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Harnessing T Cells: Cellular Immunity's Role in Vaccine Induced Protection

Yongxin Zhang[1, 2*] and Ying Wang[1, 3]

[1]Zyxell Inc. Carrollton, Texas, USA

[2]ZYX Biotech Company, Carrollton, Texas, USA

[3]Quest Diagnostics, Lewisville, Texas, USA

[*]**Corresponding Author:** Yongxin Zhang, Zyxell Inc. Carrollton, Texas, USA.

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Abstract

This review highlights the pivotal role of cellular immunity, specifically T cell-mediated responses, in driving vaccine-induced protection and its broader implications for combating infectious diseases, cancer, and chronic infections. Recent advancements reveal that T lymphocytes play a crucial role in identifying and eradicating infected cells, offering not only a rapid immune response but also sustained long-term immunity. Despite these benefits, heightened T cell responses can lead to unintended side effects, thereby limiting vaccine dosage and reducing antibody production, durability and efficacy. This article examines the underlying mechanisms of T cell-driven immunity, the therapeutic potential of these responses in cancer and chronic diseases, and the challenges posed by their associated adverse effects. The concept of polarized vaccines, designed to balance immune activation while minimizing harmful outcomes, is also discussed as a promising strategy for improving vaccine safety and effectiveness.

Keywords: Vaccine, Cellular Immune Response, T Cell, B Cell, Side Effect, Polarized Vaccine, Infectious Disease, Cancer, Chronic Infection.

Background

Vaccines have revolutionized public health by providing protection against a wide range of infectious diseases [1]. Traditionally, the focus has been on humoral immunity, driven by the production of neutralizing antibodies. However, recent advances in immunology highlight the significant role of cellular immunity, mediated by T lymphocytes, in enhancing vaccine efficacy [2]. This article explores how vaccines stimulate cellular immune responses to accelerate the clearance of infected cells, discusses the implications for infectious disease control, cancer therapy, and chronic infections, and examines the challenges and future directions in vaccine development. Additionally, the article introduces innovative approaches, such as polarized vaccines, which aim to optimize immune responses and reduce potential side effects.

Increased Cellular Immune Responses Induced by Vaccines Accelerate the Removal of Infected Cells

Vaccines are among the most significant achievements in medicine, protecting populations against numerous infectious diseases. Traditionally, the effectiveness of vaccines has been attributed primarily to the induction of humoral immunity, which involves the production of neutralizing antibodies that provide protection against pathogens. However, recent evidence highlights the critical role of cellular immunity in vaccine-mediated protection, particularly in accelerating the clearance of infected cells [1, 2].

The cellular arm of the immune system, primarily driven by T lymphocytes, plays a crucial role in recognizing and eliminating infected cells, thereby curbing the spread of infectious agents within the host. Unlike antibodies, which mainly neutralize extracellular pathogens and toxins, T cells are adept at detecting and eliminating intracellular pathogens, including viruses,

bacteria, and parasites, that have invaded host cells. This ability to target infected cells directly provides a crucial advantage in controlling infections, especially those characterized by intracellular replication [2-4].

A hallmark of an effective vaccine is its ability to stimulate robust and durable immune responses that mimic those elicited by natural infection, without causing disease [5-7]. In this regard, vaccines that harness the power of cellular immunity offer a promising avenue for enhancing host defenses against a broad spectrum of pathogens. By priming the immune system to generate antigen-specific T cells, vaccines can effectively arm the body's immune arsenal with the necessary weaponry to identify and eliminate infected cells upon encountering the pathogen [6-8].

The process by which cellular immune responses induced by vaccines accelerate the removal of infected cells is multifaceted and encompasses several key mechanisms. Central to this process is the activation of antigen-specific T cells, which occurs upon recognition of pathogen-derived antigens presented by specialized antigen-presenting cells, such as dendritic cells [9, 10]. Upon activation, T cells undergo clonal expansion, giving rise to a large pool of effector cells with cytotoxic capabilities [10].

These effector T cells, including CD8+ cytotoxic T lymphocytes (CTLs) and CD4+ helper T cells, play complementary roles in orchestrating the immune response against infected cells. CD8+ CTLs directly recognize and eliminate infected cells by releasing cytotoxic molecules, such as perforin and granzymes, which induce apoptosis and subsequent clearance of the infected cell. Meanwhile, CD4+ helper T cells provide crucial support by secreting cytokines that enhance the activation and function of CTLs, as well as facilitating the generation of long-lasting immunological memory [10-13].

