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Review article

Research progress of microneedles in the treatment of melanoma

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ABSTRACT

Melanoma is an aggressive malignancy deriving from melanocytes, which is characterized by high tendency of metastases and mortality rate. Current therapies for melanoma, like chemotherapy, immunotherapy and targeted therapy, have the problem of systemic exposure of drugs, which will lead to many side effects and premature degradation of drugs. The resulting low drug accumulation at the lesion limits the therapeutic effect on melanoma and makes the cure rate low. As an emerging drug delivery system, microneedles (MNs) can efficiently deliver drugs through the skin, increase the drug distribution in deeper tumor sites and minimize the leakage of therapeutic drugs into adjacent tissues, thus improving the therapeutic effect. In addition, compared with traditional drug delivery methods, MN-based drug delivery system has the advantages of simplicity, safety and little pain. So MNs can be developed for the treatment of melanoma, which can relieve the pain of patients and improve the survival rate. This review aims to introduce an update on the progress of MNs as an innovative strategy for melanoma, especially when MNs combining with different therapies against melanoma, such as chemotherapy, targeted therapy, immunotherapy, photothermal therapy (PTT), photodynamic therapy (PDT) and synergic therapy.

1. Introduction

Melanoma is the most lethal form of skin cancer, accounting for 75% of skin cancer deaths though it only accounts for 4% of skin cancer cases [1]. Different therapy options are currently available depending on the stage of the disease, as well as the location of melanoma tumor [2]. Common treatments, like surgical tumor removal, chemotherapy or radiation, cause serious side effects related to immune reactions [3]. What's more, the clinical translation of some highly promising anti-melanoma therapies has been severely hampered by their low ability to accumulate into the tumor issues [4]. Therefore, it is necessary to develop a new, more efficient and safer drug delivery system for melanoma treatment.

In the past 30 years, the MN, a novel transdermal drug delivery method, has been developed to improve the permeability of drugs into the skin [5]. MNs can be used to efficiently deliver compounds with different molecular weights, like chemotherapy drugs, polypeptides, proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and vaccines [6]. Such ability prompts the applications of MNs in anti-melanoma therapies, and MNs have exerted unique advantages compared with traditional therapies. Firstly, in conventional oral or intravenous ways, drugs tend to circulate in the body and degrade in advance before reaching to the lesions, which limit the therapeutic effect. While MNs can bypass the first-pass effect, deliver the drugs into deep melanoma sites and improve the accuracy of drug targeting, thus enhancing the curative effect. Secondly, traditional therapies for melanoma are prone to drug resistance. MNs can promote the combination of different drugs in monotherapy or synergetic therapy, and allow drugs to release in response, which can exert the best curative effect and reduce the drug resistance. Thirdly, compared with the systemic exposure of drugs in traditional chemotherapy or targeted therapy, MN-based therapies can avoid the spread of drugs to healthy tissues and organs to the greatest extent, thus reducing side effects and prolonging the survival time of patients. Fourthly, compared with subcutaneous injection, MNs can achieve better curative effect with a smaller dose because they can concentrate the drugs on the tumor sites. At the same time, MNs are easy to use and have little pain, which can improve the compliance of patients. Those advantages make it possible for MNs combined with melanoma therapies to be applied to clinical practice in the future.

In this review, the applications of MNs in the therapies for melanoma will be systematically introduced, including chemotherapy, targeted therapy, immunotherapy, PTT, PDT, and synergic therapy (Fig. 1). We hope this review could lay a foundation for the research of MN-based

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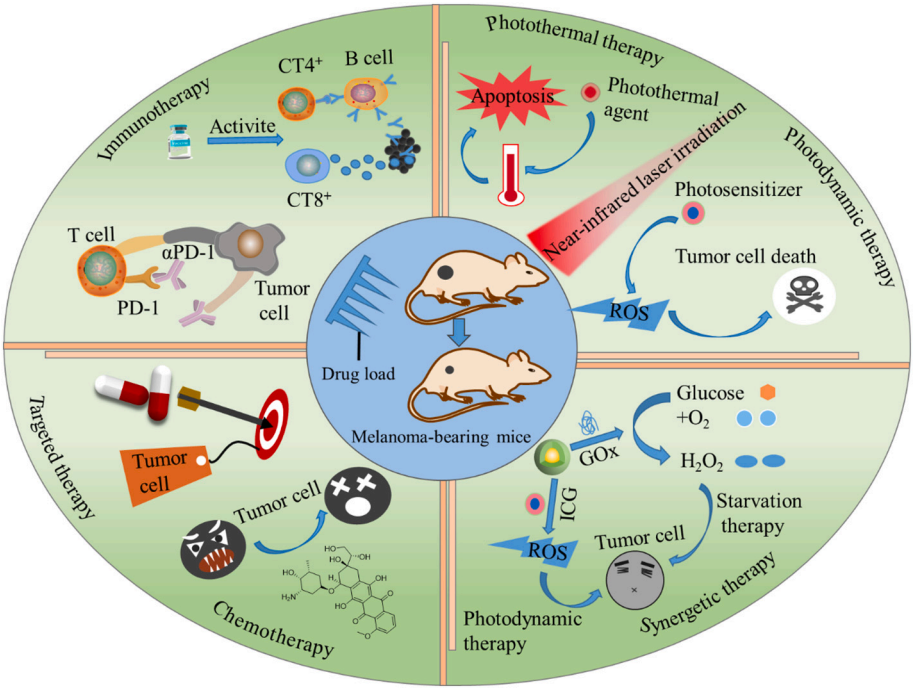

Fig. 1. Schematic illustration of the applications of MNs in different therapies of melanoma.

drug delivery system in anti-melanoma and accelerate the clinical transformation of MNs in the future.

2. Epidemiology and molecular defects of melanoma

Compared to any other types of cancer, the global incidence of melanoma has been increasing at a faster rate each year [7]. In 2012, 232,000 new cases and 55,000 deaths of melanoma were recorded globally, which ranked 15th among the most common cancers worldwide [8]. Melanoma has been one of the fastest growing cancer diseases in the developed countries. New Zealand and Australia leaded the world in this respect, with an incidence rate of 54/100000 and a mortality rate of 5.6/100000 in 2015 [9]. Importantly, early-stage melanoma is very treatable with high long-term survival. For example, the 10-year overall survival (OS) of stage I melanoma is 94%–98%. However, the OS of stage IV melanoma is only 10%–15% [10]. Clearly, early detection and long-running of melanoma prevention approaches can conducive to reduce the global incidence and mortality of melanoma [11]. The incidence of melanoma varies between populations, with a lifetime risk of 2.6% among Caucasians, 0.58% among Hispanics and 0.1% among African Americans. Caucasians are at a ten-fold increased risk of developing cutaneous melanoma compared with people who have dark skin pigmentation [12]. Moreover, the incidence of melanoma is also related to both gender and age. The average age at diagnosis of melanoma is 57 years, with a higher incidence rate for females in the younger age groups while it is opposite in old age groups with a higher incidence rate for males. It is estimated that the lifetime risk of melanoma is 1 in 37 for males and 1 in 56 for females and the mortality rate of males is higher than that of females [13].

One of the environmental risk factors for developing melanoma is ultraviolet (UV) light radiation, especially the UV-B spectrum, which is directly related to the increased risk of melanoma due to sun exposure. It is reported that a history of sunburn in childhood is associated with a higher risk of developing melanoma, with a two-fold increase in melanoma risk in people who have experienced more than five times of severe sunburn [14]. UV exposure from artificial sources can also increase the risk of melanoma's development, as confirmed by follow-up of individuals who have used sunbeds and patients with psoriasis receiving UV-A radiation phototherapy [15]. Besides UV radiation, there are other factors that play important roles in the development of melanoma, such as skin phototypes, pigmented nevi, heredity, immunosuppressive conditions, use of pesticides and geographical location. In general, these risk factors can be divided into genetic factors and environmental factors, but melanoma is actually developed by the interaction between environments and genetics [16].

With the development of molecular biology, it has been proved that the transformation of melanocytes into malignant melanoma is related to the activation of proto-oncogenes and the inactivation of tumor suppressor genes into their malignant derivatives [17]. The carcinogenesis of melanoma is associated with the changes of some signaling pathways, including tumor suppressor, phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and P53 protein pathways. Specifically, the long-term activation of these pathways is related to the survival, proliferation, metastasis and invasion of melanoma [18]. Among these signaling pathways, MAPK is activated in almost all subtypes of melanoma, which is reacted with overactivation in the cases of melanoma [19]. In vivo, the most commonly reason of disruption in the MAPK pathway is single nucleotide substitutions at codon 600 in the BRAF (V-raf murine sarcoma viral oncogene homologue B1) oncogene that encodes the BRAF protein [20]. Understanding of these signaling pathways could facilitate the development of targeted inhibitor drugs for melanoma treatment. For example, vemurafenib, the first BRAF inhibitor approved by food and drug administration (FDA) in 2011, showed promising efficacy in the phase III clinical trial in 675 previously untreated patients with unresectable or advanced melanoma, with an overall response rate of 48% [21].

3. Microneedles

Microneedles (MNs) are microscale arrays with a height of 150–1500 μm, a width of 50–250 μm and a thick tip of 1–25 μm. They are developed to penetrate the skin's stratum corneum layer without damaging blood vessels or stimulating nerves, and form microchannels through which active molecules diffuse passively [22]. Hence MNs have many advantages when used in transdermal drug delivery, such as safety, convenience, minimal invasiveness, improved drug

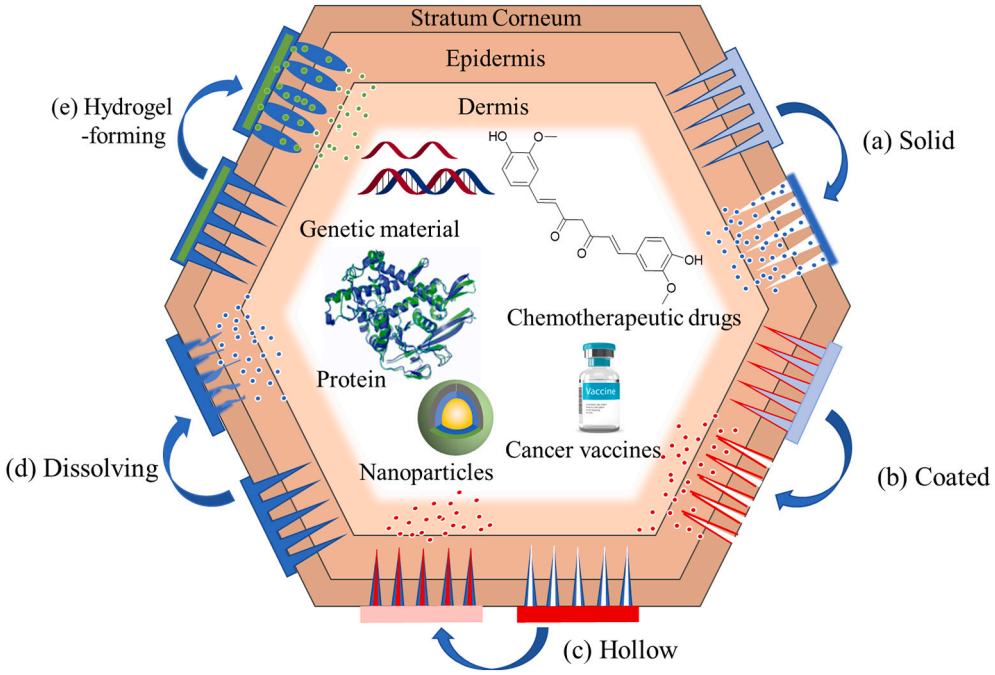

Fig. 2. Classification of MNs and representative drug payloads.

bioavailability and efficient drug delivery [23].

3.1. Types of microneedles

In terms of morphology, MNs can be divided into five types: solid, coated, hollow, dissolving and hydrogel-forming MNs (Fig. 2). Different types of MNs have different mechanisms of delivering drugs into the skin epidermis [24].

Solid MNs adapt a mechanism of "poke-and-patch", that is, the solid MNs are used to pierce into the skin to deliver drugs through the channels hereby created. Solid.

MNs can be used as a skin pretreatment and can be made by different kinds of metals, like stainless steel, titanium and silicon. The advantage of solid MNs is that after MNs are removed, toxic substances or infection can be avoided because the channels formed by MNs are closed [25]. However, pretreatment of human skin with solid MNs may have the biocompatibility problem, and broken solid MN patches will cause damage to the skin. Besides, solid MNs need to be administrated through two steps, lacking precise dosing [26].

Coated MNs adapt a mechanism of "coat-and-poke", which is to coat the cargoes directly on the tips of MNs. Several methods, like dip-coating, casting and deposition techniques, have been developed for coating and drying drug molecules onto the surface of MNs [27]. Coated MNs have strong mechanical strength, allowing drugs to penetrate into

Table 1
Overview: Types of MNs.

MN type	Mechanism	Materials	Advantages	Disadvantages	Applications	Ref.
Solid	Poke-and-patch	Silicon Titanium Polymers Stainless steel	Strong mechanical strength; enhance the permeability of drugs into the skin	Poor biocompatibility; damage to the skin; imprecise dose control	Drug delivery; cosmetic	[22,23]
Coated	Coat-and-poke	Silicon Stainless steel	Deliver the drugs quickly to the skin; extend the cargo life	Drug loss; biohazardous waste generation	Skin delivery of a variety of active materials, like peptides	[24]
Hollow	Poke-and-flow	Glass Metal Silicon Ceramics Polymers	Deliver high-dose drug solution; appropriate mechanical strength	Easy to cause clogging	Vaccine delivery; disease surveillance and diagnosis; blood extraction	[25,26]
Dissolving	Poke-and-release	Sugars Water-soluble substrates Biodegradable polymers	Convenient; ease of administration; good biocompatibility; controlled drug release	Long dissolving time; high manufacturing and storage requirements; dose limitation	Drug delivery; vaccine delivery; cosmetic	[34,36]
Hydrogel-forming	Poke-and-swell	Polymers	High drug-loading capacity; accurately control drug release amount	Poor mechanical strength and physical stability	Drug delivery; monitor or quantify drug substances; biological diagnosis	[35,39]

Table 2
Comparisons between MNs and different administration methods.

	MNs	Non-transdermal patches	Subcutaneous injection	Intratumor injection	Ref.
Onset of action	Fast	Slow	Fast	Fast	[44]
Pain	Little pain	Painless	Painful	Painful	[48,50]
Bioavailability	Sufficient	Insufficient	Sufficient	Sufficient	[62,63]
Self-administration	Yes	Yes	No	No	[71]
Side effects	Mild	Mild	Serious	Modest	[53,100]
Melanoma volume after treatment	Smaller	Bigger than that in MN group	Bigger than that in MN group	Bigger than that in MN group	[77,108]
Survival rate of melanoma-bearing mouse	Higher	Lower than that in MN group	Lower than that in MN group	Lower than that in MN group	[126,94,114]
Therapeutic effect	Strong inhibitory effect on melanoma; no recurrence after treatment	Limited drug types; weak inhibitory effect on melanoma	Show a strong inhibitory effect on melanoma only in the initial stage of treatment; easy to relapse	Relatively strong inhibitory effect on melanoma; possible recurrence after treatment	[75,51,70,110]

the skin and dissolve rapidly, which are especially suitable for delivering drug molecules with high molecular weight. The limitation is that drugs may be lost prematurely from the surface of the needles, and the biohazardous waste generated after coated MN insertion requires careful disposal [28].

Hollow MNs adapt a mechanism of "poke-and-flow". There are holes on the tips of hollow MNs and the holes are full of drug solution or dispersion. When hollow MNs pierce the skin, the drugs are released through the holes and then are diffused into the blood circulation. Hollow MNs offer constant flow rate, high drug dose accuracy and loading capacity, which are primarily used to deliver biomacromolecules like oligonucleotides, proteins and vaccines [29]. The disadvantage of hollow MNs is that their tips will compress the surrounding dense dermal tissue after insertion, thus hindering the flow of drug solution and causing blockage [30].

