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Research Status and Progress of Light-Activated Antibody-Drug Conjugates

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Abstract: Antibody-drug conjugates (ADCs) combine the specific recognition capability of antibodies with the potent cytotoxicity of chemotherapeutic agents to achieve precise tumor cell killing. This cancer therapy holds great promise and has garnered widespread attention, having achieved breakthrough progress in the treatment of various malignancies, including breast cancer and gastric cancer. The therapeutic efficacy of ADCs depends on their ability to localize toxic molecules within the tumor microenvironment while maintaining stability in the circulatory system or other normal tissues. Photoactivated ADCs represent a targeted cancer therapy strategy characterized by light-triggered activation, which transfers the cleavage of ADCs to the extracellular environment rather than relying on traditional lysosomal processing. This approach reduces dependence on intracellular endocytosis efficiency and tumor-specific processing variations, offering novel options for targeted cancer therapy. This article primarily reviews the technical pathways and current development status of photoactivated ADCs, discusses challenges encountered during clinical translation and potential breakthrough directions, aiming to provide theoretical references and practical guidance for future research.

Keywords: Light-activated ADC; Photocaging; Photodosimetry; Therapeutic index

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1. Introduction

Cancer remains one of the most globally concerning diseases, with persistently high mortality rates. According to the 2024 Global Cancer Statistics, nearly 20 million new cancer cases and 9.7 million cancer-related deaths were reported in 2022 [1]. Among existing treatment regimens, highly cytotoxic chemotherapeutic agents remain the most widely used approach, demonstrating potent antitumor effects. However, challenges such as low target specificity, narrow therapeutic windows, and the emergence of drug resistance continue to pose significant obstacles [2]. Monoclonal antibody (mAb) drugs play a pivotal role in tumor therapy due to their high specific binding capacity. However, compared to traditional chemotherapeutic agents, they typically exhibit lower intrinsic cytotoxicity and may carry the risk of drug resistance [3].

Antibody-drug conjugates (ADCs) integrate highly specific monoclonal antibodies with potent cytotoxic drugs through chemical linkers. This design enables precise drug delivery to tumor cells, releasing therapeutic agents exclusively within targeted tumor regions while minimizing leakage into non-target areas [4]. Upon binding to tumor cell-specific

antigens, the antibody structure facilitates drug internalization and lysosomal fusion. Within lysosomes, the linker undergoes enzymatic or chemical cleavage, releasing cytotoxic factors that induce apoptosis or necrosis, thereby exerting cytotoxic effects on tumor cells. ADCs address the lack of target specificity in conventional chemotherapy, significantly enhancing antibody-based therapeutic efficacy. This breakthrough represents a pivotal milestone in targeted therapy, opening new avenues for oncology treatment [5].

Photoactivatable antibody-drug conjugates (paADCs) represent a targeted cancer therapy strategy characterized by light-triggered activation [6]. These therapeutics aim to strictly confine cytotoxic effects to the spatial range exposed to excitation light, with their onset time being controllable through irradiation. Traditional ADCs primarily rely on receptor-mediated endocytosis, lysosomal processing, and linker cleavage to release toxic payloads. In contrast, light-activated ADCs shift the "trigger mechanism" to the extracellular environment, enabling cytotoxic activation to occur in the extracellular microenvironment, near cell membranes, within endosomes or lysosomes, or even at the cytoplasmic level [7]. Light-activated ADCs can be regarded as a reconstruction of the pharmacodynamic pathway of conventional ADCs. It no longer relies solely on endocytosis efficiency, lysosomal activity, and tumor heterogeneity processing capacity to achieve desired effects, but instead actively triggers cytotoxicity by controlling light conditions and determining the corresponding temporal or spatial parameters. This external controllability naturally makes it suitable for localized therapies or intraoperative/intra-abdominal treatment scenarios. Simultaneously, it provides novel insights and alternatives for targeting biological sites that are challenging to design as traditional drugs [8].

2. Technical lineage and current development status of light-activated ADCs

2.1. Chemical gate control route

From a chemical perspective, the most straightforward approach to light-activated ADCs involves designing the linker or toxin payload to remain stable in the dark state but undergo rapid transition upon light activation [7]. The prevailing strategy currently in use involves embedding photolysis groups into the linker, which facilitates bond cleavage under irradiation to achieve localized release or exposure of the free toxin payload [9]. The advantage of this strategy lies in its rapid response speed, making it suitable for achieving transient high drug concentrations in localized areas. However, there remain significant design challenges in this approach. It is essential to minimize uncoupling in non-target regions while ensuring sufficient photolysis efficiency and quantum yield in the targeted regions [10].

