REVIEW

EXPERIMENTAL ONCOLOGY

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N. KHRANOVSKA [1,*], O. SKACHKOVA [1], O. GORBACH [1], I. SEMCHUK [1], Yu. SHVETS [2], I. KOMAROV [2]

[1] Nonprofit organization "National Cancer Institute", Kyiv, Ukraine
[2] Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

* Correspondence: Email: nkhranovska@ukr.net

ANTICANCER IMMUNOGENIC POTENTIAL OF ONCOLYTIC PEPTIDES: RECENT ADVANCES AND NEW PROSPECTS

Oncolytic peptides are derived from natural host defense peptides/antimicrobial peptides produced in a wide variety of life forms. Over the past two decades, they have attracted much attention in both basic research and clinical applications. Oncolytic peptides were expected to act primarily on tumor cells and also trigger the immunogenic cell death. Their ability in the tumor microenvironment remodeling and potentiating the anticancer immunity has long been ignored. Despite the promising results, clinical application of oncolytic peptides is still hindered by their unsatisfactory bioactivity and toxicity to normal cells. To ensure safer therapy, various approaches are being developed. The idea of the Ukrainian research group was to equip peptide molecules with a "molecular photoswitch" — a diarylethene fragment capable of photoisomerization, allowing for the localized photoactivation of peptides within tumors reducing side effects. Such oncolytic peptides that may induce the membrane lysis-mediated cancer cell death and subsequent anticancer immune responses in combination with the low toxicity to normal cells have provided a new paradigm for cancer therapy. This review gives an overview of the broad effects and perspectives of oncolytic peptides in anticancer immunity highlighting the potential issues related to the use of oncolytic peptides in cancer immunotherapy. We summarize the current status of research on peptide-based tumor immunotherapy in combination with other therapies including immune checkpoint inhibitors, chemotherapy, and targeted therapy.

Keywords: oncolytic peptides, immunogenic cell death, anticancer immunity, molecular photoswitch.

At present, different forms of non-viral oncolysis have been characterized such as hyperthermic methods, cryotherapy, electrochemotherapy, photodynamic therapy, which induces apoptosis of tumor cells by inducing large amounts of reactive singlet oxygen using photosensitizing agents and high-intensity light, local injection of chemical agents causing the death of tumor cells (transarterial chemoembolization, radioembolization) and the use of oncolytic peptides. The latter is very promising for immunotherapy since, like oncolytic virotherapy, it causes cell lysis and potentiates antitumor immunity [1]. This review focuses on the antitumor properties of oncolytic peptides, their potential for cancer immunity strengthening, and the problems and prospects for their harnessing in antitumor immunotherapy.

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Origin and antitumor properties of oncolytic peptides

Natural products and their structural analogues historically made a major contribution to pharmacotherapy, especially in the treatment of cancer and infectious diseases. This is due to their particular biological functions: natural products are structurally "optimized" by evolution to serve as natural host defense mechanisms, which explains their high potential to fight infectious diseases and cancer. For example, in the area of cancer treatment, in the period from 1981 to the end of 2019, of the 185 small molecules approved, 156 (84.3%) are non-synthetic, with 76 of them (41%) actually being either natural products or directly derived therefrom [2].

Over the past two decades, much attention has been focused on the development of a new class of antitumor agents called oncolytic peptides. Peptides are unique pharmaceutical compounds composed of amino acids with molecular weights between proteins and small molecules. The research community has gradually confirmed many advantages of peptides over small molecules and biological agents, including lower production cost, higher tumor tissue penetration, lower immunogenicity and toxicity, easier binding to the targets, more flexible sequence selectivity, and more significant efficacy [3]. In addition, technologies for their production that are being actively developed can further optimize the effects of oncolytic peptides. Oncolytic peptides are derived from natural host defense peptides or antimicrobial peptides produced by a range of life forms [4].

