGFR. This work verifies the potential application of self-powered devices as electrical adjuvants in enhancing drug efficacy and provides valuable insights for the future development of devices aimed at augmenting pharmacological effects.

5. Summary and Future Outlook

In this review, we have collected relevant studies on drug-controlled release systems based on nanogenerators. NGs can harvest micro- and nano-mechanical energy from the human body and convert it into electrical energy, thereby enabling long-term self-powered. With the continuous development of NG technology, NGs is widely used in various aspects, including in vitro to in vivo delivery, wearable to implantable systems, and transdermal to site-specific administration for internal diseases. These advancements enhance the targeted and controlled release of multiple conventional drugs and hold significant implications for the development of precision medicine. Although NGs have been developed for various disease treatments, there are still some research areas of NGs-based CDRs that are blank and require researchers to continue to explore and comprehensively investigate. In this regard, we discussed the current challenges of NG-based CDRs and looked forward to their future development from the perspective of clinical needs and practical transformation (**Figure 11**).

5.1. Optimizing the Performance

5.1.1. Closed-Loop Systems

Precision medicine is essentially an interactive, closed-loop integrated diagnosis and treatment model. The core of closed-loop systems involves real-time monitoring of the disease microenvironment, timely feedback on abnormal changes in status, and autonomous precision-controlled drug release. Individual differences in diseases necessitate the intervention of precision medicine to meet the personalized management needs of different patients. Current NG-based CDRs lack real-time monitoring and prompt feedback on diseases, which limits autonomous administration for patients. Therefore, the integration of embedded sensors, intelligent feedback systems, and drug release devices based on closed-loop CDRs is crucial. Closed-loop self-powered therapeutic devices have shown progress in other fields.[109] Closed-loop NG-based CDRs may greatly promote the realization of precision medicine in the future.

5.1.2. Long-Term Biocompatibility

Long-term biocompatibility in vivo is critical for invasive NGs-based CDR devices. First, each component needs to be prepared from materials with good biocompatibility; second, long-term retention of large-volume devices or hard materials in the body will

lead to rejection of the body and trigger local inflammatory reactions. Flexible and miniaturized devices and stable encapsulation layers can ensure great long-term biocompatibility of implanted devices in vivo, which is an issue that needs to be considered in future research on NG-based CDRs.

5.1.3. Fully Degradable CDRs

The biggest problem facing implantable devices is what to do with them after they fail.[110] The current treatment for implanted CDRs is in situ or secondary surgery. Either way produces unpredictable effects on the organism. Fully degradable NG-based CDRs undoubtedly provide a feasible solution to this problem. In the drug delivery module within this system, it is of utmost importance to minimize the inclusion of inactive ingredients that may have a significant impact on its overall degradation. In the future, the all-drug molecules derived CDRs may be a highly valuable research direction. Currently, complete drug-loading of small molecules, particularly those that are naturally derived from traditional Chinese medicine, has been achieved through the synthesis of carrier-free hydrogels via self-assembly.[111] This approach not only enhances drug delivery efficiency but also circumvents the incorporation of poorly degradable carriers. Furthermore, achieving controlled degradation would better satisfy the practical requirement for on-demand dosing.

5.1.4. NGs Optimization

The control unit of NGs-based CRDs is NGs, which require NGs to have adjustable and stable outputs. Nanogenerators mainly collect low-frequency mechanical energy and convert it into electrical energy, and the energy conversion efficiency is low. Due to the complex in vitro and in vivo environments, the stability of nanogenerators is also a concern. How to use structural design, material optimization, and engineering technology to improve the energy harvesting efficiency and stability of nanogenerators is one of the directions that need to be studied in the next step.

Moreover, the design of NGs should align with practical application scenarios. A review of the literatures reveals that current NG-based CDRs encompass a variety of rotation mode TENGs. However, achieving rotation mode within the human body presents difficulty compared with flexion and extension motions. In the subsequent design and optimization of NG-based CDRs, it is paramount to consider mechanical motions readily available in the human body, such as flexion and extension, contraction, organ pulsation, or other rhythmic movements. Subsequently, more attentions should be given to the pathological characteristics of the specific disease. For instance, in cases where NG-based CDRs are required for paralyzed patients, an NG that exploits energy from organ spontaneous and autonomous beating may emerge as a more favorable choice.

5.2. Push the Clinical Trials of NG-Based CDRs

5.2.1. Standardized Guidelines for NG-Based CDRs

Although progress has been made in terms of drug release time, space, and rate for NG-based CDRs, specific standards are lacking in the following aspects: 1) the output performance of NG-based CDRs for the same disease treatment; 2) treatment standards for different types of diseases; 3) standards for drug release rate and other performance parameters required for individual differences in different groups of people (such as different ages, genders, body weights, etc.); 4) standardized guidelines for the practical application of wearable and implantable NG-based CDRs. To address the above issues, the following strategies can be employed in future research: 1) Clearly define the disease types that NG-based CDRs are suitable for and further categorize them into subtypes and stages. This requires determining the disease stage in animal models and conducting effective validation in fundamental experiments. 2) Collaborate with clinical experts in relevant disease fields to develop initial standardized protocols for drug control release in different diseases. These protocols may include parameters such as the effective output of nanogenerators and drug release rate.

5.2.2. Initiate Large Animal Experiments

In the existing research on NG-based CDRs, most studies have primarily focused on small animal disease models, with only one study conducting validation in medium-sized animals (rabbits). It is widely recognized that large animals, including pigs, dogs, and monkeys, have similar physiological structures and metabolic processes to humans. Therefore, it is imperative to evaluate the performance, effectiveness, and biosafety of NG-based CDRs in large animal experiments to facilitate the standardization and drive the next human clinical trials.

5.2.3. Plan and Launch Human Clinical Trials

The vast majority of wearable NG-based CDRs are non-invasive to organisms. It is worthwhile to explore the potential of utilizing wearable NG-based CDRs for drug delivery trials among specific patient populations, particularly focusing on individuals with chronic diseases such as diabetes who require long-term medication. In addition, it is essential to enhance and broaden the variety of medications conveyed, encompassing chemical drugs, biologics, and natural products, such as herbal medicines. By implementing periodic experimentation, gathering real-time information, and obtaining robust data, the optimization of various performance aspects of NG-based CDRs can be progressively achieved.

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Conflict of Interest

The authors declare no conflict of interest.

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controlled drug release, nanogenerator, precision medicine, self-powered

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