Furthermore, the induction of cellular immune responses by vaccines not only enables the rapid elimination of infected cells but also confers long-term protection against reinfection. Memory T cells, generated following vaccination, persist in the body for extended periods and are poised to mount a rapid and robust response upon re-exposure to the pathogen [13]. This phenomenon of immunological memory serves as a cornerstone of vaccine-induced protection, providing enduring defense against infectious threats.

Given the growing recognition of the importance of cellular immunity in vaccine-mediated protection, there is increasing interest in developing vaccines that specifically target and enhance cellular immune responses. Such vaccines hold tremendous promise for combating a diverse array of infectious diseases, particularly viral infections like AIDS and hepatitis C, bacterial infections such as tuberculosis and anthrax, and protozoal diseases like malaria [14-22]. Moreover, integrating cellular immune responses into vaccine design may offer novel therapeutic avenues for combating cancer and other chronic diseases characterized by dysregulated immune responses [23-26].

It is imperative to further explore the intricate interplay between vaccines and cellular immunity, gaining insight into how the augmentation of cellular immune responses accelerates the removal of infected cells. Understanding the mechanisms underlying vaccine-induced cellular immunity, examining its implications for infectious disease control, and developing potential therapeutic applications in cancer immunotherapy and chronic infection management will shed light on the future directions of vaccine development and immunotherapy strategies.

The Contribution of Cellular Immune Responses Induced by Vaccines to Cancer Therapy

Cancer remains one of the most formidable challenges in modern medicine, exacting a devastating toll on millions of lives worldwide each year [27]. Despite significant advancements in cancer research and treatment modalities, the quest for effective therapeutic strategies continues unabated. In recent years, the intersection of immunology and oncology has emerged as a promising frontier in the battle against cancer, with immunotherapy revolutionizing the landscape of cancer treatment. Central to this paradigm shift is the recognition of the critical role played by cellular immune responses induced by vaccines in harnessing the power of the immune system to combat cancer [28-31].

Traditionally, cancer has been viewed as a disease of uncontrolled

cell proliferation, driven by intrinsic genetic alterations and extrinsic environmental factors. However, it is now increasingly appreciated that cancer is also a disease of immune evasion, characterized by the ability of malignant cells to evade detection and elimination by the immune system [32-36]. This concept forms the basis of cancer immunosurveillance, wherein the immune system continuously surveys the body for aberrant cells and mounts an immune response to eliminate nascent tumors.

The concept of cancer immunosurveillance was first proposed by Paul Ehrlich in the early 20th century and later refined by Macfarlane Burnet and Lewis Thomas [37, 38]. However, it wasn't until the advent of modern immunology that the intricate mechanisms governing the interplay between cancer and the immune system began to be elucidated. Central to this understanding is the recognition that tumors express a plethora of antigens, both tumor-specific and tumor-associated which can be recognized by the immune system as foreign and targeted for destruction [39, 40].

In this context, vaccines have emerged as a powerful tool for harnessing the immune system to mount an effective antitumor response. Unlike traditional prophylactic vaccines, which aim to prevent infectious diseases by priming the immune system against pathogens, cancer vaccines are designed to stimulate specific immune responses against tumor-associated antigens, with the goal of eradicating or controlling the growth of cancer cells. The rationale behind cancer vaccines lies in the premise that by augmenting the immune system's ability to recognize and target tumor cells, it can be unleashed to mount a potent antitumor response [41-43].

The cellular arm of the immune system, comprising T lymphocytes and natural killer (NK) cells, plays a central role in tumor immunosurveillance [35, 36] and response to cancer vaccines [41, 43]. Tumor-specific T cells, generated in response to vaccination or natural exposure to tumor antigens, are capable of recognizing and eliminating cancer cells through a variety of effector mechanisms [35, 36]. Importantly, these effector T cells exhibit a degree of specificity and memory, allowing for targeted and sustained antitumor activity [44-46]. In our studies with cancer cell vaccines transfected with cytokine-expressing plasmids, it was found that Th1 cytokines (IL-12/IL-18) enhanced the potency of the vaccine in inducing stronger cytotoxicity of CD8+ T cells to corresponding cancer cells compared to Th2 cytokine (IL-16)-expressing vaccines, which reduced the cancer-killing abilities of cancer-specific T cells. This indicates that cytotoxic CD8+ T cells play major roles in cancer cell elimination and is consistent with others' findings [47, 48].