Dissolving MNs adapt a mechanism of "poke-and-release". They are made by encapsulating drugs into water-soluble substrates (e.g., hyaluronic acid, HA), sugars (e.g., trehalose), or biodegradable polymers (e.g., chitosan) [31]. When dissolving MNs are inserted into the skin, either dissolution or polymer degradation occurs and then the drugs are released. Compared with solid or coated MNs, dissolving MNs are more convenient and have higher drug-loadings. However, there are also many problems need to be focused on, such as low mechanical strength and loss of drug activity during manufacturing and storage [32].

Hydrogel-forming MNs, also known as swellable MNs, are composed of polymers with good swelling ability. Those polymers form hydrophilic structures that allow them to absorb large amounts of water into their three-dimensional polymeric network. Hydrogel-forming MNs adapt a mechanism of "poke-and-swell". After inserted into the skin, the MNs swell by contacting with the interstitial fluid and drugs are released into the skin by osmosis, diffusion, capillary action or application of external negative-pressure. Hydrogel-forming MNs can improve drug loading and accurately control drug release amount but have poor mechanical strength and physical stability [33]. The types, pros and cons, and application scenarios of these MNs are summarized in Table 1.

3.2. Materials and applications of microneedles

Materials used in the MNs determine the basic properties of MNs, including flexibility, strength and permeability. Therefore, the properties of materials should be fully considered in applications. Various materials used to make MN patches are usually divided into six types: silicon, metals, ceramics, silica glass, carbohydrates and polymers [36]. Silicon exerts excellent biocompatibility and adequate mechanical strength, however, it is costly and the brittle characteristic of which probably produces sharp wastes remaining in the skin and causing inflammation [37]. Metals used mainly are titanium, stainless-steel, nickel and palladium. Metals are suitable for the production of MNs because of their intensity but there is a possibility of causing allergy [38]. Ceramics are naturally porous so they can endow the MNs with the capacity to load cargoes without extra fabrication process. But ceramics are prone to brittle fracture and the production process of ceramics-based MNs is complicated [39]. Glass is chemically inert and brittle in nature. Currently, glass-based MNs have not been commercialized and only used for experimental purposes [40]. Carbohydrates (e.g., sugar, maltose, sucrose) are natural and safe for application but the fabrication process of MNs is often difficult due to carbohydrates' degradation at high temperature [41]. Polymeric materials have been efficiently used to make MNs, such as polyvinyl pyrrolidone (PVP), polymethyl methacrylate (PMMA), and polylactic acid (PLA). Polymers have low toxicity and cost, as well as excellent biocompatibility, but they also possess inadequate strength compared to metals and silicon [42].

Different materials have their own advantages and disadvantages and each material is suitable for fabricating certain kinds of MNs to meet the application needs. For example, natural biopolymers can be used to manufacture biodegradable MNs that can deliver vaccines, DNA and proteins [43]. MNs can be used in different fields because of their excellent characteristics of high drug delivery efficiency, convenience and painlessness. To date, MN-based drug delivery systems have been widely used in diagnosis, cancer therapy, anti-inflammatory therapy and diabetes treatment, among others [44]. This review will focus on the applications of MNs in the treatment of melanoma.

4. Microneedles in the treatment of melanoma

For years, researchers have been working to find new therapies against melanoma. Traditional treatment methods mainly revolve around surgical resection, chemotherapy and immunotherapy. However, conventional administration modes via oral and subcutaneous routes in these therapies tend to result in limited drug accumulation concentrations. And systemic exposure of anti-melanoma drugs often causes undesirable toxic side effects, thereby inhibiting the therapeutic efficacy. MN is such an innovative strategy that can enhance the transdermal permeability of drugs, improve the curative effect and reduce the side effects, showing a remarkable highlight in the treatment of melanoma. Here, comparisons between MNs and conventional administration methods are summarized in Table 2 for an intuitive understanding about the pros of MNs. Then in the following, we will discuss the advantages and features of different therapies combined with MNs for melanoma.

4.1. Microneedles for chemotherapy

Many chemotherapy drugs have been used to treat melanoma, such as paclitaxel, doxorubicin (DOX), cisplatin and curcumin (CUR). However, chemotherapy can produce systemic toxicity and has adverse side effects [45]. It is a safe treatment that using MNs to topically deliver chemotherapeutics into tumor tissues [46]. Luo et al. [47] fabricated

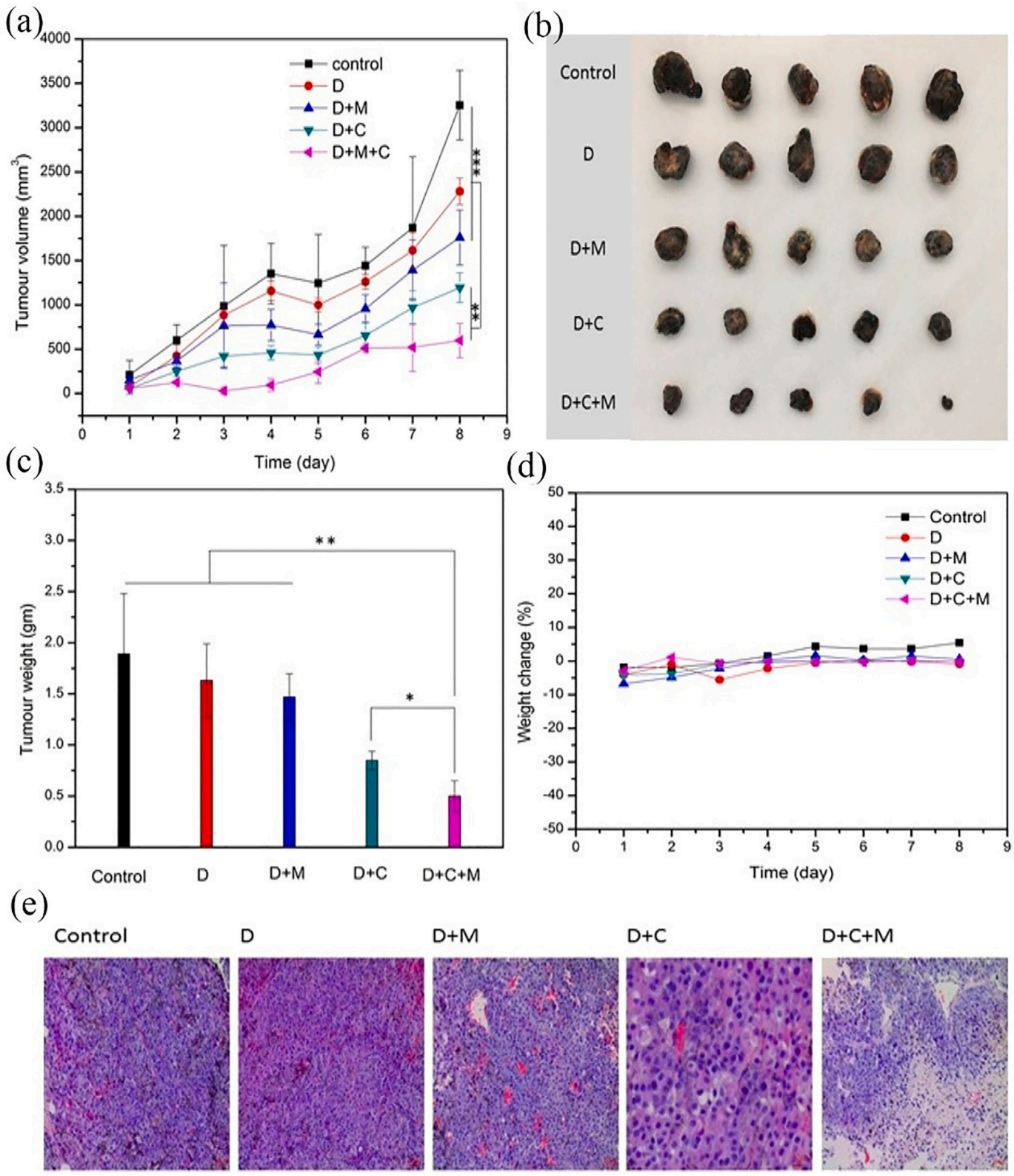

Fig. 3. Therapeutic effect of DOX/CEL co-loaded lipsome MNs on melanoma-bearing mouse. (a) Changes of tumor volume. The appearance (b) and weight (c) of tumor. (d) Changes in body weight of mouse. (e) Tumor-section images at day 12. (D/DOX: doxorubicin, C/CEL: celecoxib, M: microneedles). Reprinted from [53]. Copyright 2019, Elsevier.

biocompatible and biodegradable MNs by using gelatin methacryloyl (GelMA) as matrix for delivering anti-cancer drug DOX. Compared with conventional administrations, the GelMA MNs exhibited a gradual release of DOX, reducing the concern about the toxicity caused by burst release. In the other study, Kim et al. [48] designed a bioresorbable, porous-silicon MN patch with covalently linked DOX. In vitro and in vivo experiments showed that the MN patch successfully inhibited postsurgical residual melanoma with minimal side effects. In order to

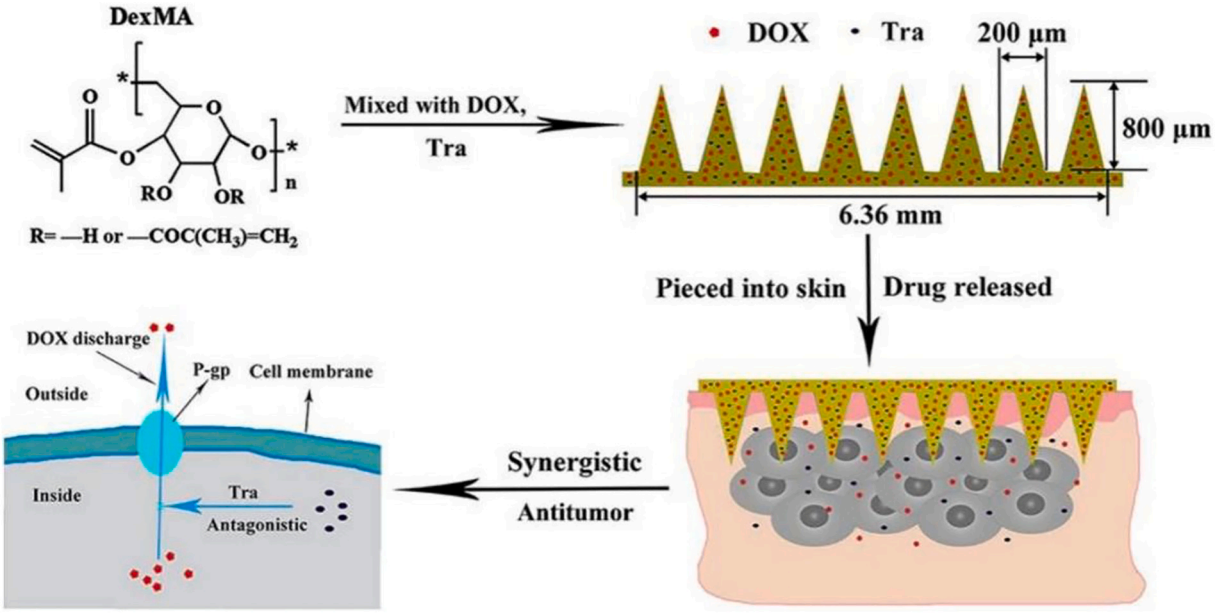

Fig. 4. Overview of MNs for the targeted therapy of melanoma. The hydrogel-forming MN could simultaneously deliver trametinib (Tra) and doxorubicin (DOX) to achieve a superimposed anti-melanoma effect. Reprinted from [63]. Copyright 2020, Elsevier.

reduce the adverse reactions of DOX for the treatment of melanoma, Chen et al. [49] designed a prodrug of DOX, N-allyloxycarbonyl-caged doxorubicin (alloc-DOX) and loaded it into a MN patch device with catalytic activity. In situ local bioorthogonal catalysis of palladium, the prodrug was converted to DOX. The experimental results showed that this MN patch suppressed melanoma growth well, without inducing inflammation and limiting the side effects towards healthy organs and tissues.

Some chemotherapy drugs have excellent efficacy and low side effects, but the poor water solubility and instability lead to their low bioavailability in vivo, for example, CUR. The utilization of MNs can increase drugs' solubility and improve the efficacy [50]. In a study [51], CUR was loaded as a model drug in a biodegradable MN system. The matrix of MNs was polymer GelMA-β-CD that was fabricated by conjugating gelatin methacryloyl with β-cyclodextrin. Researchers demonstrated the potential of the GelMA-β-CD based materials to deliver water-insoluble drugs. The results showed that the solubility of CUR in GelMA was limited (84.8 ± 13.5 μg/mL), but the loading capacity of CUR in GelMA-β-CD-based MN patches was about 5.5 times (466.0 ± 31.2 μg/mL). The anti-melanoma efficacy of the fabricated MN patches was tested on melanoma B16F10 cell culture and a 3D melanoma spheroid embedded hydrogel, which indicated that the MN patches yielded a higher local concentration of CUR and had a better inhibitory effect on melanoma compared with GelMA-β-CD/CUR non-transdermal patches.

Sometimes, the widespread use of a single chemotherapeutic agent in melanoma treatment shows some limitations, such as drug resistance and the lack of lasting efficiency [52]. So, it is necessary to take diverse pharmaceutical strategies to enhance chemotherapy efficacy, like combined delivery of multiple drugs. Ahmed et al. [53] developed a promising treatment for melanoma which combined dermal roller MNs with drug-loaded liposomes for co-delivery of DOX and CEL (celecoxib). In this system, CEL could enhance the intracellular accumulation and the tumor growth inhibition of DOX [54]. The results showed that the transdermal rate of DOX was increased about two times by liposomes-pretreated MNs compared with passive drug delivery. The combination of MNs and DOX/CEL co-loaded liposomes efficiently inhibited melanoma tumor growth and significantly improved the anti-melanoma effect compared with single-drug-encapsulated liposomes or liposomes without being pretreated with MNs (Fig. 3).

4.2. Microneedles for targeted therapy

As mentioned above, melanoma is a gene-related cancer disease. Activation of some signaling pathways is often in connection with the growth and proliferation of tumor cells, for instance, the MAPK signaling pathway [55]. In the past decade, inhibitors targeting these signaling pathways have been marketed, including BRAF inhibitors, MEK inhibitors and so on. However, malignant melanoma occurs in the basal layer of the epidermis and the delivery of exogenous agents to the tumor sites is often blocked by stratum corneum, the outermost skin layer [56]. The microchannels produced by MNs can efficiently deliver targeted drugs across the skin to melanoma sites, exerting a high anti-melanoma effect. Small interfering RNA (siRNA) used in cancer therapy exhibits relatively high specificity and low toxicity due to its properties of targeting and silencing specific cancer-related genes. So, it has potential therapeutic applications in melanoma [57]. Ruan et al. [58] developed a coated MN based on cell penetrating peptide octaarginine (R8) nanocomplexes to delivery BRAF siRNA (siBraf) for targeted therapy of melanoma. The interaction of R8 and siBraf improved the stability of siBraf. In vitro experiments showed that the R8/siBraf coated MN could silence BRAF gene, down-regulate BRAF protein and exert anti-proliferation effect on A375 melanoma cells. In vivo anti-tumor experiments presented that the MN could effectively deliver R8/siBraf into the tumor issues, inducing the tumor cells apoptosis and inhibiting the melanoma growth. The topical application of siRNA to treat melanoma faces mainly two challenges: how to deliver the macromolecular siRNA into skin and how to target melanoma cells [59]. Hence Pan et al. [60] fabricated a safe dissolving MN for transdermal delivery of STAT3 (signal transducer and activator of transcription 3) siRNA by using polyethylenimine (PEI) as a carrier. The STAT3 signal pathway played a key role in melanoma invasion and metastasis. In this MN system, the PEI carrier enhanced cellular uptake of STAT3 siRNA and the loaded drug effectively silenced STAT3 gene, inhibiting melanoma cells growth. As it turned out, MNs improved the skin penetration of STAT3 siRNA, increasing therapeutic effect. Anti-melanoma effect was evaluated on B16F10 melanoma tumor-bearing mouse and the results demonstrated that siRNA/PEI was effectively delivered into the body, down-regulated the expression of STAT3 gene and exerted a specific anti-melanoma effect.