Scientists have developed an innovative strategy that introduces photocage groups at the drug efficacy group sites. This design prevents effective target interaction or active conformation entry in non-irradiated states, while the photocage groups are removed upon irradiation to allow the drug efficacy groups to function [11,12]. Compared to conventional bond-breaking approaches, the photocaging strategy selectively masks key drug efficacy groups on the payload through reversible or irreversible mechanisms, enabling controlled reaction initiation [13]. Unlike the direct release of free toxic payload, photocaging theoretically reduces off-target diffusion of free toxins and concentrates drug toxicity effects within target regions. However, this strategy imposes stringent requirements on drug design and synthesis, and the introduction of photocages often alters the physicochemical properties of toxic payload, membrane permeability, and metabolic pathways, resulting in potentially inferior therapeutic efficacy compared to traditional ADCs [10]. Additionally, under complex *in vivo* conditions, factors such as thermal cycling, spectral drift, and reduced effective excitation efficiency due to protein-lipid interactions have kept this approach largely at the proof-of-concept stage [8,14].

2.2. Photosensitizer route

In addition to the aforementioned two approaches, the antibody-photoimmunoconjugate (PIC) strategy centered on photosensitizers has garnered widespread attention and recognition. Near-infrared phototherapy (NIR-PIT) achieves cell-selective killing by photoinactivating the photosensitizer ADC [15]. These substances can damage cellular structures such as cell membranes, mitochondria, and endoplasmic reticulum, thereby inducing cell death, accompanied by microvascular

injury and local inflammatory responses [16]. Photodynamic-induced damage is often accompanied by immune cell death (ICD), exposure or release of certain signaling molecules, enhanced antigen presentation, and amplified inflammatory responses. Therefore, the optimal regimen for phototoxic ADC therapy is frequently combined with immune checkpoint inhibitors, innate immune agonists, or tumor vaccines [17,18].

Photocursors ADC typically exhibit low cytotoxicity under dark conditions, but upon light activation, they can rapidly generate reactive oxygen species and other substances [19]. This makes them safer and more controllable compared to the aforementioned two approaches [20]. Additionally, since photocursor ADCs do not entirely rely on lysosomal processing, they demonstrate adaptability for targets with low endocytosis efficiency or unclear processing pathways [21]. However, photocursors ADC also face significant engineering limitations. Most photosensitizers exhibit hydrophobic properties and are prone to π-π stacking interactions, which lead to aggregation after conjugation. This aggregation can trigger self-quenching, reduce effective quantum yield, and even alter drug metabolism [21,22]. Additionally, reactive oxygen species (ROS) have short diffusion distances, and some reactions require oxygen. These factors make single-dose irradiation regimens ineffective in the hypoxic microenvironment of solid tumors. Consequently, fractionated irradiation protocols and hypoxia mitigation strategies have gained increasing attention [23].

2.3. Irradiation engineering and operability

Currently, numerous light-activated ADCs have been developed or published in research. However, the practical application of light-activated ADCs in therapeutic scenarios depends not only on molecular-level activation capability [24], but more critically on two key factors: clinically achievable irradiation conditions and the feasibility of repeated light dose calibration. Mature therapeutic applications predominantly target superficial or accessible lesion sites, including skin and superficial tumors, intraoperative exposed intracavitary lesions (gastrointestinal and respiratory tracts), endoscopically accessible luminal tumors (head and neck, breast), as well as residual areas requiring localized irradiation postoperatively or after interventional procedures. In these scenarios, treatment regimens such as near-infrared phototherapy (NIR-PIT)—which employ an antibody-light sensor conjugate combined with localized irradiation—have established clear translational pathways from laboratory to clinical practice with substantial evidence support [20]. Supporting equipment for these therapies has progressively matured, encompassing fiber optic or endoscopic light guidance systems and interstitial irradiation devices. Concurrently, irradiation protocols have undergone multiple engineering optimizations, including fractionated irradiation to reduce tissue thermal load, restore oxygen reperfusion, and refine irradiation rhythms for enhanced efficacy. These foundational advancements have provided critical support for the transition of light-controlled conjugated drugs from laboratory research to clinical application [25].

Conversely, for deep-seated solid tumors, the penetration depth of external light sources and dose uniformity in tumor regions are simultaneously constrained by physical factors such as tissue light scattering and absorption. This results in difficulty in achieving uniform delivery of effective light doses within deep-seated solid tumors. This challenge has prompted researchers to develop near-infrared window materials with longer wavelengths, while also proposing more sophisticated drug delivery and activation methods. However, these advancements have increased the complexity of therapeutic systems, posing additional challenges for drug-device synergy and regulatory compliance [26]. Therefore, during the actual translation process, the selection of optically activated ADCs for therapeutic applications is typically guided by operational feasibility and standardizable implementation, followed by gradual expansion to deeper anatomical sites and broader disease categories [21].