The development of cancer vaccines has been facilitated by advances in our understanding of tumor immunology and antigen presentation. Strategies for vaccine design encompass a range of approaches, including whole tumor cell vaccines, peptide vaccines, dendritic cell-based vaccines, and genetic vaccines (including mRNA vaccines), each tailored to exploit different aspects of the immune response and antigen presentation pathways [42, 43].

It is essential to further explore the multifaceted role of cellular immune responses induced by vaccines in cancer therapy, delve into the mechanisms underlying the generation of antitumor immunity, examine the clinical efficacy and challenges of cancer vaccines, and discuss emerging strategies for enhancing vaccine-induced immune responses. By elucidating the intricate interplay between vaccines and cellular immunity in the context of cancer therapy, we can gain insights into the future directions of cancer immunotherapy and the quest for effective cancer treatments.

Potential Benefits of Cellular Immune Responses Induced by Vaccines for the Treatment of Chronic Infections

Chronic viral infections present a significant global health challenge, impacting millions worldwide and placing substantial burdens on healthcare systems [49, 50]. Unlike acute infections that typically resolve within a short period, chronic viral infections persist for extended durations, often evading the host immune response and establishing long-term reservoirs within the body [49]. This persistence leads to ongoing morbidity and mortality and increases the risk of severe complications such as liver cirrhosis, hepatocellular carcinoma, and immune-mediated disorders [49, 50]. The cellular immune responses induced by vaccines offer a promising avenue for combating chronic viral infections and restoring immune homeostasis [51, 52].

The pathogenesis of chronic viral infections is characterized by

a delicate balance between viral replication and host immune control [53]. This equilibrium involves an interplay between the virus and the host immune system, wherein the virus employs various strategies to evade detection and elimination, while the host immune response strives to contain and eradicate the virus. However, in chronic infections, this balance often tips in favor of the virus, resulting in persistent viral replication and immune dysfunction [53, 54].

T lymphocytes and NK cells of the immune system play a pivotal role in controlling and clearing viral infections. T cells, in particular, are crucial for recognizing and eliminating virus-infected cells through cytotoxicity, wherein infected cells are targeted for destruction by CTLs and NK cells. This cellular immunity mechanism is essential for limiting viral spread, containing infection, and preventing the establishment of persistent reservoirs [55, 56].

Vaccines are a cornerstone of modern medicine, providing effective means of preventing and controlling infectious diseases. While conventional vaccines primarily target acute infections, the potential for harnessing vaccines to combat chronic viral infections has garnered increasing interest. Unlike prophylactic vaccines, which aim to prevent infection by priming the immune system before exposure to the pathogen, therapeutic vaccines are administered after infection to boost existing immune responses or induce new immunity against the virus [57-59].

In the context of chronic viral infections, therapeutic vaccines hold significant promise for restoring immune function and controlling viral replication. By stimulating robust and durable cellular immune responses, vaccines can enhance the immune system's ability to recognize and eliminate virus-infected cells, thereby curbing viral spread and reducing disease burden. Additionally, vaccines may modulate the immune response to promote viral clearance and prevent immune exhaustion, often observed in chronic infections. Recent studies on therapeutic vaccines for HIV, HPV, hepatitis B, and hepatitis C have made significant progress [60, 61], and clinical trials are underway for some of these vaccines [62, 63].

The potential benefits of cellular immune responses induced by vaccines for treating chronic viral infections and the mechanisms underlying vaccine-mediated immunity will be further explored. Studies on the clinical efficacy and challenges of therapeutic vaccines and emerging strategies for enhancing vaccine-induced immune responses in chronic viral infections will elucidate the multifaceted role of vaccines in combating chronic viral infections and provide insights into novel therapeutic interventions and effective treatments for chronic viral diseases.

Side Effects of Vaccines: The Role of Cellular Immune Responses

Vaccines are among the most effective public health interventions, significantly reducing the burden of infectious diseases and saving countless lives worldwide. However, despite their undeniable benefits, vaccines can sometimes elicit adverse reactions in a subset of individuals, ranging from mild local reactions to rare but serious systemic events [64-66]. Recently, the side effects of COVID-19 vaccines have been particularly spotlighted [67-71]. While many vaccine-related side effects are transient and self-limiting, understanding the underlying mechanisms is crucial for ensuring the safety and efficacy of vaccination programs [72-74].