The thiazole benzenesulfonamide compound HA15 is a novel anti-

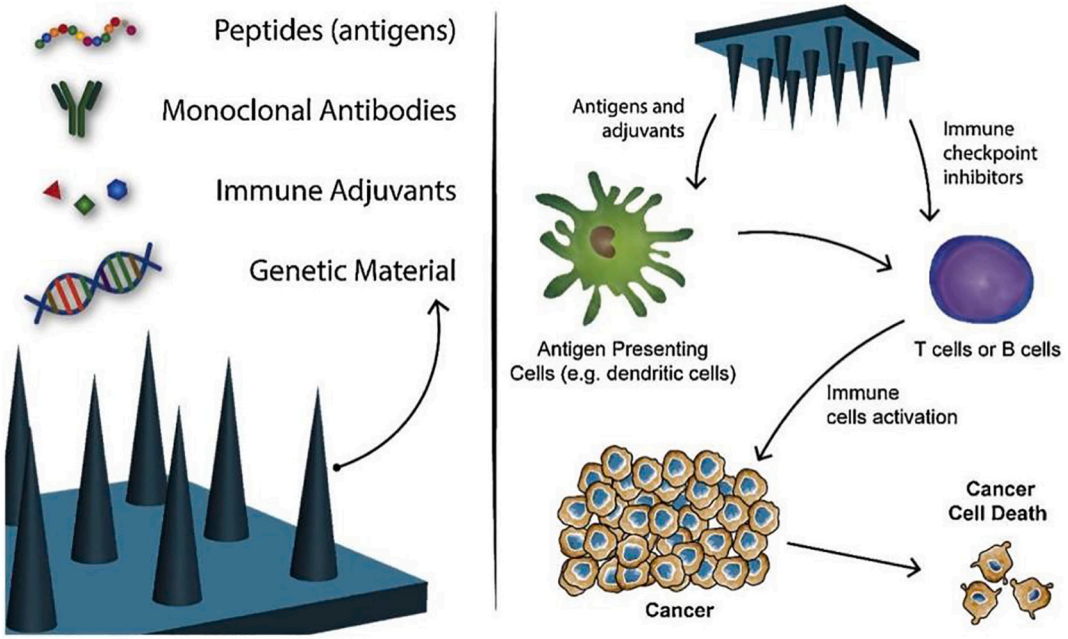

Fig. 5. Examples of the MNs' applications in melanoma immunotherapy. Reprinted with permission from [4]. Copyright 2019, Elsevier.

melanoma drug targeting HSPA5/BiP, the master regulator of the unfolded protein response (UPR), and can kill melanoma cells by concomitant induction of apoptosis and autophagy [61]. Chen et al. [62] produced multifunctional dissolving MNs for efficient and safe delivery of HA15 into vivo by incorporating a small quantity of graphene oxide (GO) into the biodegradable and biocompatible polymers used for MN preparation. Three representative polymers selected to add GO are PVP, HA, and carboxymethyl cellulose (CMC). In addition to its anti-melanoma effect demonstrated in vivo experiments, the GO-doped polymeric MNs yielded important new properties, like self-sterilization, antibacterial activity, anti-inflammation, significantly improved mechanic strength, enhanced moisture resistance, and near-infrared light-activated controlled drug release, which made the MNs safe and easy to be used in the treatment of melanoma as well as reduced infection risk in clinical applications. Drug administration with single targeted drug is often accompanied by the development of melanoma resistance. Huang et al. [63] used MNs to deliver trametinib (Tra) and DOX simultaneously to achieve a synergistic anti-melanoma effect (Fig. 4). The MNs were based on photocrosslinkable dextran methacrylate (DexMA). After the two drugs were delivered to the tumor-bearing mice, they showed a synergistic anti-tumor effect because Tra could block the efflux effect of P-glycoprotein (P-gp) on DOX, resulting in more accumulation of DOX in tumor cells. In general, the DexMA hydrogel MNs loaded with Tra and DOX reduced drug resistance in melanoma, achieved optimal tumor suppression and cut down systemic toxicity and side effects.

4.3. Microneedles for immunotherapy

Immunotherapy has been proved to be effective in treating melanoma and changed the landscape of melanoma [64]. Immunotherapy works by activating or suppressing the body's own immune system to control or fight cancer [65]. Various types of cancer immunotherapies can be roughly divided into the following five categories: checkpoint blockade, vaccine, cytokine, adoptive cell transfer and small molecule immunotherapy [66]. Currently, immunotherapy has some limitations, including tissue heterogeneity, off-target toxicity and inadequate persistence, which indicate the need for forward researches of advanced therapeutic options [67]. MNs have good biocompatibility and can directly transport drugs into systematic circulation to avoid the first-pass metabolism, which make them excellent candidates for delivering immunological biomolecules to the dermal antigen-presenting cells in the skin (Fig. 5). Various types of MNs have been proposed in order to overcome the drawbacks and challenges related to cancer immunotherapy [68].

4.3.1. Microneedles deliver checkpoint inhibitors

The MNs can locally deliver immune checkpoint inhibitors to targeted sites and improve anti-tumor immunity by inhibiting intrinsic down-regulators of immunity [69]. Programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) is one of the most studied immune checkpoints at present, and many aiti-PD-1/anti-PD-L1 antibodies (αPD-1/αPD-L1) have been developed for cancer immunotherapy. Wang et al. [70] designed a pH-sensitive MN patch consisting of HA and dextran nanoparticles (NPs) loaded with glucose oxidase (GOx) and αPD-1. In the presence of oxygen, GOx could convert blood glucose to gluconic acid. The resulting acidic environment promoted the dissociation of the NPs and achieved continuous release of αPD-1. This administration strategy improved melanoma immunogenicity and had shown greater efficacy in combination with other immunomodulators. Currently, only a few small molecule hydrophobic drugs have been approved for transdermal delivery, and it is difficult to deliver most hydrophilic molecules. Cao et al. [71] developed a novel platform for efficient and continuous delivery of hydrophilic drugs. The platform was based on coating αPD-1 drug powders on polycarbonate MNs array patches. Then, the MNs patches were locally applied to the skin microchannels generated by ablative fractional laser to deliver αPD-1 for melanoma treatment. The platform showed a better anti-melanoma effect than intraperitoneal injection in B16F10 melanoma models. The αPD-1 therapy has become the first choice of immunotherapy due to its good curative effect in patients with advanced melanoma. However, the response rate of single αPD-1 therapy is still not high, only 50% [72]. Therefore, it is necessary for researchers to explore new treatments based on αPD-1. Chen et al. [73] designed an approach to address the problems including low objective response rate and serious systemic side effects associated with immune checkpoint blockade (ICB). They used hollow MNs loaded with αPD-1 as microchannels to deliver cold atmospheric plasma (CAP) into tumors through the skin, achieving a combined anti-melanoma effect. Plasma was an ionized gas that depended on the synergistic action of reactive nitrogen species (RNS)

and reactive oxygen species (ROS) with targeted tissues. The proposed MN delivery system successfully improved the response rate of αPD-1, had strong inhibition on both primary and metastatic melanoma tumors, and enhanced the survival rate of tumor-bearing mouse.

Anti-CTLA-4 (cytotoxic T-lymphocyte antigen 4) is another checkpoint antibody that blocks inhibitory action and promotes strong T-cell activity against tumor antigens. However, anti-CTLA-4 is primarily administered intravenously, which may overstimulate the immune system and lead to associated adverse events [74]. Ramirez et al. [75] designed an autonomous, degradable and active MN platform for more efficient delivery of anti-CTLA-4 antibody into melanoma sites which greatly enhanced the immune response. The structure of the MN patch contained both spherical magnesium (Mg) microparticles and the anti-CTLA-4 antibody within a PVP matrix. After the active MN patch was applied to the skin, it dissolved and then the Mg particles reacted with the interstitial biofluid to rapidly produce hydrogen bubbles which provided the power to break through the skin barrier and enhanced drug delivery, thereby increasing drug permeability. Compared with passive delivery, this method of active delivery was faster and deeper, significantly delaying the increase of tumor volume of tumor-bearing mouse in melanoma models.

Except the two immune checkpoints mentioned above, there is another immune checkpoint that is important for melanoma treatments-indoleamine 2,3-dioxygenase (IDO). IDO is an enzymatic protein utilized by tumors cells to suppress the activity of cytotoxic T-lymphocyte around the tumor microenvironment (TME). IDO inhibitors can manipulate this immunizing interaction and thus favor the anti-tumor activity of T cells [76]. At present, there are no clinical examples about using IDO inhibitors alone for anti-cancer, but combined applications of IDO inhibitors and αPD-1 have been developed for the treatment of melanoma. Ye et al. [77] developed an advanced immunotherapy that synergistically blocked IDO and PD-1 in the TME for the treatment of melanoma by a dissolving MN system. In this combination strategy, an IDO inhibitor, 1-methyl-DL-tryptophan (1-MT), was used to modify HA to prepare αPD-1-encapsulated nanocapsules, which were then integrated into the MN array patches. The researchers evaluated the anti-melanoma effect of this technique by establishing melanoma models in mouse, which demonstrated that the synergistic administration reduced local immunosuppression and effectively improved T cell immunity. Moreover, the αPD-1/1-MT dissolving MN patch was a safer and more biocompatible therapy compared with the other similar immunotherapies without MNs. Various experiments had shown that the delivery of checkpoint inhibitors by MN systems could reduce systemic exposure, improve bioavailability and achieve targeted delivery, showing great potential in melanoma immunotherapy [78]. However, the drug loading of MNs is limited due to their microstructures of small volume and drug diffusion during MN preparations makes it challenging for sufficient encapsulation. Therefore, a highly drug-concentrated mixed core-shell MN system (CSMN) was developed for co-delivery of checkpoint inhibitors αPD-1 and 1-MT [79]. The CSMN system increased the amounts of 1-MT encapsulated in the MN patch and local retention time of αPD-1, exhibiting high transdermal delivery efficiency. The structure of the CSMN drug delivery system consisted of a chitosan shell for adsorption αPD-1 and a hydrophilic polymer core (PVP and PVA, Polyvinyl alcohol) containing 1-MT that could form hydrogen bonds with 1-MT and keep its concentration at a supersaturated state. Compared with intratumoral injection with the same dosage in mouse models of melanoma, the CSMN system showed a longer drug retention time at the tumor tissues, smaller tumor volume and higher survival rate. That is to say, the co-administration of αPD-1 and 1-MT via the MN system is a promising drug delivery platform and has a great prospect in immunotherapy of melanoma.

4.3.2. Microneedles deliver cancer vaccines

Cancer vaccines and vaccine adjuvants are developed to prevent or treat cancer diseases by targeting tumor antigens, thereby promoting tumor-specific response [80]. Several strategies for developing cancer vaccines include the use of proteins, peptides, dendritic cells (DCs), tumor lysates, tumor cells, DNA, mRNA, and viral vectors [81]. The skin is a significant component of immune system which contains a large amount of antigen presenting cells (APCs). The APCs can transport antigens to lymph nodes and present peptide fragments to lymphocytes which then drive adaptive immune response [82]. The high concentration of APCs combining with ease-of-access enable the skin to be one of the most efficient inoculation ways [83]. However, the accuracy and precision of intradermal injection are very low, and vaccine preparations often leak out of the skin, making it difficult to induce an effective immune response [84]. MNs for delivering cancer vaccines can accurately deliver antigens or immune adjuvants to specific skin layers, effectively target the immune cells residing in the skin and induce stronger immune response than intradermal injection, thus improving the therapeutic effect of melanoma [85]. In addition, compared with intradermal injection, MNs can decrease injection-related pain and medical waste, achieve self-administration, simplify vaccine cold-chain logistics and reduce the risk of blood-borne pathogen transmission from repeated needle use [86]. Therefore, MN-based vaccine delivery is a promising technology that is not only more convenient and safer, but also improves the survival rate of patients. For example, Zeng et al. [87] designed a novel immune polyelectrolyte multilayers coated MN to deliver a peptide antigen and a vaccine adjuvant for melanoma immunotherapy. The MN was based on poly (d,L-lactide-*co*-glycolide) acid (PLGA) and the cargoes released from the MN could enlarge tumor-specific T cells, resulting in great memory recall response in mouse. The result indicated that the manufactured MN patch could increase the stability of peptides, proteins and other molecules, generating tumor-specific immune responses and having the potential to be combined with other immunotherapies for the treatment of melanoma in the future. At present, only a few simple antigen-peptide delivery systems are developed for melanoma immunotherapy. In order to open up more delivery platforms for clinical transformation, Kim et al. [88] fabricated a dissolving MN patch loaded with antigenic peptides to induce an antigen-specific $CD8^+$ T-cell response, which subsequently suppressed the growth of antigen-carrying tumors. Cytotoxic T-cell epitope peptide (SIINFEKL) was conjugated to HA by reductive amination and HA promoted the internalization of antigens into APCs through HA receptor-mediated endocytosis. There was no significant changes or inflammatory cell infiltration at the administration site of this SIINFEKL-HA MN, reflecting the biosafety of MN-assisted peptide delivery. This SIINFEKL-HA MN delivery system increased the accumulation of the peptide-based cancer vaccine at tumor sites and elicited a strong specific immune response, which significantly inhibited the growth of melanoma.

Currently, DCs vaccines have been confirmed to be a safe therapy for melanoma. MNs can deliver a variety of drugs, like proteins and peptides, but none of these existing MN techniques can inject living agents into the skin without the help of additional equipment [89]. To carry living cells, Chang et al. [90] designed cryogenic MN (cryoMNs) patches that were prepared by stepwise micromoulding of cryogenic medium (combining sucrose and dimethyl sulfoxide) with pre-suspended DCs. Loaded with OVA-DCs (ovalbumin-pulsed DCs), the cryoMNs could activate a higher antigen specific immune response. The cryogenic environment allowed DCs to remain activity during the production and storage of MNs, avoiding complex and redundant procedures. In melanoma mouse models, the OVA-DCs-cryoMNs showed significantly stronger anti-tumor activity than two conventional methods, namely, subcutaneous and intravenous injections. Overall, this technique not only enabled simple intradermal delivery of living cells with minimal invasions, but also had fewer side effects and a stronger therapeutic effect for melanoma.