More than 20,000 antimicrobial peptides have been discovered up to now; some of them have significant oncolytic properties (http://crdd.osdd.net/raghava/cancerppd/index.php). Such peptides as gymnopeptide B (isolated from mushrooms [5]), didemnins (from marine invertebrates [6], and viequeamide A (from cyanobacteria [7]) are considered very promising anticancer agents of natural origin or suitable as templates. They are extremely cytotoxic and induce lysis of cancer cells of any type, which is known to be important for eliciting an immune response. For example, gymnopeptide B demonstrated exceptional cytotoxic activity (IC50 in the nanomolar range) against various cancer cells including those resistant to anticancer agents. Peptides [D]-K3H3L9, LTX-315, LL37, LTX-401, pardaxin, RT53, AMP, CSP32, DTT-205, and DTT-304 also exert a pronounced cytotoxicity when injected directly into the targeted lesions [1].

Cationic antimicrobial peptides (CAPs) are natural molecules that are a part of the biological defense against a wide range of microorganisms, parasites, fungi, and viruses. They are found in many bacterial and eukaryotic cells (as part of the innate immune system) [8]. Being cationic and amphipathic, CAPs are capable to interact with lipid membranes. Such a mode of action has made them in demand for the research in the therapeutic field [9]. Membrane pore-forming CAPs bind to cell membranes and spontaneously assemble in a lipid bilayer as a channel or pore-like structure, though not all of them possess cytolytic activity. The well-known natural examples of CAPs are gramicidin, colistin, melittin, maculatin, and alamethicin [10].

The antitumor effects of CAPs are still under investigation, but several peptides have already demonstrated a cytotoxic potential against a wide range of malignantly transformed cells. Anticancer peptides of this group (mostly in the range of 10—60 amino acid residues) exhibit a membranolytic effect or bind to the intracellular targets of malignant cells. The onset of antitumor activity is determined by their binding to the cell due to the electrostatic interaction between the anionic cell membrane and the positively charged peptide and leads to the opening of pores, destabilization and destruction of the membrane, and cell death [11].

To date, the identification and modification of structural parameters of anticancer peptides critical for their antitumor activity have led to the discovery of safer peptides with increased activity, a well-known example of which is a derivative of bovine lactoferrin, *de novo* designed membrane-active cationic amphilytic nonapeptide (9-mer cationic peptide) LTX-315 (trade name OncoporeTM). By forming pores and disrupting cytoplasmic membranes, as well as by damaging mitochondria, LTX-315 promotes immunogenic cell death, which is accompanied by the release of damage-signaling molecules and active involvement of the immune system in the elimination of the malignantly transformed cells. LTX-315 was found to induce the BAX/BAK1-regulated cell death close to the necrotic phenotype with-

out involving the caspase-3-dependent apoptotic pathway [12, 13]. Tumor cell lysis is accompanied by the simultaneous release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs), such as high mobility group box protein 1 (HMGB1), which combine to enhance dendritic cell TAA uptake and their presentation to T cells [4].

Local immunotherapies, such as the intratumoral injection of oncolytic compounds, aim at the restoration and enhancement of systemic anticancer immune responses. LTX-315 is a first-in-class clinically evaluated oncolytic peptide assessed for local immunotherapy [14, 15]. It showed high efficacy against both drug-resistant and drug-sensitive cancer cells with lower off-target toxicity. This peptide possesses a high ability to bind to plasma proteins followed by the formation of non-toxic metabolites, the half-life of which is 160 minutes. Moreover, LTX-315 has a relatively low ability to inhibit CYP450 enzymes. Therefore, LTX-315 has displayed a superior anticancer activity and was assessed as a very promising compound for intratumoral administration [15].