Increasing evidence suggests that many vaccine-induced side effects are primarily driven by the activation of cellular immune responses, particularly those mediated by T lymphocytes [75, 76]. T cells play a central role in the adaptive immune response, orchestrating the elimination of infected or aberrant cells through various effector mechanisms. Upon encountering antigens presented by antigen-presenting cells, such as dendritic cells, T cells undergo activation and clonal expansion, culminating in the generation of antigen-specific effector and memory T cell populations [77, 78].

The specificity of T cell responses is determined by recognizing peptide fragments, known as epitopes, derived from antigens presented in the context of major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells. While vaccines typically contain antigens that elicit both humoral and cellular immune responses, certain vaccines may preferentially stimulate T cell responses by incorporating epitopes with high affinity for MHC molecules, particularly those recognized by CD4+ helper T cells or CD8+ CTLs [35, 77].

The selective targeting of T cell epitopes in vaccine design is motivated by several factors, including the desire to enhance vaccine efficacy, promote long-term immunity, and target intracellular pathogens that are inaccessible to antibodies. However, the heightened immunogenicity of T cell epitopes may also predispose vaccinated individuals to an increased risk of vaccine-related side effects, particularly those mediated by exaggerated or dysregulated cellular immune responses [75, 76].

One of the most common side effects associated with T cell-mediated immunity is inflammation, characterized by localized redness, swelling, and pain at the vaccination site. This inflammatory response is orchestrated by activated T cells and other immune cells recruited to the site of antigen deposition, leading to the release of pro-inflammatory cytokines and chemokines. While transient inflammation is a normal part of the immune response to vaccination, excessive or prolonged inflammation can result in discomfort and local tissue damage [77, 78].

In addition to local reactions, vaccine-induced T cell responses may give rise to systemic side effects, including fever, malaise, and myalgia. These symptoms, collectively known as systemic reactogenicity, reflect the systemic activation of the immune system in response to vaccination. Our previous studies also suggested cellular immune responses enhanced by DNA vaccines should be responsible for the systemic side effects [77, 79]. While systemic reactogenicity is typically mild and self-limiting, it can occasionally manifest as more severe systemic inflammatory syndromes, such as fever-related seizures or febrile illness. Excessive cellular immune responses induced by vaccines can also contribute to vaccine-induced enhancement of viral infection (VIEVI), causing vaccinated individuals to be more susceptible to the corresponding virus and develop more severe conditions [78-82].

In rare instances, T cell-mediated immune responses induced by vaccines may precipitate immune-mediated adverse events, such as hypersensitivity reactions or autoimmune phenomena. These reactions are thought to arise from molecular mimicry or bystander activation, wherein vaccine-induced T cells inadvertently target self-antigens or cross-react with host tissues, leading to tissue damage and autoimmune pathology. The increased myocarditis following COVID-19 vaccination has been considered highly associated with T cell-mediated immune responses [75, 85-87]. Since aged individuals have significantly weakened cellular immune responses to new antigens [80, 88-91], it is understandable why myocarditis following COVID-19 vaccination mainly occurred in young individuals [86, 87].

Although T cell-mediated severe side effects are uncommon in most currently available vaccines for disease prevention, they can pose significant challenges in vaccine development. When Vaccine-Induced Enhanced Viral Infection (VIEVI) and hypersensitivity reactions occur in clinical trials, careful management and regulation of cellular immune responses elicited by the vaccine are crucial for successful vaccine development.

Regulation of Cellular Immune Responses in Vaccine Development

In vaccine development, the orchestration of cellular immune responses represents a critical aspect of vaccine design and evaluation. While traditional vaccines have primarily focused on eliciting humoral immunity, there is growing recognition of the importance of harnessing cellular immune responses for enhanced vaccine efficacy and durability. Central to this endeavor is understanding how cellular immune responses are regulated, manipulated, and optimized in the context of vaccine development [92-94].

The regulation of cellular immune responses in vaccine development is a multifaceted process that encompasses several key considerations, including antigen selection, adjuvant formulation, vaccine delivery platforms, and dosing schedules. Each of these factors plays a crucial role in shaping the magnitude, quality, and longevity of cellular immune responses induced by vaccines, ultimately influencing vaccine efficacy and safety profiles [92-95].