Projects of DC cancer vaccines often involve expensive and complex design and manipulation. Moreover, the DCs transformed in vitro will lost some of their natural properties, resulting in limited anti-melanoma

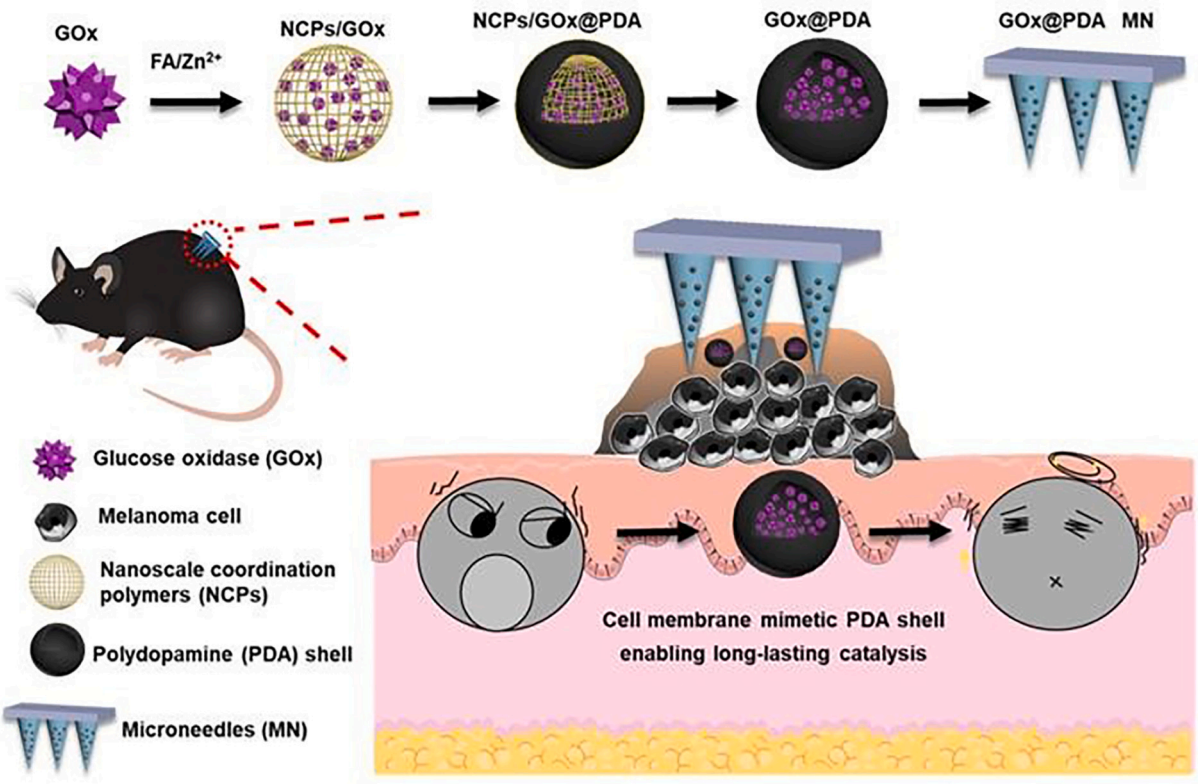

Fig. 6. Schematic diagram of MNs used in starvation therapy against melanoma. Reprinted with permission from [105]. Copyright 2021 Ivyspring International Publisher.

efficacy [91]. Vaccination with tumor lysates offers a new approach of immunotherapy that is cheaper and more convenient. Ye et al. [92] developed a B16F10 whole melanoma tumor lysate-mediated vaccine through a MN patch device for immunotherapy strategy. Melanin, existing in the B16F10 melanoma tumor lysates, was capable of converting the absorbed light energy into thermal energy in combination with a controlled near-infrared light irradiation, which greatly enhanced the uptake of tumor antigens by DCs and led to the improved anti-melanoma effect. Notably, the MN patch could co-deliver with a vaccine adjuvant (granulocyte-macrophage colony-stimulating factor, GM-CSF) that could synergistically produce a stronger immune response. It could be said that the MN-mediated tumor-lysate vaccine provided new ideas for the treatment of melanoma.

DNA vaccines play an important role in cancer vaccines, potentially improving the therapeutic effect. The challenge is that in non-human primates and human volunteers, only high doses of DNA induce optimal antibodies and $CD8^+$ cytotoxic T lymphocytes. Therefore, a MN-assisted DNA vaccine was fabricated by Hu et al. [93] to improve the immunogenicity and reduce the dose of vaccines. A polymeric vector was synthesized and the DNA solution was added to the polymer solution to form a DNA vaccine. Then the DNA vaccine was administered in combination with a vaccine adjuvant into skin with pretreatment of MNs. The skin penetration was improved and cellular uptake of DNA was facilitated, as evidenced by the detection of more $CD4^+$ and $CD8^+$ T cells in the DNA vaccine-administered tumor slices. The anti-cancer effect was tested in mouse melanoma models, which indicated that this MN-based DNA vaccine showed longer survival time and smaller tumor size than the control group. Huu et al. [94] designed a pH-responsive MN delivery system which could efficiently deliver DNA vaccines to the epidermis/dermis and thus stimulate humoral and cellular immunity. In this system, MNs were assembled with layer-by-layer coating of ultra-pH-responsive oligo sulfamethazine conjugated poly (β-aminoester urethane) and an immunostimulant. At physiological pH (pH 7.4), more than 90% cargoes could be released, ingested and processed by DCs, promoting immune response. In a mice model of pulmonary metastasis of melanoma, this MN-based DNA smart vaccine greatly enhanced the immunotherapy effect of melanoma. When using solid or coated MNs, biohazardous sharp waste is often generated. Dissolving MNs, which are biodegradable and biosafe, are alternative platforms to deliver DNA vaccines. Duong et al. [95] proposed an array of dissolving MN for painless implantation and facilitating the release of DNA vaccines in skin tissues. The matrix of the MN was a biological polypeptide copolymer, which was safe, degradable and environmentally friendly. The dissolving MN could transport DNA vaccines and a vaccine adjuvant into the intracellular compartments of DCs and macrophages, eliciting stronger antigen-specific antibody responses than subcutaneous injection of the same drugs in the treatment of melanoma. Especially, it had a high lung clearance rate of cancer cells and 20 % of melanoma mouse treated with this treatment survived for 34 days, compared with none in the control group.

MNs can also be used to deliver viral vaccines to initiate a systemic anti-tumor immune response, generate immune memory, and treat cancer diseases like melanoma [96]. Boone et al. [97] presented an active dissolving MN delivery system for directly delivering cowpea mosaic virus nanoparticles (CPMV), a powerful immunoadjuvant, in vivo. Mg microparticles were added into the dissolving matrix during the fabrication of MNs. After Mg microparticles contacted with the interstitial fluid of the skin, they produced bubbles, which strongly drove the drug payload into the tumor sites. The drug payload ultimately converted the immunosuppressive state in the TME into an immune-activated state. Compared with passive administration by MNs or traditional intradermal injection, this active MN delivery system showed deeper payload penetration, more significant tumor regression and higher survival rate in melanoma-bearing mouse. This study increased the accessibility and feasibility of in situ inoculation of cancer vaccines, which could further promote the development of novel treatments for

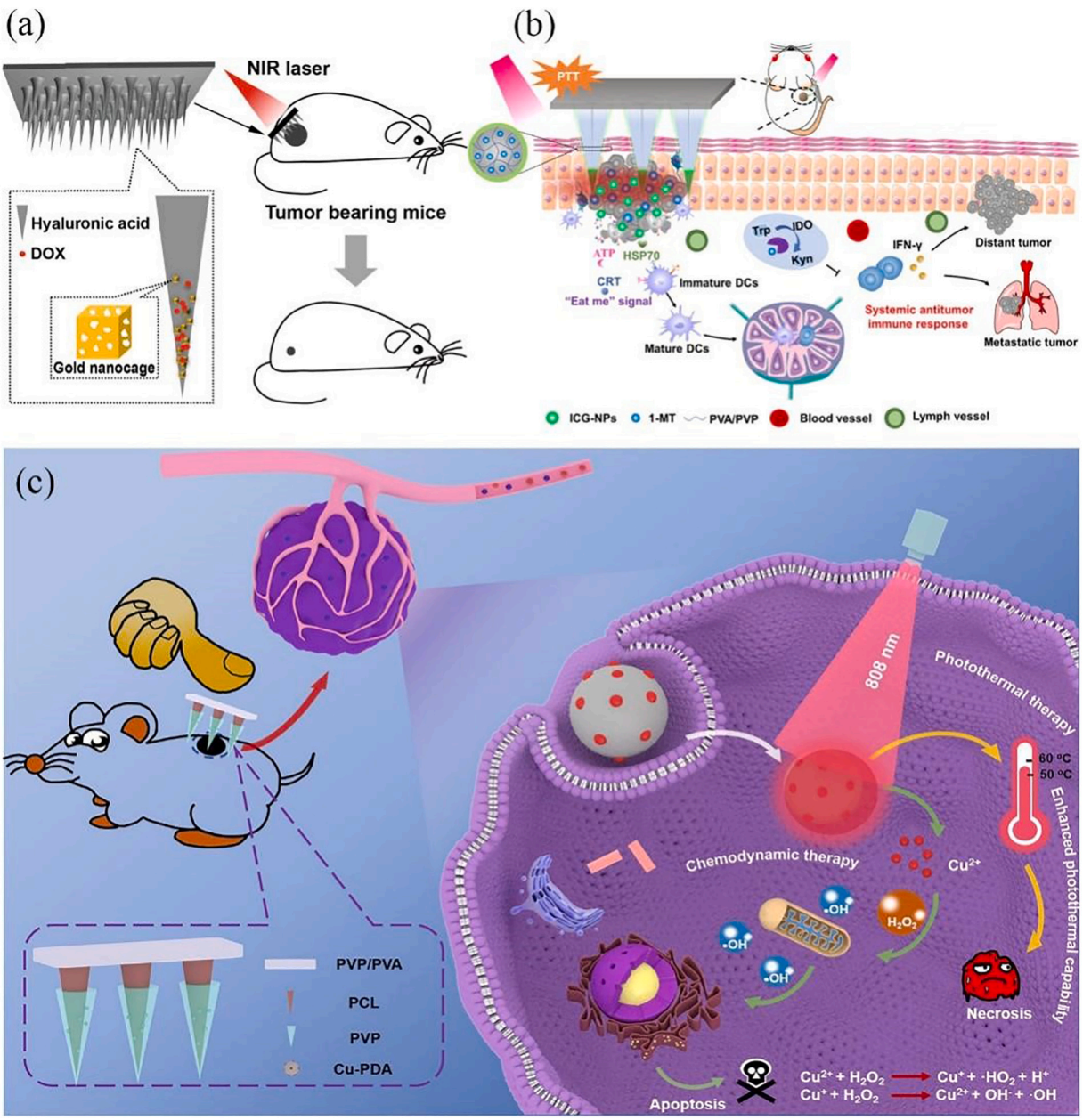

Fig. 7. MN-based synergetic therapies for anti-melanoma. (a) Chemo-photothermal therapy. Reprinted from [107]. Copyright 2018, with permission from American Chemical Society. (b) Immuno-photothermal therapy. Reprinted with permission from [116]. Copyright 2020 American Chemical Society. (c) chemodynamic-photothermal synergistic therapy of melanoma. Reprinted with permission from [122]. Copyright 2021, Elsevier.

advanced and metastatic melanoma.

4.4. Microneedles for other therapies

For advanced melanoma, traditional therapies have some disadvantages, such as serious side effects and low drug concentration. New targeted therapy and immunotherapy have shown higher efficacy than traditional therapies, nevertheless, a large number of patients have developed drug resistance, which leads to unsatisfactory clinical outcomes [98]. In order to improve the therapeutic effect, researchers have developed more suitable and newer therapies, including photothermal therapy (PTT), photodynamic therapy (PDT), and starvation therapy.

PTT is a phototherapy technique used to treat cancer diseases which causes irreversible damage to tumor cells via absorbing the thermal energy produced by optical photothermal therapy reagents [99]. Wei et al. [100] combined PTT with MNs through loading polymeric micelles of photothermal agent AIEgen (NIR950) into dissolving MNs for local administration of malignant melanoma. Under laser irradiation, the drug payload rapidly accumulated in the tumor sites and reached the appropriate temperature to kill tumor cells. In addition, the micelles were pH-responsive that could be protonated in the acidic TME to promote intracellular uptake. Anti-tumor experiments in B16-melanoma bearing mouse showed that this MN delivery system significantly ablated melanoma with only one-time laser irradiation and extremely low-dose administration, avoiding in vivo circulation of photothermal agent and reducing side effects.

PDT has shown its clinical application prospect in the treatment of melanoma, which can not only induce tumor cell necrosis by producing a great deal of ROS via photosensitizers under laser irradiation, but also cause tumor immunogenic cell death and activate anti-tumor immune response [101]. Similar to chemotherapy drugs, photosensitizers are usually administrated by intravenous injection, which often causes

systemic toxicity. MNs combined with PDT can achieve accurate drug release, reduce the potential risk of systemic toxicity and amplify local immune responses [102]. Bian et al. [103] fabricated a fast-dissolving oligopeptide hyaluronic acid (oligo-HA) MN patch with a tip enriched with approximately 3 μg of the photosensitizer chlorin e6 (Ce6). The MN had adequate mechanical strength to penetrate the skin obstruction, facilitating the transport of Ce6 into the deep layer of the skin. Under 660 nm laser irradiation, the MN fully utilized the efficacy of PDT for limiting the development of primary and metastatic melanoma. This Ce6 MN patch not only reduced the cost and systemic toxicity risk, but also enhanced anti-melanoma immune function without being combination with other chemotherapeutics or immune drugs, thereby proposing a simple and practical strategy for clinical transformation.

Starvation therapy is an emerging cancer treatment method that can block the energy supply of tumors to cause them "starving" and dying, thus restrain their growth [104]. Zeng et al. [105] produced a biocompatible dissolving MN to deliver GOx for the treatment of melanoma (Fig. 6). GOx, as a glucose-consuming enzyme, has obtained great attention in tumor starvation therapy in recent years, yet its applications in vivo are severely limited by rapid inactivation and adverse reactions of non-specific catalysis. In this MN drug delivery system, GOx was encapsulated in polydopamine-based nanocarriers and then integrated into MN patches to achieve sustained catalytic activity and effective starvation therapy. Compared with systemic administration, this long-acting nano-catalyst MN had fewer side effects and could effectively consume glucose in melanoma tumor tissues, achieving significant inhibition of melanoma tumor growth.

4.5. Microneedles for synergetic therapy

Monotherapy for the treatment of melanoma often does not show a desired effect due to non-specific drug uptake and release in the time of administration or unintended side effects of systematic drug delivery. In recent years, collaborative strategies have shown great promise for addressing these issues. Compared with monotherapy, MNs combining with synergetic therapy can achieve a better outcome with lower doses of anti-melanoma drugs and fewer times of administration. In addition, the MN-based synergetic therapy not only improves the convenience, but also reduces the damage of excessive drug diffusion to normal tissues and organs, which is very dominant in the treatment of melanoma.

4.5.1. PTT-chemotherapy synergetic therapy

Chemotherapy always inevitably causes a variety of side effects, MN-based synergetic PTT-chemotherapy can not only reduce the toxicity of chemotherapy drugs, but also shows synergistic anti-melanoma effect, leading to the better treatment effect [106]. In a study [107], the photothermal agent gold nanocage (AuNC) and chemotherapeutic drug DOX were co-encapsulated in MN patches for synergetic therapy of melanoma (see Fig. 7a). After administration by the MNs, DOX directly damaged tumor cells and AuNC transformed luminous energy into thermal energy under near-infrared laser irradiation to kill tumor cells. The combination of the two therapies with MNs had a more significant inhibitory effect on melanoma growth. Similarly, Song et al. [108] investigated a dissolving MN for safely and efficiently co-delivering indocyanine green (ICG) and DOX. The two drugs were encapsulated in lauric acid and polycaprolactone (LA/PCL) with a phase-transition temperature ranging 46–48 °C and the drugs released through the ablation of LA/PCL by the photothermal conversion of photothermal agent ICG. In vivo controlled trials had shown that the average melanoma weights after administration with single chemotherapy or PTT could decrease to 1.27 ± 0.11 and 1.21 ± 0.13 g respectively. While in this MN-based PTT-chemotherapy synergetic therapy, the average melanoma weight could be 0.90 ± 0.10 g, demonstrating that MN-based synergetic therapy could achieve a better anti-melanoma effect. Although MN systems had exhibited great potential for synergistic treatment of melanoma, the systems could be still improved further. The main disadvantage of MN systems is uncontrolled drug release. To address this problem and provide new ideas for clinical therapies of melanoma, Hao et al. [109] designed a near-infrared light-response MN delivery system. Chemotherapeutics 5-fluorouracil (5-FU) in MN arrays killed tumor cells directly and ICG could burn tumor cells by transforming near-infrared light into heat. In addition, ICG could control the release behavior of 5-FU in the dissolving MNs, so as to attain the optimal synergetic effect for melanoma treatment. It is noteworthy that the used MNs material, HA, showed excellent skin permeability. Zhao et al. [110] constructed a multifunctional integrated MN system for multi-model synergetic treatment of malignant melanoma. The MN system co-loaded chemotherapeutic drug camptothecin (CPT) and pH-responsive degradation nanoparticles, which were prepared based on a HA-functionalized framework and internal photothermal agent copper sulfide (CuS). The MN-based chemo-photothermal collaborative therapy realized smart drug release under acid environment and near-infrared irradiation in vivo, increasing the accumulation of drugs in the melanoma tumor sites and achieving good therapeutic effect.