The antiangiogenic 24-mer peptide chemokinostatin-1 (CKS1) derived from the CXCL1 chemokine also acts as an oncolytic peptide due to its structural and physical properties. It exhibits minimal toxicity for normal cells and induces both necrotic and apoptotic death for tumor cells. CKS1 actively destroys the membranes of tumor cells with subsequent activation of apoptosis mechanisms. At the same time, various immunogenic molecules are released from tumor cells treated with CKS1 indicating its ICD-inducing ability. There is evidence that CKS1 effectively suppresses not only the growth of tumor cells *in vitro* but has a pronounced antitumor effect in animal models *in vivo*. Overall, it can be concluded that CKS1 is a unique oncolytic peptide that exhibits antiangiogenic effects and has a therapeutic potential for cancer treatment [16]. Oncolytic peptides are characterized by different affinities for different cell membranes, which determines their tropism toward malignant cells. For example, peptide LTX-315 has an affinity for plasma and mitochondrial membranes, pardaxin — for plasma membranes and membranes of the endoplasmic reticulum, and DTT-205 and DTT-304 — for lysosome membranes [1].

Thus, a wide range of action, in particular, the antimicrobial and antitumor potential of oncolytic peptides has made them in demand for research in the therapeutic field [9, 17]. However, due to their unsatisfactory bioactivity and toxicity to normal cells, clinical application of oncolytic peptides is still hindered and their potential as a therapeutic agent for cancer has not been widely evaluated [18]. Reducing the toxicity and optimizing the structures are urgently needed for their effective application in cancer clinics [19]. The design and construction of effective oncolytic peptides require an understanding of the mechanisms of their effects.

Antitumor immunity induced by oncolytic peptides

It is now accepted that immunostimulation is one of the most important mechanisms of anticancer action of many widely used chemotherapeutic agents [20]. This statement fully applies to oncolytic peptides, which are capable to induce ICD due to the release of various types of DAMPs, such as high mobility group B1 (HMGB1), ATP, calreticulin, and annexin A [1]. DAMPs bind to specific receptors on antigen-presenting cells, promoting their maturation, uptake, and TAA presentation, which leads to the activation of tumor-targeting T cells and effective immune response [21—23].

The ability of oncolytic peptides to induce ICD in tumor cells and thus activate antitumor immunity has been demonstrated both *in vitro* and *in vivo* in experimental tumor models and cancer cell lines. In a series of studies, LTX-315 has been shown to exert a broad spectrum of activity and induce ICD in many types of solid tumors, such as subcutaneous sarcomas, pancreatic cancer, B16 melanoma, and MCA205 fibrosarcoma [4]. In addition to DAMPs (HMGB1 and ATP), LTX-315 can also trigger the secretion of proinflammatory cytokines such as IL-1β, IL-6, and IL-18. LTX-315 is a highly effective substance, the intratumoral injection of which promotes the infiltration of solid tumors by immunocompetent cells and the remodeling of an immunosuppressive tumor microenvironment into an antitumor immune microenvironment [1, 13]. It is also reported that RT53 and HNP1-3 have similar effects, namely, they activate local antitumor immune re-

sponses, inducing ICD in melanoma and soft tissue sarcoma cells, respectively. Moreover, injection of LTX-315 not only stimulates tumor infiltration by T cells and causes complete tumor regression but also protects mice from the rechallenge with the same tumor [1]. Thus, LTX-315 induces cell death through dual effects of cytolysis and immunogenicity and causes the disassembly of plasma membrane and cytoplasmic organelles in cancer cells via the BAX/BAK-regulated mitochondrial membrane permeability [13, 24].

It has been shown that although intratumoral injection of LTX-302 damages cancer cell membranes and causes extensive tumor necrosis in both nude and wild-type mice, the therapeutic effect in nude mice was insufficient [25]. Tumor-rechallenge experiments on wild-type mice have revealed that LTX-302 injection not only causes local effects but also boosts a strong long-term systemic antitumor immune response. Despite the fact that the main antitumor mechanism of oncolytic peptides is the direct lysis of tumor cells and their ICD, the effective development and regulation of antitumor immunity depends on the involvement of various immunocompetent cells and their interaction. In addition to the induction of ICD, the injection of oncolytic peptides leads to the release of proinflammatory cytokines and the attraction, differentiation, and maturation of proinflammatory immune cells. In particular, the intratumoral administration of LTX-315 in breast tumor models leads to the remodeling of the tumor immune microenvironment and activation of NK cells [1], CSP32 regulates the polarization of murine macrophages toward M1 macrophages [26], and LL37 administration triggers the activation and maturation of dendritic cells [27].