3. Key obstacles facing photoactivated ADCs

3.1. The boundary between covert security and overt robustness

Photodynamic systems inevitably encounter challenges such as dark reactions and background leakage in practical applications. Taking photolysis connectors as an example, even under conditions without light excitation, minor

hydrolysis, reduction reactions, or nonspecific enzymatic cleavage may lead to premature release of toxic payloads into the environment, resulting in systemic exposure to free toxic loads. This diminishes the absolute control of photodynamic systems to partial control [19,27]. For photosensitizer-conjugated systems, dark toxicity, light-dependent excitation risks, and tissue non-specific accumulation-induced damage can all narrow the safety margin, adversely affecting therapeutic outcomes [28]. Addressing these issues requires not only designing more stable chemical structures and minimizing drug leakage in dark states but also optimizing the alignment between *in vivo* drug metabolism distribution and irradiation timing windows. Key strategies include determining the optimal post-administration light activation window, managing ADC drug accumulation levels and blood clearance rates before and after irradiation, mitigating localized hyper-oxygen consumption through repeated irradiation cycles, and refining irradiation protocols [29].

Meanwhile, DAR values, aggregation patterns, and pharmacokinetic behaviors often exhibit more pronounced characteristics in light-activated ADCs. Photosensitizers generally possess high hydrophobicity with multiple toxic payloads, and increased DAR values are typically accompanied by enhanced antibody aggregation and improved clearance by the reticuloendothelial system. This leads to reduced drug accumulation in tumor regions while increasing uptake by organs such as the liver and spleen, thereby causing organ damage [19]. Unlike conventional ADCs, light-activated ADCs must also maintain stable and reproducible optical/photochemical parameters and properties. Changes in DAR values and antibody-drug conjugation sites may significantly alter the drug's molar extinction coefficient, effective quantum yield, photobleaching rate, and self-quenching extent [16]. Consequently, current development strategies are increasingly oriented toward engineering approaches that focus on novel coupling sites, hydrophilic spacer arm designs, and improving coupling quality over quantity [30].

In terms of quality control, light-activated ADCs require the development of a comprehensive methodology system integrating optics and pharmacodynamic correlation, building upon the CMC framework of conventional ADCs. In addition to routine critical quality attributes such as DAR distribution, free drug concentration, aggregate formation, and linker stability, it is essential to establish traceable spectroscopic characterization methods, standardized illumination platforms, and dosimetric conditions. These measures are crucial for maintaining batch-to-batch consistency, scaling up production, and ensuring comparable drug-light interactions during multicenter clinical implementation [31].

3.2. Optical dose distribution, hypoxia, and heterogeneity

Even within the near-infrared wavelength range, light propagation through biological tissues is subject to scattering and absorption effects, resulting in an uneven distribution of drug dose after photodynamic therapy. This phenomenon is primarily manifested as significantly higher drug concentrations at tumor margins compared to internal tissues following light excitation [32]. For drug regimens requiring specific light intensity thresholds to trigger therapeutic effects, such dose heterogeneity may lead to localized tumor activation. This occurs because while some tumor cells rapidly die upon exposure to lethal doses, others remain in sublethal stress states. Consequently, tumor cells may activate self-repair mechanisms, ultimately enabling tumor adaptation and drug resistance development [28]. Therefore, for light-activated ADCs to achieve more reliable and controllable therapeutic outcomes, it is imperative to address and resolve dose heterogeneity and the resulting dose drift effects, rather than merely validating feasibility under *in vitro* irradiation conditions [23].

Hypoxia represents another major challenge in photodynamic therapy. Solid tumors commonly exhibit both structural hypoxia and functional hypoxia. The ambient oxygen concentration determines the efficiency of reactive oxygen species (ROS) generation. However, during phototherapy, oxygen is rapidly consumed through chemical reactions, leading to a significant reduction in ROS production. Concurrently, light-induced vascular damage and secondary [33] inflammatory responses may impair microcirculatory perfusion and oxygen re-supply capacity, thereby progressively diminishing the efficacy of subsequent photodynamic therapy [16].