Paclitaxel (PTX) is a superb anti-cancer drug that is frequently used in clinical practice for treating solid tumors [111]. However, PTX alone for chemotherapy produces a single effect, so in recent years it is often used in conjunction with photothermal agents to improve efficacy. PTX has low solubility and can cause adverse effects, such as nephrotoxicity, hypersensitivity, and neurotoxicity [112]. Most photothermal agents also have undesirable side effects, therefore, researchers have used MN delivery systems to efficiently and safely deliver PTX and photothermal agents for the treatment of cancer, especially for superficial skin tumors like melanoma. Peng et al. [113] encapsulated PTX and ICG into the biphasic α-tocopheryl succinate functionalized poly (lactic-*co*-glycolic acid) NPs (PT NPs) that were embedded into dissolving MNs for reducing systemic exposure of PTX and side effects. The vivo imaging of mouse demonstrated that the MNs successfully transported the drugs to tumor tissues, avoiding systemic circulation and adverse reactions. Anti-melanoma experiments on B16 tumor-bearing mouse demonstrated that the MNs showed a best tumor suppressive effect, confirming the advantages of MN drug delivery systems used in chemo-photothermal synergistic therapy. Qin et al. [114] designed a spatiotemporally controlled drug delivery system, which combined MN device with lipid NPs loaded with PTX and the photothermal agent IR-780, to achieve multiple chemo-photothermal therapeutic effects in a single administration. Compared with intravenous and intra-tumoral injections, very few cargoes from the MNs were dispersed into other organs, giving rise to good safety and improving bioavailability. In vivo analysis showed that the MN delivery platform showed unique anti-melanoma efficacy. Notably, the primary tumor was entirely eradicated with a 100% curable rate within 30 days. In the same vein, the aforementioned team designed another self-assembled nano-micelle dissolving MN patch to co-deliver PTX and IR-780. Their work provided a generalizable and versatile framework for designing MN-based chemo-photothermal synergetic therapy to fight melanoma. Researchers demonstrated that combination therapy with MNs had better tumor suppressive effect and lower toxicity than the treatment with single agent or without MNs [115].

4.5.2. PTT-immunotherapy synergetic therapy

Most immunotherapy strategies work unsatisfactorily in patients due to low tumor immunogenicity and immunosuppression in the complex tumor microenvironment. To improve the effectiveness of melanoma cancer treatment, Chen et al. [116] combined PTT and immunotherapy by loading biodegradable chitosan NPs, which encapsulated the photosensitizer ICG and IDO inhibitor into MNs (Fig. 7b). Among tumor sites, ICG converted light energy into thermal energy to ablate melanoma. The IDO inhibitor reversed IDO-mediated immunosuppressive effect and eventually produced a powerful immune stimulation. After administration to melanoma-bearing mouse, 80% of them survived and were free of recurrence for more than 120 days. Notably, the well-designed MN array structure could spatially control the distribution

Table 3
Overview about the applications of MNs for anti-melanoma.

Types of therapy	Types of MNs	MN materials	Drug loadings	Advantages	Disadvantages	Ref.
Chemotherapy	Dissolving	GelMA	DOX	Low toxicity and high therapeutic effect; a graduate release of the drugs	Long-term trials are needed to confirm the biocompatibility of the MN matrix	[47]
	Dissolving	PVA	DOX	Sustained release of the drug cargoes; mid adverse reactions	Complex preparation technology; relatively cumbersome to use	[48]
	Hydrogel-forming	PVA	Alloc-DOX	Sufficient mechanical toughness; limited side effects	Difficult to control the amount of bioorthogonal catalysts and substrates	[49]
	Hydrogel-forming	GelMA-β-CD	CUR	Improve the solubility, stability and efficacy of drugs	There may be toxicity associated with chemical synthesis	[51]
Targeted therapy	Coated	Stainless steel	siBraf	Low cytotoxicity; strong targeted therapy	Biohazardous waste generation	[58]
	Dissolving	HA; PVP; dextran	siRNA	Enhanced skin permeability; targeted tumor inhibition; small adverse reactions	Limited depth of skin insertion and partial waste of drugs	[60]
	Dissolving	PVP; HA; CMC	HA15	Safe and efficient; controlled drug release under near-infrared laser irradiation	The compatibility of drugs with polymer materials need to be investigated	[62]
	Hydrogel-forming	DexMA	Tra/DOX	Reduced drug resistance in melanoma; low systemic toxicity and side effects	Fragile mechanical property; the toxicity from residual photoinitiators	[63]
Immunotherapy	Coated	Polycarbonate	αPD-1	Efficient and sustained delivery of drugs	Low immune response when use alone	[71]
	Coated	PLGA	Antigen protein/ Vaccine adjuvant	Simplified vaccine design; maintain the immunological properties of the vaccines	Fail to cure melanoma alone and need to be combined with other therapies	[87]
	Coated	Polycarbonate	DNA vaccine/ Vaccine adjuvant	Enhanced immunogenicity of vaccines; excellent stability	Generate biohazardous sharp waste; drug loss from the surface of MN needles	[94]
	Dissolving	HA	αPD-1	Continuous delivery of drugs and enhancement of melanoma treatment	Low drug loading and mechanical strength; high cost of use	[70]
	Dissolving	PVP	Anti-CTLA-4	Faster and deeper drug delivery; enhanced immune response	The biocompatibility issue with the Mg microparticles used and their byproducts	[75]
	Dissolving	HA	αPD-1/1-MT	Biocompatible and safe; a powerful anti-melanoma effect	Reduced drug delivery efficiency due to drug diffusion and incomplete insertion of MNs	[77]
	Dissolving	Chitosan; PVA; PVP	αPD-1/1-MT	Improve the efficacy of anti-melanoma; increase the drug loading	Complicated fabricated process; difficult to realize large-scale production	[79]
	Dissolving	HA	Antigenic peptides	Biosafety; increase the immune response of peptide vaccines	Long dissolution time; slow skin recovery after the removal of MNs	[88]
	Dissolving	Cryogenic medium	Dendritic cells	Living cell delivery; simple and convenient; strong immunogenicity	Harsh production, storage and transportation conditions; limited cell-loading capacity	[90]
	Dissolving	HA	Tumor lysates/ Vaccine adjuvant	Generate robust immune responses; low systemic toxicity	Need a prolonged safety evaluation of some potential side effects	[92]
	Dissolving	Polypeptide copolymer	DNA vaccine/ Vaccine adjuvant	Strong immunogenicity; safe and convenient; bioresorbable and biocompatibility	Relatively small micro-volume lead to the limited drug loading	[95]
	Dissolving	PVP	CPMV	Excellent biocompatibility, versatility and deep payload drug penetration	Difficult to adapt to the irregular shape of melanoma surface	[97]
	Hollow	PVA; PVP	αPD-1	Enhance the curative effect and reduce toxic side effects	Easy to cause clogging to prevent effective delivery of drugs	[73]
PTT	Dissolving	PVA; PVP	AIEgen	Spatially controlled drug distribution	Unclear mechanism of AIEgen in the body fluids	[100]
PDT	Dissolving	Oligo-HA	Ce6	Enhanced local immune response; reduced systemic toxicity	Possible damage to normal skin around the melanoma	[103]
Starvation therapy	Dissolving	HA; PVP	GOx	Efficient local administration; long-lasting catalytic activity	Incomplete melanoma eradication after MN treatment	[105]
PTT-chemotherapy	Dissolving	HA	DOX/AuNC	High mechanical strength; strong inhibition to melanoma growth	An inaccurate drug dosing due to incomplete insertion of MNs into the skin	[107]
	Dissolving	PVA; PVP	DOX/ICG	High efficacy and low toxicity	Uncontrolled drug release	[108]
	Dissolving	HA	5-FU/ICG	High drug loading; controlled drug release	Research needs of ICG about its potential toxicity	[109]
	Dissolving	PVA; PVP	CuS/CPT	Low-dose administration with high efficiency; low toxicity and minor side effects	More pharmacodynamics and long-term safety need to be further evaluated	[110]
	Dissolving	HA; PVP K90	PTX/ICG	Safe and efficient; low toxic side effects	Low drug loading efficiency due to the ICG instability during fabrication	[113]
	Dissolving	HA; PVP K90	PTX/IR-780	Effectively inhibit melanoma at a low dose	Inapplicable to deliver some kinds of drugs, such as thermal-sensitive drugs	[114]

(*continued on next page*)

Table 3 (*continued*)

Types of therapy	Types of MNs	MN materials	Drug loadings	Advantages	Disadvantages	Ref.
PTT-immunotherapy	Dissolving	PVA; PVP	1-MT/ICG	Robust synergistic anti-melanoma effect	Low drug loading	[116]
	Dissolving	PVP	Photothermal agent/immune adjuvant	Overcome the stromal barrier; significant inhibition of melanoma and anti-metastasis effect	Standardized administration apparatus need to be exploited for further practical applications	[117]
	Dissolving	HA; PVP K90	αPD-L1/1-MT /ICG	High drug loading; high transdermal absorption rate; instant tumor inhibition	Difficult to insert into the skin due to skin deformation, causing a decrease in drug utilization	[118]
PTT-CDT	Dissolving	PVA; PVP	CaO_2@Mn-PDA NFs	Safe; multifunctional synergistic therapeutic effect	Biocompatibility need to be considered because of related chemical reactions	[121]
	Dissolving	PVA; PVP	Cu-PDA NPs	Enhance the transdermal absorption of drugs; excellent photothermal conversion performance	Skin damage after long-term use; possible risk of inflammation	[122]
Immuno-synergetic therapy	Dissolving	HA	TAA/αPD-1/ Vaccine adjuvant	Improve the efficacy of immunotherapy; exhibit great potential in clinical application	High requirements for production (aseptic) and storage conditions (waterproof packing)	[124]
PTT-PDT-starvation	Dissolving	PVA; PVP K30	ICG/GOx/CAT	Dramatically strengthen anti-melanoma efficacy without obvious side effects	Long degradation time of the MN matrix in vivo; low drug load capacity	[126]
PTI-autophagy	Dissolving	HA	IR780/CQ	Optimal synergistic anti-melanoma efficacy	Insufficient drug delivery caused by the diffusion of drugs in the MNs	[130]

Abbreviation: MN: microneedle; PTT: photothermal therapy; PDT: photodynamic therapy; CDT: chemodynamic therapy; PTI: photoimmunotherapy; PVA: polyvinyl alcohol; GelMA-β-CD: gelatin methacryloyl conjugated with β-cyclodextrin; PVP: polyvinyl pyrrolidone; CMC: carboxymethyl cellulose; DexMA: dextran methacrylate; PLGA: poly (d,l-lactide-co-glycolide) acid; Oligo-HA: oligopeptide hyaluronic acid; CUR: curcumin; Alloc-DOX: N-allyloxycarbonyl-caged doxorubicin; siBraf: BRAF siRNA (V-raf murine sarcoma viral oncogene homologue B1-small interfering RNA); HA15: the leading compound of the thiazole benzenesulfonamide; Tra: trametinib; αPD-1: anti-programmed cell death protein 1; CTLA-4: cytotoxic T-lymphocyte antigen 4; 1-MT: 1-methyl-DL-tryptophan; DCs: dendritic cells; CPMV: cowpea mosaic virus; AIEgen: aggregation-induced emission; Ce6: chlorin e6; GOx: glucose oxidase; AuNC: gold nanocage; ICG: indocyanine green; 5-FU: 5-fluorouracil; CuS: copper sulfide; CPT: camptothecin; PTX: paclitaxel; CaO_2@Mn-PDA NFs: calcium peroxide/manganese-doped polydopamine nanoformulations; Cu-PDA NPs: cuprum-contained polydopamine nanoparticles; TAA: tumor associated antigen; CAT: catalase; CQ: chloroquine; Mg: magnesium.

and penetration of drugs, significantly limiting the development of melanoma with lung metastasis. He et al. [117] developed a novel PTT-immunotherapy synergetic therapy for melanoma treatment, by utilizing MNs to transport hyaluronidase-modified polymer NPs containing a photothermal agent and an immune adjuvant. Thanks to the dissolution of hyaluronidase in extracellular matrix, drugs penetrated into the tumor sites and enhanced the immune response of T cells. More importantly, local delivery of the photothermal agent could rapidly increase the temperature of tumor tissues in a short term, causing irreversible damage to tumor cells and reducing the thermal-radiation harm to normal tissues or organs around tumors. Local targeting of PTT combined with immunotherapy mediated by MN systems is a feasible treatment strategy for melanoma. Nevertheless, the small size, limited drug loading and uneven drug distribution in the tips of MNs cause a low drug absorption rate. In a study [118], a delicate and simple MN technique was developed to efficiently load the photothermal agent ICG. ICG was encapsulated in chitosan NPs, which was then mixed with MN's matrix material. This design not only improved the stability of ICG, but also enhanced the drug loading capacity of MNs and promoted the concentration of drugs in the tips of MNs. Experimental results confirmed that the drug loading capacity of ICG in this MNs system was 7 times than that of ICG-embedded MNs without nanoparticles encapsulation. In combination with αPD-L1/1-MT-encapsulated MN patch, this technique achieved a locally targeted synergistic treatment for melanoma, showing strong anti-melanoma effect.

4.5.3. PTT-CDT synergetic therapy

CDT (chemodynamic therapy), similar to PDT, can generate reactive ROS to cause damage to tumor cells through external stimulation or endogenous triggers in the TME [119]. Different from PDT, CDT has no use for consuming oxygen that is scarce in tumor cells [120]. CDT is usually combined with other approaches for melanoma treatment, which has offered significant advantages over monotherapy, but it still suffers from low efficiency and unexpected toxicity. Therefore, Ruan et al. [121] designed a MN-based transdermal delivery system to achieve PTT-CDT synergetic therapy for melanoma treatment. Multifunctional CaO_2@Mn-PDA NFs (polydopamine nanoformulations) were delivered to the lesions via MNs. Under near-infrared irradiation, the fabricated MNs showed the combined therapeutic effect, including CDT, PTT, and modulating hypoxia, which showed outstanding chemo-dynamic reactions and boosted the generation of ROS. No significant toxicity was observed in the melanoma-bearing mouse, which was demonstrated by little weight change of these mouse after administration. At the same time, the combined therapy showed a strong anti-melanoma effect by comparing the tumor sizes in excised mouse with different treatment methods. To realize PTT-CDT synergistic therapy, Song et al. [122] prepared Cu-contained polydopamine NPs (Cu-PDA NPs), which were encapsulated into biodegradable MNs for fighting melanoma (Fig. 7c). Compared with PDA, Cu-PDA NPs exerted better Fenton-like catalytic activities and a higher photothermal effect (~50.40%) to convert the energy from near-infrared radiation into heat, leading to serious oxidative damage to tumor tissues. This new minimally invasive therapy restrained the growth and metastasis of melanoma tumor, providing a novel and safe MN-based delivery approach for local combined anti-melanoma therapy.

4.5.4. Other synergetic therapies

There are also other synergetic therapies with MN delivery systems used for melanoma treatment. Tham et al. [123] fabricated a nanovehicle with dual loading of photosensitizer-phthalocyanine and targeted drugs-dabrafenib and trametinib for PDT-targeted synergetic therapy, simultaneously utilizing MNs to promote their permeation into deep tissues of skin. In a three-dimensional sphere model in vitro, the drugs could inhibit the proliferation of melanoma tumor cells. In vivo study based on xenografted melanoma mouse models confirmed that the synergetic treatment method containing PDT and targeted therapy had

exemplary anti-melanoma capacity and could inhibit the growth of tumors to the greatest extent when exposed to 730 nm laser.

In another study [124], a therapy combining a cancer vaccine loaded MN and αPD-1 for transdermal immunization was developed for fighting melanoma. Researchers constructed novel transfersomes co-loaded with tumor associated antigen (TAA), αPD-1, and an immune adjuvant. After certain structural modification, the transfersomes were functionalized with DC-targeted capacity, thus transforming the immunosuppressed TME into immune activation and enhancing immunotherapy of αPD-1. The structure and characteristics of MNs create convenient conditions for co-administration and synergetic therapies. In vivo experiments showed that the melanoma-bearing mice treated intravenously showed strong anti-melanoma effect only at the beginning, and then the therapeutic effect gradually weakened. However, the growth of melanoma in the MN group was always strongly inhibited, and the $CD8^+$ T cells in tumor were over two times higher than that in the intravenous injection group, indicating that the MN-mediated immuno-synergetic therapy caused a stronger immune response and showed a better curative effect of melanoma.