The local administration of oncolytic peptides promotes changes in the tumor microenvironment toward the immunoactive profile through the inhibition of immunosuppressive molecules, depletion of regulatory T cells (Treg), myeloid suppressor cells (MDSC), and regulatory B cells [1]. This was demonstrated in the experimental studies of LTX-315 on mouse sarcoma models. The intratumoral administration of this peptide significantly reduced the accumulation of MDSCs and Tregs in the tumor microenvironment. In addition, it was revealed that administration of another oncolytic peptide, pardaxin, in a model of oral squamous cell carcinoma induces strong anticancer immunity by reducing the level of immunosuppressive PGE2. It is noteworthy that the immunotherapeutic potential of the most studied oncolytic peptide LTX-315 was validated in clinical trials. It has been shown that the intratumoral injection of LTX-315 not only promotes the activation of local immunity by increasing tumor infiltration by $CD8^+$ T lymphocytes but also increases the number of cytotoxic T cells in the peripheral blood of patients [4].

Oncolytic peptides offer a new therapeutic modality, and their membranolytic mode of action includes the release of DAMPs and tumor antigens from cancer cells resulting in the regression of solid tumors and systemic tumor specific immune responses. A range of evidence has been revealed that oncolytic peptides exert anticancer activity by activating systemic and local antitumor immunity promoting ICD of tumor cells and immune infiltration in tumors. Consequently, the development of oncolytic peptides into novel anticancer therapeutics is a promising immunotherapeutic strategy.

Strategies to reduce off-target toxicity of oncolytic peptides

We have already mentioned that the clinical application of oncolytic peptides is still hindered by significant non-specific cytotoxicity to normal cells, uncontrolled hemolytic activity, and unsatisfactory bioactivity. To overcome these limitations, strategies to obtain modified natural peptides analogs with superior properties are needed [28—31].

Modified analogs of natural products can be produced through a total chemical synthesis followed by chemical derivatization, through semisynthesis from natural products as a starting point for chemical modifications, and through the biosynthetic engineering using the producer organism to create analogs of natural products. As a result, oncolytic peptides that mimic synthetic amphiphilic cationic polymers (named oncolytic polymers) have been developed for cancer treatment [1]. It is known that the modifications of both the main and side chains of peptides can contribute to increasing their penetration into the target cells. The positive peptide charge is critical for electrostatic interactions; synthetic peptides LK-13 and IK-13 were created based on this principle [32].

As of today, thanks to the developments in this direction, more than 80 drugs based on peptides have been presented for the treatment of a wide range of diseases, including cancer, osteoporosis, and diabetes [33]. The use of photocontrolled bioactive compounds (we call these compounds "lumobiotics") is one of the new promising approaches to reducing excessive systemic toxicity and improving the spatio-temporal selectivity of potential anticancer drugs. The development of photocontrolled peptides gives a second chance to the drugs that have not passed the clinical stages of research because of their insufficient safety [34].