The bystander effect serves as a double-edged sword in light-activated ADC therapy. On one hand, the bystander effect facilitates the clearance of regions where antibodies struggle to penetrate and expands the therapeutic reach of drugs

[34]. On the other hand, the spread of inflammation, vascular leakage, and effects on adjacent normal tissues may reduce the therapeutic window in areas adjacent to the mucosa, nerves, and vital organs [16]. Especially in anatomically intricate regions such as the head and neck and digestive tract, even with reduced systemic toxicity, therapeutic safety may still be compromised [24]. Therefore, photoactivated ADCs must redefine the drug safety window through more precise dosimetry, irradiation boundary control, and device operability [25].

3.3. Pharmaceutical-device coordination, trial design, and scalability

The clinical application of light-activated ADCs is inherently constrained by irradiation conditions. Consequently, in clinical practice, their indications predominantly involve diseases susceptible to radiation exposure, such as superficial, intracavitary, or intraoperative exposed lesions, rather than the most severe, urgent, or critical deep solid tumors [21]. This situation creates a paradoxical scenario where academic research focuses on addressing targeted drug delivery and pharmacokinetic challenges across various solid tumors, while clinical studies tend to validate drug efficacy and feasibility in a limited population with superficial, intracavitary, or intraoperative exposed lesions [35]. The ability to demonstrate clear and irreplaceable clinical significance in these limited scenarios will largely determine whether light-activated ADCs can transition from early proof-of-concept stages to scaled development [36].

Furthermore, light-activated ADCs are not limited to a single variable such as drug dosage, but rather employ a therapeutic strategy involving three variables: administration dose, irradiation dose, and the interval between administration and irradiation [33]. We aim to obtain answers to numerous questions from clinical trials, including the maximum tolerated dose or recommended dose of the drug, optimal irradiation time window, single-session energy density and intensity, whether fractionated irradiation is required, how to define irradiation area and boundaries, as well as the standardization of device parameters and operational training across different centers. These factors collectively determine the reproducibility and consistency of the protocol [24]. Additionally, regulatory requirements regarding the characterization of drug-device combination products, device consistency validation, and risk control measures significantly impact development timelines and cost structures. Therefore, these issues should be comprehensively addressed during preclinical studies and Phase I clinical trial design stages, rather than being addressed passively later [37].

4. Conclusion and perspectives

Light-activated ADC achieves controllable pharmacodynamic effects by relocating the efficacy-triggering mechanism from lysosomes to the extracellular space and utilizing light excitation to modulate the drug action process. This innovative approach reconstructs the pathway-dependent mechanism of traditional ADCs, encompassing endocytosis, lysosomal processing, and linker cleavage, thereby conferring temporal and spatial controllability over cytotoxic effects.

Current technical approaches for light-activated ADCs primarily include photolysis connectors, light-trapping gating, and the photosensitizer-based PIC/NIR-PIT technology pathway [38]. The latter has established relatively clear and effective transformation pathways in scenarios where lesions can be exposed, such as superficial, intracavitary, and intraoperative conditions [39].

However, the temporal and spatial controllability of light-controlled systems often exhibits only partial controllability in practical applications, primarily due to system exposure noise caused by dark reactions and background leakage [40]. Elevated DAR values can lead to payload accumulation and RES clearance, thereby reducing drug enrichment at tumor sites and increasing organ burden in the liver and spleen. Changes in conjugation sites and microenvironmental conditions may significantly disrupt molar extinction coefficients, effective quantum yields, photobleaching, and self-quenching, resulting in batch-to-batch and center-to-center inconsistencies [41]. Additionally, tissue scattering and absorption create uneven light dose distribution, compounded by dynamic oxygen consumption and insufficient reoxygenation during hypoxia, which may cause rapid cell death in some tumor cells exposed to lethal doses while leaving others in sublethal stress states. This can trigger tumor repair mechanisms, ultimately leading to tumor adaptation and drug resistance

development. While the bystander effect may expand drug-killing radius positively, it could simultaneously rapidly narrow the therapeutic window in sensitive areas such as mucous membranes and nerves [5].

Therefore, future development priorities should shift progressively from high DAR to functionalized DAR, utilizing site-specific conjugation and hydrophilic spacer arms to stabilize photochemical reactions. Establishing standardized dosimetry platforms and clinically optimizing dosing regimens, light doses, DLI (dose-limiting irradiation), and fractionation schedules will facilitate expanding research and applications to deeper solid tumors. Over the past decade, photoactivated ADCs have emerged like mushrooms after rain in R&D, with gaps in multiple indications gradually being filled. Although critical challenges remain in this field, advancements in materials science, engineering, and technologies are expected to bring more photoactivated ADC drugs into clinical use in the near future.

Disclosure statement

The authors declare no conflict of interest.

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