As described previously, starvation therapy is a new type of cancer therapies that has attracted a lot of attention by researchers. Nevertheless, several disadvantages seriously hamper its clinical applications, for instance, poor enzyme stability, low curative effect and possible adverse effects [125]. To achieve better therapeutic efficacy, Zhou et al. [126] potentiated starvation therapy with PTT and PDT via MN delivery platforms. HA-coated nanoreactors contained GOx, ICG and catalase (CAT), which were delivered by MN patches for promoting the internalization of drugs into tumor sites. Compared with other methods of administration, MNs greatly increased the drug concentration in melanoma tumor tissues with fewer adverse effects. This study had successfully combined multiple treatment approaches and improved the therapeutic effect for melanoma through cascade reactions, opening up a potential option for the anti-melanoma treatment.

Photoimmunotherapy (PTI) is a newly developed method for treating malignant melanoma via transforming light energy into thermal or chemical energy, generating adequate hyperthermia or ROS in the TME to kill tumor cells [127]. Autophagy is an internal mechanism of the body that is usually considered as a “double-edged sword” in the process of tumor development [128]. That is to say, autophagy can inhibit tumor growth in the early stage of tumor formation, while in tumors that have already formed, autophagy can help tumor cells maintain cell growth even in an undernourished environment [129]. Hence, utilizing the properties of autophagy can develop new anti-melanoma therapies. Chen et al. [130] achieved a combination of PTI and autophagy through MNs, initiating optimal anti-tumor immunity and greatly enhancing the efficacy of melanoma treatment. A dissolving MN patch was fabricated for delivering micelles into the lesions which co-encapsulated photosensitizer-IR780 and autophagy inhibitor-chloroquine (CQ). The MN patch notably enhanced the concentration of drugs in deep tumor sites. Moreover, inhibition of autophagy significantly increased IR780's photosensitivity and facilitated the death of tumor cells. Anti-melanoma studies showed that this system effectively erased primary tumors and limited the organ metastasis, extending the life up to 40 days.

5. Conclusions and perspectives

Melanoma is a highly invasive malignant tumor that is difficult to cure on account of its multi-drug resistance. Despite all the efforts, systematic anti-melanoma therapies still have some drawbacks, for instance, low therapeutic efficacy and unexpected side effects to healthy organs and tissues. Nowadays, the emergence of highly efficient transdermal delivery systems, like MNs, which could bypass the obstacle of drug delivery has shown feasible treatment schemes and unique advantages for fighting melanoma. The applications of MNs in the treatment of melanoma are summarized in Table 3. MNs combined with chemotherapy can not only avoid the first-pass effect and improve the solubility of chemotherapeutic drugs but also reduce the systemic exposure of drugs and undesired side effects. MNs combined with targeted therapy increase the concentration of targeted drugs in tumor sites, enhancing the drug bioavailability and improving the efficiency of targeted therapy against melanoma. Compared with ordinary immunotherapy for melanoma, MN-based immunotherapy preserves the activity of immunologically active substances well, causing a stronger immune response in the human body to fight melanoma. Using MNs to deliver cancer vaccines instead of intravenous injection achieves minimal invasion to reduce the pain and improve the compliance of patients. In addition to the drug itself, MNs can also deliver micelles or nanocarriers containing drugs, which increase the drug loading. So that MNs can achieve good curative effect with only one administration when applied to PTT, PDT and starvation therapy for melanoma, reducing unnecessary troubles compared to those therapies without MNs. Besides, MNs can be designed to different structures according to actual applications, such as core-shell structures for controlled drug delivery and pH-sensitive structures for intelligent drug delivery. These designs allow MNs to be well combined with synergetic therapy for melanoma, which is more effective than monotherapy and could be beneficial for clinical transformations.

Despite these advantages of MNs, there are still some issues that need to be concerned about. Firstly, the enhancement for the mechanical strength of MNs is quite important for their clinical transformation and commercialization in the future. At present, the anti-melanoma effects of MNs are mainly studied in mouse or other small animals. However, there are great differences between mouse skin and human skin. Moreover, different people and even different body parts of the same person have different skin properties. Therefore, it is necessary to carry out more studies to decide the optimal application areas. Secondly, although the minimally invasive nature of MNs makes them safe, the safety profiles still need to be cautiously evaluated, including the safety of MNs materials, the risk of allergic reactions and infection, and whether the frequency of using MNs will damage the normal skin function. Besides, the large-scale production of MNs in sterile conditions is also an issue that requires careful consideration. Thirdly, limited drug loading is a major challenge for MNs due to their small structures. Nowadays, although MNs have been widely proved to be effective in cell and animal experiments, this does not mean that MNs are still effective in patient treatment because of the huge differences in body weight and melanoma growth between humans and animals. We are likely to face the clinical translation problem, where the same dose that is effective in melanoma mouse may not be sufficient to achieve a desired efficacy in patients. Finally, a research partnership between clinicians, pharmaceutical industries and academia is needed to practically apply MNs to the clinical treatment of melanoma. Clinicians fully understand MN techniques and researchers know clinical needs, which are vital to facilitate MN studies and transform them into melanoma treatment practice.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] L.E. Davis, S.C. Shalin, A.J. Tackett, Current state of melanoma diagnosis and treatment, Cancer Biol. Ther. 20 (11) (2019) 1366–1379, https://doi.org/10.1080/15384047.2019.1640032.

[2] R. Cassano, M. Cuconato, G. Calviello, S. Serini, S. Trombino, Recent advances in nanotechnology for the treatment of melanoma, Molecules. 26 (4) (2021) 785, https://doi.org/10.3390/molecules26040785.

[3] V. Monge-Fuentes, L.A. Muehlmann, J.P. Longo, J.R. Silva, M.L. Fascineli, P. de Souza, F. Faria, I.A. Degterev, A. Rodriguez, F.P. Carneiro, C.M. Lucci, P. Escobar, R.F. Amorim, R.B. Azevedo, Photodynamic therapy mediated by acai oil (Euterpe oleracea Martius) in nanoemulsion: a potential treatment for melanoma,

J. Photochem. Photobiol. B 166 (2017) 301–310, https://doi.org/10.1016/j.jphotobiol.2016.12.002.
[4] A.F. Moreira, C.F. Rodrigues, T.A. Jacinto, S.P. Miguel, E.C. Costa, I.J. Correia, Microneedle-based delivery devices for cancer therapy: a review, Pharmacol. Res. 148 (2019), 104438, https://doi.org/10.1016/j.phrs.2019.104438.
[5] D. Zhi, T. Yang, T. Zhang, M. Yang, S. Zhang, R.F. Donnelly, Microneedles for gene and drug delivery in skin cancer therapy, J. Control. Release 335 (2021) 158–177, https://doi.org/10.1016/j.jconrel.2021.05.009.
[6] V. Singh, P. Kesharwani, Recent advances in microneedles-based drug delivery device in the diagnosis and treatment of cancer, J. Control. Release 338 (2021) 394–409, https://doi.org/10.1016/j.jconrel.2021.08.054.
[7] G.C. Leonardi, L. Falzone, R. Salemi, A. Zanghi, D.A. Spandidos, J.A. McCubrey, S. Candido, M. Libra, Cutaneous melanoma: from pathogenesis to therapy (review), Int. J. Oncol. 52 (4) (2018) 1071–1080, https://doi.org/10.3892/ijo.2018.4287.
[8] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D. M. Parkin, D. Forman, F. Bray, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, Int. J. Cancer 136 (5) (2015) E359–E386, https://doi.org/10.1002/ijc.29210.
[9] C. Karimkhani, A.C. Green, T. Nijsten, M.A. Weinstock, R.P. Dellavalle, M. Naghavi, C. Fitzmaurice, The global burden of melanoma: results from the global burden of disease study 2015, Br. J. Dermatol. 177 (1) (2017) 134–140, https://doi.org/10.1111/bjd.15510.
[10] C.H. O'Neill, C.R. Scoggins, Melanoma, J. Surg. Oncol. 120 (5) (2019) 873–881, https://doi.org/10.1002/jso.25604.
[11] F. Dimitriou, R. Krattinger, E. Ramelyte, M.J. Barysch, S. Micaletto, R. Dummer, S.M. Goldinger, The world of melanoma: epidemiologic, genetic, and anatomic differences of melanoma across the globe, Curr. Oncol. Rep. 20 (11) (2018) 87, https://doi.org/10.1007/s11912-018-0732-8.
[12] S.M. Dawes, S. Tsai, H. Gittleman, J.S. Barnholtz-Sloan, J.S. Bordeaux, Racial disparities in melanoma survival, J. Am. Acad. Dermatol. 75 (5) (2016) 983–991, https://doi.org/10.1016/j.jaad.2016.06.006.
[13] B.A. Kohler, E. Ward, B.J. McCarthy, M.J. Schymura, L.A. Ries, C. Eheman, A. Jemal, R.N. Anderson, U.A. Ajani, B.K. Edwards, Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system, J. Natl. Cancer Inst. 103 (9) (2011) 714–736, https://doi.org/10.1093/jnci/djr077.
[14] S. Candido, V. Rapisarda, A. Marconi, G. Malaponte, V. Bevelacqua, P. Gangemi, A. Scalisi, J.A. McCubrey, R. Maestro, D.A. Spandidos, C. Fenga, M. Libra, Analysis of the B-RafV600E mutation in cutaneous melanoma patients with occupational sun exposure, Oncol. Rep. 31 (3) (2014) 1079–1082, https://doi.org/10.3892/or.2014.2977.
[15] D. Lazovich, R.I. Vogel, M. Berwick, M.A. Weinstock, K.E. Anderson, E. M. Warshaw, Indoor tanning and risk of melanoma: a case-control study in a highly exposed population, Cancer Epidemiol. Biomark. Prev. 19 (6) (2010) 1557–1568, https://doi.org/10.1158/1055-9965.Epi-09-1249.
[16] C. Conforti, I. Zalaudek, Epidemiology and risk factors of melanoma: a review, Dermatology Practical & Conceptual. 11 (2021) e2021161S, https://doi.org/10.5826/dpc.11S1a161S.
[17] R.D. Hall, R.R. Kudchadkar, BRAF Mutations: Signaling, epidemiology, and clinical experience in multiple malignancies, Cancer Control 21 (3) (2014) 221–230, https://doi.org/10.1177/107327481402100307.
[18] J. Xia, P. Jia, K.E. Hutchinson, K.B. Dahlman, D. Johnson, J. Sosman, W. Pao, Z. Zhao, A Meta-analysis of somatic Mutations from next generation sequencing of 241 melanomas: a road map for the study of genes with potential clinical relevance, Mol. Cancer Ther. 13 (7) (2014) 1918–1928, https://doi.org/10.1158/1535-7163.Mct-13-0804.
[19] T.H. Erlich, D.E. Fisher, Pathways in melanoma development, G. Ital. Dermatol. Venereol. 153 (1) (2018) 68–76, https://doi.org/10.23736/s0392-0488.17.05795-9.
[20] I. Russo, L. Zorzetto, A.C. Frigo, V.C. Sileni, M. Alaibac, A comparative study of the cutaneous side effects between BRAF monotherapy and BRAF/MEK inhibitor combination therapy in patients with advanced melanoma: a single-Centre experience, Eur. J. Dermatol. 27 (5) (2017) 482–486, https://doi.org/10.1684/ejd.2017.3069.
[21] J. Sun, M.J. Carr, N.I. Khushalani, Principles of targeted therapy for melanoma, Surg. Clin. North Am. 100 (1) (2020) 175–188, https://doi.org/10.1016/j.suc.2019.09.013.
[22] R.S. Bhadale, V.Y. Londhe, A systematic review of carbohydrate-based microneedles: current status and future prospects, J. Mater. Sci. Mater. Med. 32 (8) (2021) 89, https://doi.org/10.1007/s10856-021-06559-x.
[23] A.H. Sabri, Y. Kim, M. Marlow, D.J. Scurr, J. Segal, A.K. Banga, L. Kagan, J.B. Lee, Intradermal and transdermal drug delivery using microneedles - fabrication, performance evaluation and application to lymphatic delivery, Adv. Drug Deliv. Rev. 153 (2020) 195–215, https://doi.org/10.1016/j.addr.2019.10.004.
[24] E. Larraneta, R.E.M. Lutton, A.D. Woolfson, R.F. Donnelly, Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development, Mater. Sci. Eng. R-Rep. 104 (2016) 1–32, https://doi.org/10.1016/j.mser.2016.03.001.
[25] Y. Hao, W. Li, X. Zhou, F. Yang, Z. Qian, Microneedles-based transdermal drug delivery systems: a review, J. Biomed. Nanotechnol. 13 (12) (2017) 1581–1597, https://doi.org/10.1166/jbn.2017.2474.
[26] K. van der Maaden, W. Jiskoot, J. Bouwstra, Microneedle technologies for (trans) dermal drug and vaccine delivery, J. Control. Release 161 (2) (2012) 645–655, https://doi.org/10.1016/j.jconrel.2012.01.042.
[27] Y. Ma, H.S. Gill, Coating solid dispersions on microneedles via a molten dip-coating method: development and in vitro evaluation for transdermal delivery of a water-insoluble drug, J. Pharm. Sci. 103 (11) (2014) 3621–3630, https://doi.org/10.1002/jps.24159.
[28] H.S. Gill, M.R. Prausnitz, Coated microneedles for transdermal delivery, J. Control. Release 117 (2) (2007) 227–237, https://doi.org/10.1016/j.jconrel.2006.10.017.
[29] Z.L. Hu, C.S. Meduri, R.S.J. Ingrole, H.S. Gill, G. Kumar, Solid and hollow metallic glass microneedles for transdermal drug-delivery, Appl. Phys. Lett. 116 (20) (2020), https://doi.org/10.1063/5.0008983.
[30] W. Martanto, J.S. Moore, T. Couse, M.R. Prausnitz, Mechanism of fluid infusion during microneedle insertion and retraction, J. Control. Release 112 (3) (2006) 357–361, https://doi.org/10.1016/j.jconrel.2006.02.017.
[31] N. Dabholkar, S. Gorantla, T. Waghule, V.K. Rapalli, A. Kothuru, S. Goel, G. Singhvi, Biodegradable microneedles fabricated with carbohydrates and proteins: revolutionary approach for transdermal drug delivery, Int. J. Biol. Macromol. 170 (2021) 602–621, https://doi.org/10.1016/j.ijbiomac.2020.12.177.
[32] L. Zhang, R. Guo, S. Wang, X. Yang, G. Ling, P. Zhang, Fabrication, evaluation and applications of dissolving microneedles, Int. J. Pharm. 604 (2021), 120749, https://doi.org/10.1016/j.ijpharm.2021.120749.
[33] M. Kim, B. Jung, J.H. Park, Hydrogel swelling as a trigger to release biodegradable polymer microneedles in skin, Biomaterials. 33 (2) (2012) 668–678, https://doi.org/10.1016/j.biomaterials.2011.09.074.
[34] Q. Zong, R. Guo, N. Dong, G. Ling, P. Zhang, Design and development of insulin microneedles for diabetes treatment, Drug Deliv. Transl. Res. 12 (5) (2022) 973–980, https://doi.org/10.1007/s13346-021-00981-y.
[35] N. Xu, M. Zhang, W. Xu, G. Ling, J. Yu, P. Zhang, Swellable PVA/PVP hydrogel microneedle patches for the extraction of interstitial skin fluid toward minimally invasive monitoring of blood glucose level, Analyst 147 (7) (2022) 1478–1491, https://doi.org/10.1039/d1an02288a.
[36] T. Waghule, G. Singhvi, S.K. Dubey, M.M. Pandey, G. Gupta, M. Singh, K. Dua, Microneedles: a smart approach and increasing potential for transdermal drug delivery system, Biomed. Pharmacother. 109 (2019) 1249–1258, https://doi.org/10.1016/j.biopha.2018.10.078.
[37] C.S. Kolli, Microneedles: bench to bedside, Ther. Deliv. 6 (9) (2015) 1081–1088, https://doi.org/10.4155/tde.15.67.
[38] R.F. Donnelly, T.R. Raj Singh, A.D. Woolfson, Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety, Drug Deliv. 17 (4) (2010) 187–207, https://doi.org/10.3109/10717541003667798.
[39] L. Xie, H. Zeng, J. Sun, W. Qian, Engineering Microneedles for Therapy and Diagnosis: A Survey, Micromachines (Basel) 11 (3) (2020) 271, https://doi.org/10.3390/mi11030271.
[40] D.V. McAllister, P.M. Wang, S.P. Davis, J.H. Park, P.J. Canatella, M.G. Allen, M. R. Prausnitz, Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies, Proc. Natl. Acad. Sci. U. S. A. 100 (24) (2003) 13755–13760, https://doi.org/10.1073/pnas.2331316100.
[41] R.F. Donnelly, D.I. Morrow, T.R. Singh, K. Migalska, P.A. McCarron, C. O'Mahony, A.D. Woolfson, Processing difficulties and instability of carbohydrate microneedle arrays, Drug Dev. Ind. Pharm. 35 (10) (2009) 1242–1254, https://doi.org/10.1080/03639040902882280.
[42] F.K. Aldawood, A. Andar, S. Desai, A comprehensive review of microneedles: types, materials, processes, characterizations and applications, Polymers. 13 (16) (2021) 2815, https://doi.org/10.3390/polym13162815.
[43] J.H. Park, M.G. Allen, M.R. Prausnitz, Polymer microneedles for controlled-release drug delivery, Pharm. Res. 23 (5) (2006) 1008–1019, https://doi.org/10.1007/s11095-006-0028-9.
[44] S. Mdanda, P. Ubanako, P.P.D. Kondiah, P. Kumar, Y.E. Choonara, Recent advances in microneedle platforms for transdermal drug delivery technologies, Polymers (Basel) 13 (15) (2021) 2405, https://doi.org/10.3390/polym13152405.
[45] A. Li, J. Zhao, J. Fu, J. Cai, P. Zhang, Recent advances of biomimetic nano-systems in the diagnosis and treatment of tumor, Asian J. Pharm. Sci. 16 (2) (2021) 161–174, https://doi.org/10.1016/j.ajps.2019.08.001.
[46] M.R. Prausnitz, R. Langer, Transdermal drug delivery, Nat. Biotechnol. 26 (11) (2008) 1261–1268, https://doi.org/10.1038/nbt.1504.
[47] Z. Luo, W. Sun, J. Fang, K. Lee, S. Li, Z. Gu, M.R. Dokmeci, A. Khademhosseini, Biodegradable gelatin Methacryloyl microneedles for transdermal drug delivery, Adv. Healthcare Mater. 8 (3) (2019), e1801054, https://doi.org/10.1002/adhm.201801054.
[48] H. Kim, H.S. Lee, Y. Jeon, W. Park, Y. Zhang, B. Kim, H. Jang, B. Xu, Y. Yeo, D. R. Kim, C.H. Lee, Bioresorbable, miniaturized porous silicon needles on a flexible water-soluble backing for unobtrusive, sustained delivery of chemotherapy, ACS Nano 14 (6) (2020) 7227–7236, https://doi.org/10.1021/acsnano.0c02343.
[49] Z. Chen, H. Li, Y. Bian, Z. Wang, G. Chen, X. Zhang, Y. Miao, D. Wen, J. Wang, G. Wan, Y. Zeng, P. Abdou, J. Fang, S. Li, C.-J. Sun, Z. Gu, Bioorthogonal catalytic patch, Nat. Nanotechnol. 16 (8) (2021) 933–941, https://doi.org/10.1038/s41565-021-00910-7.
[50] S. Li, W. Li, M. Prausnitz, Individually coated microneedles for co-delivery of multiple compounds with different properties, Drug Deliv. Transl. Res. 8 (5) (2018) 1043–1052, https://doi.org/10.1007/s13346-018-0549-x.
[51] X. Zhou, Z. Luo, A. Baidya, H.-j. Kim, C. Wang, X. Jiang, M. Qu, J. Zhu, L. Ren, F. Vajhadin, P. Tebon, N. Zhang, Y. Xue, Y. Feng, C. Xue, Y. Chen, K. Lee, J. Lee, S. Zhang, C. Xu, N. Ashammakhi, S. Ahadian, M.R. Dokmeci, Z. Gu, W. Sun, A. Khademhosseini, Biodegradable beta-Cyclodextrin conjugated gelatin