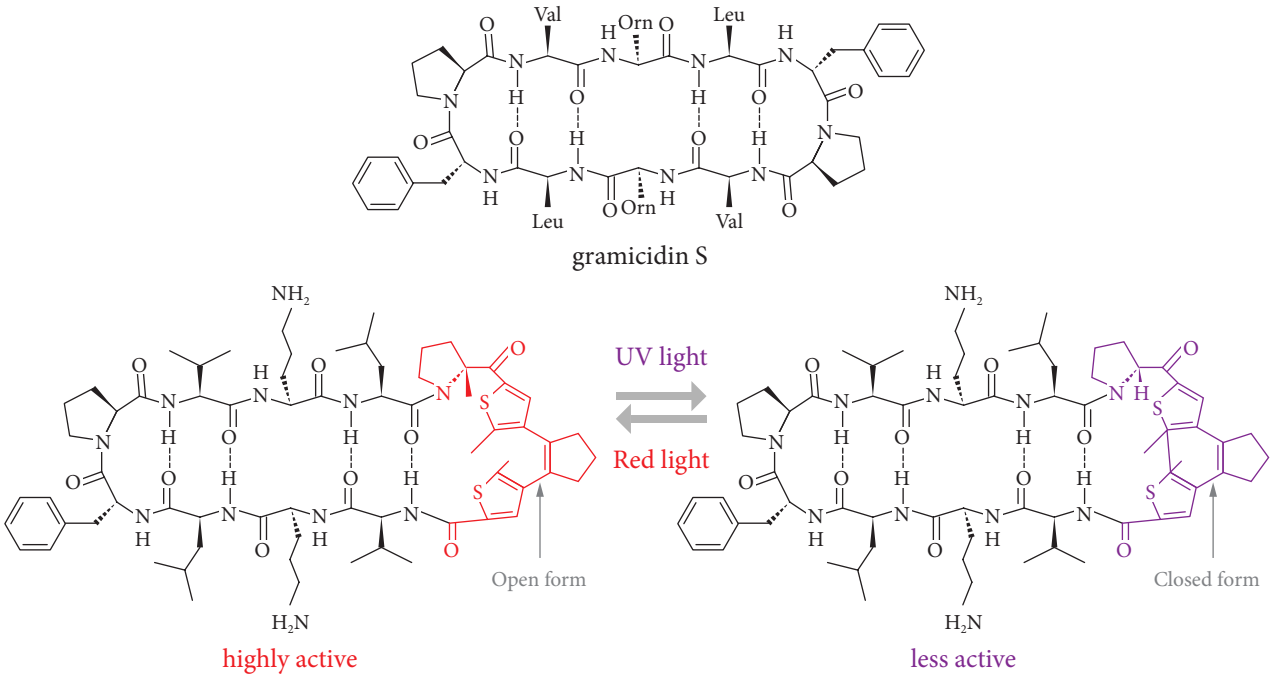
After several decades of research, it has become possible to achieve certain successes in this direction, which paves the way for the creation of a new generation of anticancer drugs [35]. Lumobiotics contain photoisomerizable fragments in their molecular framework. Consequently, they can exist in two photoisomeric forms (photoforms), interconvertible when exposed to light of different wavelengths. They are designed as less bioactive and less toxic in one photoform, becoming more active and attaining the desired level of biological activity when converted to another photoform. This approach is based on the principles of photodynamic therapy (PDT) that was introduced into clinical practice in the middle of the 20th century, mainly as an approach to cancer treatment [36]. Initially, PDT was aimed at the generation of reactive cytotoxic singlet oxygen by light with the participation of photosensitizers. A significant disadvantage of this therapeutic strategy is the dependence on oxygen, which requires high saturation of the tumor with oxygen. However, most solid neoplasms are characterized by a hypoxic microenvironment due to the active cell division and accelerated metabolic processes of malignant cells, which increases the risk of invasiveness, resistance, and metastasis and makes classical PDT less effective [37]. A promising direction of modern research is the development of oxygen-independent PDT based on the use of photocontrolled analogs of natural cytotoxic peptides (peptidomimetics) [38].

A typical approach to the photomodulation of cytotoxic biological substances with antitumor potential is "azologization" [39], where an azobenzene fragment capable of photoisomerization is incorporated into the peptide molecule. Similarly, such alternative types of photoswitches are used as spiropyrans, diarylethylenes, and indigoid switches [40].