Methacryloyl microneedle for delivery of water-insoluble drug, Adv. Healthcare Mater. 9 (11) (2020), e2000527, https://doi.org/10.1002/adhm.202000527.
[52] Y. Li, X. Tan, X. Liu, L. Liu, Y. Fang, R. Rao, Y. Ren, X. Yang, W. Liu, Enhanced anticancer effect of doxorubicin by TPGS-coated liposomes with Bcl-2 siRNA-corona for dual suppression of drug resistance, Asian J. Pharm. Sci. 15 (5) (2020) 646–660, https://doi.org/10.1016/j.ajps.2019.10.003.
[53] K.S. Ahmed, X. Shan, J. Mao, L. Qiu, J. Chen, Derma roller (R) microneedles-mediated transdermal delivery of doxorubicin and celecoxib co-loaded liposomes for enhancing the anticancer effect, Mater. Sci. Eng. C-Mater. Biol. Appl. 99 (2019) 1448–1458, https://doi.org/10.1016/j.msec.2019.02.095.
[54] J. van Wijngaarden, E. van Beek, G. van Rossum, C. van der Bent, K. Hoekman, G. van der Pluijm, M.A. van der Pol, H.J. Broxterman, V.W. van Hinsbergh, C. W. Löwik, Celecoxib enhances doxorubicin-induced cytotoxicity in MDA-MB231 cells by NF-kappaB-mediated increase of intracellular doxorubicin accumulation, Eur. J. Cancer 43 (2) (2007) 433–442, https://doi.org/10.1016/j.ejca.2006.09.010.
[55] Y. Zhang, X. Zhan, S. Peng, Y. Cai, Y.S. Zhang, Y. Liu, Z. Wang, Y. Yu, Y. Wang, Q. Shi, X. Zeng, K. Yuan, N. Zhou, R. Joshi, M. Zhang, Z. Zhang, W. Min, Targeted-gene silencing of BRAF to interrupt BRAF/MEK/ERK pathway synergized photothermal therapeutics for melanoma using a novel FA-GNR-siBRAF nanosystem, Nanomedicine. 14 (5) (2018) 1679–1693, https://doi.org/10.1016/j.nano.2018.04.010.
[56] C. Luo, J. Shen, Research progress in advanced melanoma, Cancer Lett. 397 (2017) 120–126, https://doi.org/10.1016/j.canlet.2017.03.037.
[57] M. Dorrani, O.B. Garbuzenko, T. Minko, B. Michniak-Kohn, Development of edge-activated liposomes for siRNA delivery to human basal epidermis for melanoma therapy, J. Control. Release 228 (2016) 150–158, https://doi.org/10.1016/j.jconrel.2016.03.010.
[58] W. Ruan, Y. Zhai, K. Yu, C. Wu, Y. Xu, Coated microneedles mediated intradermal delivery of octaarginine/BRAF siRNA nanocomplexes for anti-melanoma treatment, Int. J. Pharm. 553 (1–2) (2018) 298–309, https://doi.org/10.1016/j.ijpharm.2018.10.043.
[59] R. Kanasty, J.R. Dorkin, A. Vegas, D. Anderson, Delivery materials for siRNA therapeutics, Nat. Mater. 12 (11) (2013) 967–977, https://doi.org/10.1038/nmat3765.
[60] J. Pan, W. Ruan, M. Qin, Y. Long, T. Wan, K. Yu, Y. Zhai, C. Wu, Y. Xu, Intradermal delivery of STAT3 siRNA to treat melanoma via dissolving microneedles, Sci. Rep. 8 (1) (2018) 1117, https://doi.org/10.1038/s41598-018-19463-2.
[61] M. Cerezo, S. Rocchi, New anti-cancer molecules targeting HSPA5/BIP to induce endoplasmic reticulum stress, autophagy and apoptosis, Autophagy. 13 (1) (2017) 216–217, https://doi.org/10.1080/15548627.2016.1246107.
[62] Y. Chen, Y. Yang, Y. Xiang, P. Singh, J. Feng, S. Cui, A. Carrier, K. Oakes, T. Luan, X. Zhang, Multifunctional graphene-oxide-reinforced dissolvable polymeric microneedles for transdermal drug delivery, ACS Appl. Mater. Interfaces 12 (1) (2020) 352–360, https://doi.org/10.1021/acsami.9b19518.
[63] S. Huang, H. Liu, S. Huang, T. Fu, W. Xue, R. Guo, Dextran methacrylate hydrogel microneedles loaded with doxorubicin and trametinib for continuous transdermal administration of melanoma, Carbohydr. Polym. 246 (2020), 116650, https://doi.org/10.1016/j.carbpol.2020.116650.
[64] L.D. Rothermel, A.A. Sarnaik, N.I. Khushalani, V.K. Sondak, Current immunotherapy practices in melanoma, Surg. Oncol. Clin. N. Am. 28 (3) (2019) 403–418, https://doi.org/10.1016/j.soc.2019.02.001.
[65] L. Milling, Y. Zhang, D.J. Irvine, Delivering safer immunotherapies for cancer, Adv. Drug Deliv. Rev. 114 (2017) 79–101, https://doi.org/10.1016/j.addr.2017.05.011.
[66] M. Chang, Z. Hou, M. Wang, C. Li, J. Lin, Recent advances in hyperthermia therapy-based synergistic immunotherapy, Adv. Mater. 33 (4) (2021), e2004788, https://doi.org/10.1002/adma.202004788.
[67] R.S. Riley, C.H. June, R. Langer, M.J. Mitchell, Delivery technologies for cancer immunotherapy, Nat. Rev. Drug Discov. 18 (3) (2019) 175–196, https://doi.org/10.1038/s41573-018-0006-z.
[68] H. Amani, M.A. Shahbazi, C. D'Amico, F. Fontana, S. Abbaszadeh, H.A. Santos, Microneedles for painless transdermal immunotherapeutic applications, J. Control. Release 330 (2021) 185–217, https://doi.org/10.1016/j.jconrel.2020.12.019.
[69] P. Sharma, J.P. Allison, The future of immune checkpoint therapy, Science. 348 (6230) (2015) 56–61, https://doi.org/10.1126/science.aaa8172.
[70] C. Wang, Y. Ye, G.M. Hochu, H. Sadeghifar, Z. Gu, Enhanced Cancer immunotherapy by microneedle patch-assisted delivery of anti-PD1 antibody, Nano Lett. 16 (4) (2016) 2334–2340, https://doi.org/10.1021/acs.nanolett.5b05030.
[71] Y. Cao, P. Kakar, M.N. Hossen, M.X. Wu, X. Chen, Sustained epidermal powder drug delivery via skin microchannels, J. Control. Release 249 (2017) 94–102, https://doi.org/10.1016/j.jconrel.2017.01.030.
[72] C. Robert, J. Schachter, G.V. Long, A. Arance, J.J. Grob, L. Mortier, A. Daud, M. S. Carlino, C. McNeil, M. Lotem, J. Larkin, P. Lorigan, B. Neyns, C.U. Blank, O. Hamid, C. Mateus, R. Shapira-Frommer, M. Kosh, H. Zhou, N. Ibrahim, S. Ebbinghaus, A. Ribas, K.-. Investigators, Pembrolizumab versus Ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (26) (2015) 2521–2532, https://doi.org/10.1056/NEJMoa1503093.
[73] G. Chen, Z. Chen, D. Wen, Z. Wang, H. Li, Y. Zeng, G. Dotti, R.E. Wirz, Z. Gu, Transdermal cold atmospheric plasma-mediated immune checkpoint blockade therapy, Proc. Natl. Acad. Sci. U. S. A. 117 (7) (2020) 3687–3692, https://doi.org/10.1073/pnas.1917891117.
[74] S. Kwon, F.C. Velasquez, J.C. Rasmussen, M.R. Greives, K.D. Turner, J.R. Morrow, W.-J. Hwu, R.F. Ross, S. Zhang, E.M. Sevick-Muraca, Nanotopography-based lymphatic delivery for improved anti-tumor responses to checkpoint blockade immunotherapy, Theranostics. 9 (26) (2019) 8332–8343, https://doi.org/10.7150/thno.35280.
[75] M.A. Lopez-Ramirez, F. Soto, C. Wang, R. Rueda, S. Shukla, C. Silva-Lopez, D. Kupor, D.A. McBride, J.K. Pokorski, A. Nourhani, N.F. Steinmetz, N.J. Shah, J. Wang, Built-in active microneedle patch with enhanced autonomous drug delivery, Adv. Mater. 32 (1) (2020), e1905740, https://doi.org/10.1002/adma.201905740.
[76] G.V. Long, R. Dummer, O. Hamid, T. Gajewski, C. Caglevic, S. Dalle, A. Arance, M.S. Carlino, J.-J. Grob, T.M. Kim, L.V. Demidov, C. Robert, J.M.G. Larkin, J. Anderson, J.E. Maleski, M.M. Jones, S.J. Diede, T.C. Mitchell, Epacadostat (E) plus pembrolizumab (P) versus pembrolizumab alone in patients (pts) with unresectable or metastatic melanoma: results of the phase 3 ECHO-301/KEYNOTE-252 study, J. Clin. Oncol. 36 (15) (2018), https://doi.org/10.1200/JCO.2018.36.15_suppl.108.
[77] Y. Ye, J. Wang, Q. Hu, G.M. Hochu, H. Xin, C. Wang, Z. Gu, Synergistic transcutaneous immunotherapy enhances antitumor immune responses through delivery of checkpoint inhibitors, ACS Nano 10 (9) (2016) 8956–8963, https://doi.org/10.1021/acsnano.6b04989.
[78] H. Marwah, T. Garg, A.K. Goyal, G. Rath, Permeation enhancer strategies in transdermal drug delivery, Drug Deliv. 23 (2) (2016) 564–578, https://doi.org/10.3109/10717544.2014.935532.
[79] P. Yang, C. Lu, W. Qin, M. Chen, G. Quan, H. Liu, L. Wang, X. Bai, X. Pan, C. Wu, Construction of a core-shell microneedle system to achieve targeted co-delivery of checkpoint inhibitors for melanoma immunotherapy, Acta Biomater. 104 (2020) 147–157, https://doi.org/10.1016/j.actbio.2019.12.037.
[80] J. Liu, L. Miao, J. Sui, Y. Hao, G. Huang, Nanoparticle cancer vaccines: design considerations and recent advances, Asian J. Pharm. Sci. 15 (5) (2020) 576–590, https://doi.org/10.1016/j.ajps.2019.10.006.
[81] L.H. Butterfield, Cancer vaccines, Bmj-British Med. J. 350 (2015), h988, https://doi.org/10.1136/bmj.h988.
[82] F.O. Nestle, P. Di Meglio, J.Z. Qin, B.J. Nickoloff, Skin immune sentinels in health and disease, Nat. Rev. Immunol. 9 (10) (2009) 679–691, https://doi.org/10.1038/nri2622.
[83] Y.C. Kim, J.H. Park, M.R. Prausnitz, Microneedles for drug and vaccine delivery, Adv. Drug Deliv. Rev. 64 (14) (2012) 1547–1568, https://doi.org/10.1016/j.addr.2012.04.005.
[84] K. van der Maaden, J. Heuts, M. Camps, M. Pontier, A. Terwisscha van Scheltinga, W. Jiskoot, F. Ossendorp, J. Bouwstra, Hollow microneedle-mediated micro-injections of a liposomal HPV E7(43-63) synthetic long peptide vaccine for efficient induction of cytotoxic and T-helper responses, journal of controlled release, Off. J. Control. Release Soc. 269 (2018) 347–354, https://doi.org/10.1016/j.jconrel.2017.11.035.
[85] L. Han, K. Peng, L.Y. Qiu, M. Li, J.H. Ruan, L.L. He, Z.X. Yuan, Hitchhiking on controlled-release drug delivery systems: opportunities and challenges for Cancer vaccines, Front. Pharmacol. 12 (2021), 679602, https://doi.org/10.3389/fphar.2021.679602.
[86] L. Niu, L.Y. Chu, S.A. Burton, K.J. Hansen, J. Panyam, Intradermal delivery of vaccine nanoparticles using hollow microneedle array generates enhanced and balanced immune response, journal of controlled release, Off. J. Control. Release Soc. 294 (2019) 268–278, https://doi.org/10.1016/j.jconrel.2018.12.026.
[87] Q. Zeng, J.M. Gammon, L.H. Tostanoski, Y.-C. Chiu, C.M. Jewell, In vivo expansion of melanoma-specific T cells using microneedle arrays coated with immune-polyelectrolyte multilayers, Acs Biomater. Sci. Eng. 3 (2) (2017) 195–205, https://doi.org/10.1021/acsbiomaterials.6b00414.
[88] H. Kim, K.-Y. Seong, J.H. Lee, W. Park, S.Y. Yang, S.K. Hahn, Biodegradable microneedle patch delivering antigenic peptide-hyaluronate conjugate for Cancer immunotherapy, Acs Biomater. Sci. Eng. 5 (10) (2019) 5150–5158, https://doi.org/10.1021/acsbiomaterials.9b00961.
[89] H. Chang, M.J. Zheng, S.W.T. Chew, C.J. Xu, Advances in the formulations of microneedles for manifold biomedical applications, Adv. Mater. Technol. 5 (4) (2020), https://doi.org/10.1002/admt.201900552.
[90] H. Chang, S.W.T. Chew, M. Zheng, D.C.S. Lio, C. Wiraja, Y. Mei, X. Ning, M. Cui, A. Than, P. Shi, D. Wang, K. Pu, P. Chen, H. Liu, C. Xu, Cryomicroneedles for transdermal cell delivery, Nat. Biomed. Eng. 5 (9) (2021) 1008–1018, https://doi.org/10.1038/s41551-021-00720-1.
[91] J.V. Kim, J.B. Latouche, I. Riviere, M. Sadelain, The ABCs of artificial antigen presentation, Nat. Biotechnol. 22 (4) (2004) 403–410, https://doi.org/10.1038/nbt955.
[92] Y. Ye, C. Wang, X. Zhang, Q. Hu, Y. Zhang, Q. Liu, D. Wen, J. Milligan, A. Bellotti, L. Huang, G. Dotti, Z. Gu, A melanin-mediated cancer immunotherapy patch, Sci. Immunol. 2 (17) (2017), eaan5692, https://doi.org/10.1126/sciimmunol.aan5692.
[93] Y. Hu, B. Xu, J. Xu, D. Shou, E. Liu, J. Gao, W. Liang, Y. Huang, Microneedle-assisted dendritic cell-targeted nanoparticles for transcutaneous DNA immunization, Polym. Chem. 6 (3) (2015) 373–379, https://doi.org/10.1039/c4py01394h.
[94] D. Huu Thuy Trang, Y. Yin, T. Thambi, N. Thanh Loc, V.H.G. Phan, M.S. Lee, J. E. Lee, J. Kim, J.H. Jeong, D.S. Lee, Smart vaccine delivery based on microneedle arrays decorated with ultra-pH-responsive copolymers for cancer immunotherapy, Biomaterials. 185 (2018) 13–24, https://doi.org/10.1016/j.biomaterials.2018.09.008.
[95] H.T.T. Duong, Y. Yin, T. Thambi, B.S. Kim, J.H. Jeong, D.S. Lee, Highly potent intradermal vaccination by an array of dissolving microneedle polypeptide

cocktails for cancer immunotherapy, J. Mater. Chem. B 8 (6) (2020) 1171–1181, https://doi.org/10.1039/c9tb02175b.
[96] A.A. Murray, M.R. Sheen, F.A. Veliz, S.N. Fiering, N.F. Steinmetz, In situ vaccination of tumors using plant viral nanoparticles, Methods Mol. Biol. (Clifton, N.J.) 2000 (2019) 111–124, https://doi.org/10.1007/978-1-4939-9516-5_10.
[97] C.E. Boone, C. Wang, M.A. Lopez-Ramirez, V. Beiss, S. Shukla, P.L. Chariou, D. Kupor, R. Rueda, J. Wang, N.F. Steinmetz, Active microneedle Administration of Plant Virus Nanoparticles for Cancer in situ vaccination improves immunotherapeutic efficacy, Acs Appl. Nano Mater. 3 (8) (2020) 8037–8051, https://doi.org/10.1021/acsanm.0c01506.
[98] A. Mohammadpour, M. Derakhshan, H. Darabi, P. Hedayat, M. Momeni, Melanoma: where we are and where we go, J. Cell. Physiol. 234 (4) (2019) 3307–3320, https://doi.org/10.1002/jcp.27286.
[99] B.-P. Jiang, L. Zhang, X.-L. Guo, X.-C. Shen, Y. Wang, Y. Zhu, H. Liang, Poly(N-phenylglycine)-based nanoparticles as highly effective and targeted near-infrared Photothermal therapy/photodynamic therapeutic agents for malignant melanoma, Small. 13 (8) (2017), https://doi.org/10.1002/smll.201602496.
[100] S. Wei, G. Quan, C. Lu, X. Pan, C. Wu, Dissolving microneedles integrated with pH-responsive micelles containing AIEgen with ultra-photostability for enhancing melanoma photothermal therapy, Biomater. Sci. 8 (20) (2020) 5739–5750, https://doi.org/10.1039/d0bm00914h.
[101] X. Li, J.F. Lovell, J. Yoon, X. Chen, Clinical development and potential of photothermal and photodynamic therapies for cancer, Nat. Rev. Clin. Oncol. 17 (11) (2020) 657–674, https://doi.org/10.1038/s41571-020-0410-2.
[102] A.K. Jain, C.H. Lee, H.S. Gill, 5-Aminolevulinic acid coated microneedles for photodynamic therapy of skin tumors, J. Control. Release 239 (2016) 72–81, https://doi.org/10.1016/j.jconrel.2016.08.015.
[103] Q. Bian, L. Huang, Y. Xu, R. Wang, Y. Gu, A. Yuan, X. Ma, J. Hu, Y. Rao, D. Xu, H. Wang, J. Gao, A facile low-dose photosensitizer-incorporated dissolving microneedles-based composite system for eliciting antitumor immunity and the Abscopal effect, ACS Nano 15 (12) (2021) 19468–19479, https://doi.org/10.1021/acsnano.1c06225.
[104] M.-K. Zhang, C.-X. Li, S.-B. Wang, T. Liu, X.-L. Song, X.-Q. Yang, J. Feng, X.-Z. Zhang, Tumor starvation induced spatiotemporal control over chemotherapy for synergistic therapy, Small. 14 (50) (2018), e1803602, https://doi.org/10.1002/smll.201803602.
[105] Y. Zeng, H. Zhou, J. Ding, W. Zhou, Cell membrane inspired nano-shell enabling long-acting glucose oxidase for melanoma starvation therapy via microneedles-based percutaneous delivery, Theranostics. 11 (17) (2021) 8270–8282, https://doi.org/10.7150/thno.60758.
[106] W. Zhang, Z.Y. Guo, D.Q. Huang, Z.M. Liu, X. Guo, H.Q. Zhong, Synergistic effect of chemo-photothermal therapy using PEGylated graphene oxide, Biomaterials. 32 (33) (2011) 8555–8561, https://doi.org/10.1016/j.biomaterials.2011.07.071.
[107] L. Dong, Y. Li, Z. Li, N. Xu, P. Liu, H. Du, Y. Zhang, Y. Huang, J. Zhu, G. Ren, J. Xie, K. Wang, Y. Zhou, C. Shen, J. Zhu, J. Tao, Au Nanocage-strengthened dissolving microneedles for chemo-Photothermal combined therapy of superficial skin tumors, ACS Appl. Mater. Interfaces 10 (11) (2018) 9247–9256, https://doi.org/10.1021/acsami.7b18293.
[108] G. Song, G. Jiang, T. Liu, X. Zhang, Z. Zeng, R. Wang, P. Li, Y. Yang, Separable microneedles for synergistic chemo-Photothermal therapy against superficial skin tumors, Acs Biomater. Sci. Eng. 6 (7) (2020) 4116–4125, https://doi.org/10.1021/acsbiomaterials.0c00793.
[109] Y. Hao, Y. Chen, X. He, F. Yang, R. Han, C. Yang, W. Li, Z. Qian, Near-infrared responsive 5-fluorouracil and indocyanine green loaded MPEG-PCL nanoparticle integrated with dissolvable microneedle for skin cancer therapy, Bioact. Mater. 5 (3) (2020) 542–552, https://doi.org/10.1016/j.bioactmat.2020.04.002.
[110] Y. Zhao, Y. Zhou, D. Yang, X. Gao, T. Wen, J. Fu, X. Wen, G. Quan, X. Pan, C. Wu, Intelligent and spatiotemporal drug release based on multifunctional nanoparticle-integrated dissolving microneedle system for synergetic chemo-photothermal therapy to eradicate melanoma, Acta Biomater. 135 (2021) 164–178, https://doi.org/10.1016/j.actbio.2021.09.009.
[111] D.J. Zhao, H.Y. Zhang, S.F. Yang, W.X. He, Y.X. Luan, Redox-sensitive mPEG-SS-PTX/TPGS mixed micelles: an efficient drug delivery system for overcoming multidrug resistance, Int. J. Pharm. 515 (1–2) (2016) 281–292, https://doi.org/10.1016/j.ijpharm.2016.10.029.
[112] X. Wang, J. Li, Y.Q. Wang, K.J. Cho, G. Kim, A. Gjyrezi, L. Koenig, P. Giannakakou, H.J.C. Shin, M. Tighiouart, S.M. Nie, Z. Chen, D.M. Shin, HFT-T, a targeting nanoparticle, enhances specific delivery of paclitaxel to folate receptor-positive tumors, ACS Nano 3 (10) (2009) 3165–3174, https://doi.org/10.1021/nn900649v.
[113] T. Peng, Y. Huang, X. Feng, C. Zhu, X. Ma, X. Wang, X. Bai, X. Pan, C. Wu, Dissolving microneedles loading TPGS biphasic functionalized PLGA nanoparticles for efficient chemo-Photothermal combined therapy of melanoma, Adv. Ther. 3 (6) (2020), https://doi.org/10.1002/adtp.201900190.
[114] W. Qin, G. Quan, Y. Sun, M. Chen, P. Yang, D. Feng, T. Wen, X. Hu, X. Pan, C. Wu, Dissolving microneedles with spatiotemporally controlled pulsatile release Nanosystem for synergistic chemo-photothermal therapy of melanoma, Theranostics. 10 (18) (2020) 8179–8196, https://doi.org/10.7150/thno.44194.
[115] Y. Sun, M. Chen, D. Yang, W. Qin, G. Quan, C. Wu, X. Pan, Self-assembly nanomicelle-microneedle patches with enhanced tumor penetration for superior chemo-photothermal therapy, Nano Res. 15 (3) (2021) 2335–2346, https://doi.org/10.1007/s12274-021-3817-x.
[116] M. Chen, G. Quan, T. Wen, P. Yang, W. Qin, H. Mai, Y. Sun, C. Lu, X. Pan, C. Wu, Cold to hot: binary cooperative microneedle Array-amplified Photoimmunotherapy for eliciting antitumor immunity and the Abscopal effect, ACS Appl. Mater. Interfaces 12 (29) (2020) 32259–32269, https://doi.org/10.1021/acsami.0c05090.
[117] T. He, Y. Luo, Q. Zhang, Z. Men, T. Su, L. Fan, H. Chen, T. Shen, Hyalase-mediated Cascade degradation of a matrix barrier and immune cell penetration by a Photothermal microneedle for efficient anticancer therapy, ACS Appl. Mater. Interfaces 13 (23) (2021) 26790–26799, https://doi.org/10.1021/acsami.1c06725.
[118] P. Yang, M. Chen, W. Qin, C. Shi, X. Bai, G. Quan, X. Pan, C. Wu, Effective Photothermal therapy mediated by Indocyanine Green nanoparticle tip-loaded microneedles to enhance checkpoint inhibitor immunotherapy for melanoma treatment, Acs Appl. Nano Mater. 4 (6) (2021) 5921–5931, https://doi.org/10.1021/acsanm.1c00832.
[119] Z. Yu, Y. Hu, Y. Sun, T. Sun, Chemodynamic therapy combined with multifunctional nanomaterials and their applications in tumor treatment, Chem. Eur. J. 27 (56) (2021) 13953–13960, https://doi.org/10.1002/chem.202101514.
[120] C.H. Liu, Y. Cao, Y.R. Cheng, D.D. Wang, T.L. Xu, L. Su, X.J. Zhang, H.F. Dong, An open source and reduce expenditure ROS generation strategy for chemodynamic/photodynamic synergistic therapy, Nat. Commun. 11 (1) (2020) 1735, https://doi.org/10.1038/s41467-020-15591-4.
[121] L. Ruan, G. Song, X. Zhang, T. Liu, Y. Sun, J. Zhu, Z. Zeng, G. Jiang, Transdermal delivery of multifunctional CaO2@Mn-PDA nanoformulations by microneedles for NIR-induced synergistic therapy against skin melanoma, Biomater. Sci. 9 (20) (2021) 6830–6841, https://doi.org/10.1039/d1bm01117k.
[122] G. Song, Y. Sun, T. Liu, X. Zhang, Z. Zeng, R. Wang, P. Li, C. Li, G. Jiang, Transdermal delivery of cu-doped polydopamine using microneedles for photothermal and chemodynamic synergistic therapy against skin melanoma, Chem. Eng. J. 426 (2021), 130790, https://doi.org/10.1016/j.cej.2021.130790.
[123] H.P. Tham, K. Xu, W.Q. Lim, H. Chen, M. Zheng, T.G.S. Thng, S.S. Venkatraman, C. Xu, Y. Zhao, Microneedle-assisted topical delivery of Photodynamically active mesoporous formulation for combination therapy of deep-seated melanoma, ACS Nano 12 (12) (2018) 11936–11948, https://doi.org/10.1021/acsnano.8b03007.
[124] Z. Zhou, J. Pang, X. Wu, W. Wu, X. Chen, M. Kong, Reverse immune suppressive microenvironment in tumor draining lymph nodes to enhance anti-PD1 immunotherapy via nanovaccine complexed microneedle, Nano Res. 13 (6) (2020) 1509–1518, https://doi.org/10.1007/s12274-020-2737-5.
[125] S. Dinda, S. Sarkar, P.K. Das, Glucose oxidase mediated targeted cancer-starving therapy by biotinylated self-assembled vesicles, Chem. Commun. 54 (71) (2018) 9929–9932, https://doi.org/10.1039/c8cc03599g.
[126] Y. Zhou, B. Niu, Y. Zhao, J. Fu, T. Wen, K. Liao, G. Quan, X. Pan, C. Wu, Multifunctional nanoreactors-integrated microneedles for cascade reaction-enhanced cancer therapy, J. Control. Release 339 (2021) 335–349, https://doi.org/10.1016/j.jconrel.2021.09.041.
[127] H. Kobayashi, P.L. Choyke, Near-infrared Photoimmunotherapy of Cancer, Acc. Chem. Res. 52 (8) (2019) 2332–2339, https://doi.org/10.1021/acs.accounts.9b00273.
[128] Y. Ma, L. Galluzzi, L. Zitvogel, G. Kroemer, Autophagy and cellular immune responses, Immunity. 39 (2) (2013) 211–227, https://doi.org/10.1016/j.immuni.2013.07.017.
[129] N.S. Katheder, R. Khezri, F. O'Farrell, S.W. Schultz, A. Jain, M.M. Rahman, K. O. Schink, T.A. Theodossiou, T. Johansen, G. Juhasz, D. Bilder, A. Brech, H. Stenmark, T.E. Rusten, Microenvironmental autophagy promotes tumour growth, Nature. 541 (7637) (2017) 417–420, https://doi.org/10.1038/nature20815.
[130] M. Chen, D. Yang, Y. Sun, T. Liu, W. Wang, J. Fu, Q. Wang, X. Bai, G. Quan, X. Pan, C. Wu, In situ self-assembly Nanomicelle microneedles for enhanced Photoimmunotherapy via autophagy regulation strategy, ACS Nano 15 (2) (2021) 3387–3401, https://doi.org/10.1021/acsnano.0c10396.