The Ukrainian research group from the Faculty of Chemistry at the Taras Shevchenko National University of Kyiv together with researchers from the Karlsruhe Institute of Technology in Germany developed a novel technology enabling the control of peptide activity using light [41]. Initially, this idea was proposed with the aim of creating a new class of antimicrobial drugs — peptide antibiotics. Therefore, drug prototypes were created that can be easily activated ("turn on") to neutralize pathogenic bacteria and deactivated ("turn off") to avoid the destruction of beneficial representatives of healthy human body microbiota and other undesirable effects. To ensure a safer therapy, peptide molecules were equipped with a "molecular photoswitch" capable of photoisomerization, allowing for localized photoactivation of peptides in the target place along with reducing side effects. It was postulated that the administration of such substances in less active forms followed by the activation by light at the site of lesion, in particular local inflammation, tumor, etc, might be safer drug candidates than the original, non-photocontrollable analogs due to decreased toxicity.

The same methodology was applied to anticancer cytotoxic peptides, namely, analogs of the known antibiotic gramicidin S [42]. Gramicidin S is a cyclic decapeptide cationic peptide of seventy-year history. It displays antibiotic activity against both Gram-negative and Gram-positive bacteria by interacting with bacterial lipid bilayers [19 43]. More specifically, gramicidin is a pore-forming peptide that forms ion channels as a transmembrane dimer. However, its potential as an agent for cancer treatment has not been widely evaluated [18]. The elaborated photocontrolled gramicidin S derivative contains a photoswitch — a diarylethene fragment that undergoes reversible photoinduced transformations between the so-called red light-generated "ring-open" and UV-generated "ring-closed" photoforms, which, in turn, changes their biological activity. Using different light wavelengths, it is possible to switch between two photoforms of peptides: "off" with low activity and toxicity and "on" characterized by a high activity (Figure, compound LMB002).

S. Afonin and colleagues in both *in vitro* and *in vivo* experiments showed that the photocon-



Membranolytic peptide gramicidin S and its light-controllable analogs. The diarylethene-derived unit is colored (closed form in blue, open form in red)

trolled analogs are safe enough; they can be activated in tumors by red light with a significant antitumor effect [44]. The high cytotoxic activity of diarylethene-containing analogs of gramicidin S LMB002 has been shown in the experiments using the 2D (adherent) and 3D (spheroids) cell cultures of Lewis lung carcinoma (LLC), live tissue surrogates (pork meat mince), and an allograft cancer model (subcutaneous LLC) in immunocompetent mice. Additionally, this compound demonstrated efficient photoswitching at a depth of 1—1.5 cm in the model tissue [45].

It was shown that the "photoswitchable" cytolytic peptide LMB040 can reach a sufficiently high concentration in the tumor and, when photoconverted to a more active photoform, provides a cytotoxic effect. This study was conducted on a model of chemically induced hepatocellular carcinoma in immunocompetent rats. The use of a less toxic LMB040 form followed by photoconversion *in vivo* into a more toxic form led to an increase in the overall survival of animals with the development of a robust immune response compared to control animals [46]. However, the immune response to therapy with such peptides has never been studied.

Thus, such photocontrol is capable of increasing the safety of the therapy since the cytotoxicity of peptides can be turned on only in tumor tissues by the action of harmless red light (delivered to tumors by optical fiber), avoiding affecting healthy tissues. Therefore, they can be administered to patients in a safe, inactive, and non-toxic form. The activation of photocontrolled drugs can be carried out exclusively in the affected areas to protect the patient's normal tissues from the toxic impact, thus reducing unwanted side effects.

Combination therapy

The possibility of a synergistic effect of oncolytic peptides and chemotherapy drugs was shown back in 1992 when it was demonstrated that magainin analogs enhance the antitumor effect of cisplatin, etoposide, and doxorubicin against SCLC cells; cecropin A demonstrates a synergistic effect with S-fluorouracil and cytarabine in leukemia cells; mastoparan, a cationic peptide derived from wasp venom, acts synergistically with etoposide and gemcitabine; nisin, a membrane-lytic peptide produced by *Lactococcus lactis*, has a synergistic antitumor effect against MCF-7 cells when combined with doxorubicin [4]; pardaxin, an AMP peptide isolated from the marine fish species *Pardachirus marmoratus*, may provide a synergistic effect with 5-fluorouracil in the treatment of oral carcinoma

in hamsters [4]. In addition, it is stated that the combined use of oncolytic peptides and chemotherapy drugs may be potentially effective in overcoming drug resistance.

As we have already mentioned, one of the most promising and studied oncolytic peptide LTX-315 has the ability to reactivate the tumor immune microenvironment, promoting immune suppressive cells depletion with a simultaneous abundant infiltration and accumulation of polyfunctional T cells within tumor tissue. In turn, it was found that the significant decrease in the number of Tregs leads to a decrease in the level of PD-1 expression in effector T cells, which may sensitize the tumor response to PD-1/PD-L1 blockade during treatment with LTX-315. *In vitro* studies have shown that LTX-315 has an ability to inhibit the PD-L1 expression via ATP11B [1]. ATP11B interacts with PD-L1 in a CMTM6-dependent manner. In pancreatic cancer, downregulation of ATP11B causes the PD-L1 depletion through the lysosomal degradation mediated by CMTM6. The synergistic effect of LTX-315 with anti-PD-1/PD-L1 targeted therapy on the tumor growth was confirmed in tumor models. In pioneering clinical study [8], it was shown that LTX-315 is highly efficient against cancer at the metastatic stages in combination with checkpoint inhibitors [47].

Such depletion of immune suppressive cells in tumor microenvironment and increased T cells infiltration contribute to a better response to another checkpoint inhibitor anti-CTLA-4. Oncolytic peptides demonstrate synergistic or additive effects in cancer therapy when combined with other chemotherapeutic agents.

Camilio et al. [48] found that the intratumoral administration of LTX-315 significantly improved the therapeutic efficacy of intravenous doxorubicin combined with surgery. At the same time, the survival rate of experimental animals increased by 60%—97% compared to controls [1]. The significant antitumor effect of the combined use of doxorubicin and LTX-315 was accompanied by the activation of the antitumor immune response and increase in the infiltration of $CD4^+$ and $CD8^+$ T cells in tumor tissues. It should be noted that the administration schedule and dosage of the drugs need further optimization, since LTX-315 was administered intratumorally while doxorubicin — intravenously, and in such conditions, it is difficult to control precisely the delivery time of drugs toward the tumor and determine their actual ratio within the tumor.

Yang et al. [49] used a peptide mixture containing a melittin hybrid (melittin-RADA32) to create a hydrogel that also included doxorubicin. The injection of such peptide-based hydrogel had a significant antitumor effect in some localized tumors and caused a decrease in the manifestations of immunosuppression and the development of persistent systemic immunological memory. Chen's group developed the cationic peptide PAH6 for use as a carrier for doxorubicin [50]. The administration of such a construct makes it possible to reduce the IC50 of doxorubicin to achieve a strong inhibitory effect in the monolayer of A-549 cells and to improve its penetration into A-549 spheroids.

Li et al. [51] used the LTX-315 peptide to obtain the lysate of 4T1 tumor cells and developed an autologous antitumor vaccine based on the obtained lysate. They then designed a hydrogel to co-deliver the vaccine and dexamethasone. It was found that although the injection of the antitumor vaccine can increase the level of cytotoxic T cells in the remaining tumor tissue after surgery, the existing immunosuppressive cells and cytokines interfere with the functions of $CD8^+$ T cells. Therefore, the combination of dexamethasone and an autologous tumor vaccine not only alleviates the inflammatory/immunosuppressive microenvironment but also disrupts the premetastatic niche, thereby reducing the risk of postoperative relapse and metastasis.

Conclusion remarks

Oncolytic peptides are among the most promising chemical oncolytic compounds derived from natural products. Some of them demonstrate toxicity against eukaryotic cells and have been trialed for applications in clinical oncology. Besides acting on the tumor cells, oncolytic peptides also trigger ICD and promote positive immune regulation. The local injection of oncolytic peptides is able to turn a "cold" tumor microenvironment into a "hot" one promoting the immune infiltration of tumor [52]. Nevertheless, it should be noted that the mechanisms underlying the ability of oncolytic peptides to reprogram the immune microenvironment are still under investigation.

Among the most promising oncolytic peptides, LTX-315 is the most investigated compound due to its pronounced effect on triggering tumor growth inhibition followed by anticancer immunity. It is currently tested in clinical phase I/IIa trials [53]. However, despite the encouraging results in the use of oncolytic peptides in preclinical models, the results of their clinical use are still unsatisfactory, and their potential as activators of the immune system against cancer remains unexplored.

Since the main method of delivery of oncolytic peptides is an intratumoral injection, their widespread use in tumors with deep location is practically impossible. In addition, the non-specific cytotoxicity of these peptides is a serious limitation for their clinical use. To overcome these limitations, novel strategies to obtain modified natural peptides analogs with superior properties are required.

One such a promising strategy is to combine the cytotoxic properties and immunogenic potential of natural anticancer peptides with their photocontrol, which is achieved by incorporating a diarylethene fragment capable of photoisomerizing into their molecules. Such a photocontrol will increase the safety of therapy since the cytotoxicity of peptides can be "turned on" only in tumor tissues by the action of harmless light, practically without affecting healthy tissues.

Currently, cancer immunotherapy based on oncolytic peptides is in the early stages of clinical trials. Further preclinical and clinical studies are needed to improve their efficacy, reduce off-target toxicity, and expand the indications for their clinical use.

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Н. Храновська [1], О. Скачкова [1], О. Горбач [1], І. Семчук [1], Ю. Швець [2], І. Комаров [2]
[1] Державне некомерційне підприємство «Національний інститут раку», Київ, Україна
[2] Київський національний університет імені Тараса Шевченка, Київ, Україна

ПРОТИПУХЛИННИЙ ІМУНОГЕННИЙ ПОТЕНЦІАЛ ОНКОЛІТИЧНИХ ПЕПТИДІВ: ОСТАННІ ДОСЯГНЕННЯ ТА НОВІ ПЕРСПЕКТИВИ

Онколітичні пептиди отримують із природних захисних пептидів хазяїна/антимікробних пептидів, які виробляються в різноманітних формах життя. За останні два десятиліття ці пептиди широко досліджувалися як в експериментальних, так і клінічних умовах. Очікувалося, що вони діятимуть переважно на пухлинні клітини, а також спровокують імуногенну загибель цих клітин. Їхня здатність ремоделювати та потенціювати протипухлинний імунітет у мікрооточенні пухлини довгий час ігнорувалась. Незважаючи на багатообіцяльні результати, клінічному застосуванню онколітичних пептидів все ще перешкоджає їхня незадовільна біоактивність і токсичність для нормальних клітин. Для забезпечення більш безпечної терапії розробляються різні підходи. Ідея української дослідницької групи полягала в тому, щоб оснастити молекули пептидів «молекулярним фотоперемикачем» — діарилетеновим фрагментом, здатним до фотоізомеризації, що дозволяє локалізовану фотоактивацію пептидів у пухлинах, зменшуючи побічні ефекти на нормальні клітини. Такі онколітичні пептиди, які можуть індукувати загибель ракових клітин, опосередковану лізисом мембран, і наступні протипухлинні імунні відповіді в поєднанні з низькою токсичністю для нормальних клітин, забезпечили нову парадигму терапії раку. Цей огляд містить аналіз механізмів дії онколітичних пептидів на протипухлинний імунітет, висвітлює потенційні проблеми та напрями застосування онколітичних пептидів в імунотерапії раку. Ми підсумовуємо поточний стан досліджень в області імунотерапії пухлин на основі пептидів у поєднанні з іншими методами лікування, включаючи інгібітори імунних контрольних точок, хіміотерапію і таргетну терапію.

Ключові слова: онколітичні пептиди; імуногенна загибель клітин; протипухлинний імунітет; молекулярний фотоперемикач.