Antigen selection is a fundamental determinant of vaccine immunogenicity, dictating the specificity of the immune response and the breadth of epitopes recognized by T cells [94-96]. Advances in antigen discovery and characterization have facilitated the identification of novel vaccine targets, including conserved antigens shared among multiple pathogens and tumor-specific antigens expressed by cancer cells. By selecting antigens that elicit robust cellular immune responses, vaccine developers can enhance the potency and breadth of vaccine-induced immunity [92-96].

Adjuvants, or immunostimulatory agents, play a critical role in potentiating and directing immune responses to vaccines.

By engaging pattern recognition receptors on immune cells, adjuvants can enhance antigen presentation, cytokine production, and T cell activation, augmenting cellular immune responses. The selection and formulation of adjuvants are guided by considerations of safety, efficacy, and compatibility with vaccine antigens, maximizing immunogenicity while minimizing adverse effects [97-99].

Vaccine delivery platforms represent another avenue for modulating cellular immune responses, offering diverse strategies for antigen delivery, presentation, and targeting. From traditional live attenuated and inactivated vaccines to novel nanoparticle-based formulations, vaccine delivery platforms vary in their ability to elicit cellular immune responses, influence immune cell trafficking, and promote immunological memory. The rational design of vaccine delivery systems involves careful consideration of factors such as stability, immunogenicity, scalability, and ease of administration, with an eye towards optimizing cellular immune responses [100-102].

Dosing schedules and vaccination protocols also play a crucial role in regulating cellular immune responses and shaping long-term immunity. The timing, frequency, and route of vaccine administration can impact the kinetics and magnitude of immune responses, as well as the establishment of immunological memory. Rational dosing strategies aim to balance the need for rapid induction of protective immunity with the desire for sustained and durable immune responses, while minimizing the risk of immune exhaustion or tolerance [103, 104].

Ideally, one dose of vaccine is able to induce sustained and durable immune responses. However, only a few vaccines can reach this level, and most vaccines need repeatedly boosting for building effective immunity. The effective immunity induced by current mRNA COVID vaccines only lasts several months, even after several boosts [105]. This is far from optimal. In contrast to some vaccines that can only stimulate short term, temporary immunity, the others, such as those for small pox vaccine and measles can sustain the effective immunity for years, even lifetime. The differences in the effects among these vaccines are due to the differences in the amino acid sequences of the epitopes within their antigen proteins [106, 107].

Each antigen consists of many, possibly thousands, of epitopes. Some epitopes have higher affinity to B cells, some to T cells, and most lie in between [108, 109]. Those with higher affinity to B cells predominately bind to B cells and tend to stimulate stronger antibody production, while those with higher affinity to CD8+ T cells predominately bind to CD8+ T cells and tend to stimulate more robust cytotoxic T cell responses. In contrast, those with higher affinity to CD4+ T cells are more likely to bind to CD4+ T cells and stimulate more CD4+ T cells. Since CD4+ T cells are essential for the regulation of immune responses, epitopes with higher affinity to CD4+ T cells usually induce more effective and sustained immunity. Our studies showed that vaccines derived from virus antigens with a higher number of epitopes exhibiting strong affinity to B cells and lower affinity to CD8+ cells can generate stronger and more durable humoral immunity against their target microbiological pathogens. In contrast, vaccines with more epitopes that have lower affinity to B cells and higher affinity to CD8+ cells tend to induce only temporary, weaker humoral immunity. Further research revealed that CD8+ cells activated by vaccines with more antigen epitopes possessing higher affinity to CD8+ cells not only destroy their target cells (such as virus-infected cells and cancer cells) but also induce apoptosis in antigen-presenting cells. These findings are consistent with the studies of Delamarre L, et al [110]. Our results demonstrate that an increased number of epitopes with higher affinity to CD8+ cells significantly reduces the durability of the humoral immunity elicited by the vaccines. For stronger and more durable anti-microbial humoral immunity, vaccines require more epitopes with higher affinity to B cells and fewer epitopes with higher affinity to T cells.

Considering that cellular immunity from vaccines may cause side effects and restrict the administrative dose, reducing epitopes with higher affinity to CD8+ cells can greatly increase vaccine efficacy in preventing infectious diseases. Based on these findings, polarized vaccines were designed by altering the amino acid sequences of epitopes to regulate the vaccine's ability to stimulate humoral and/or cellular immunity. Specifically, for preventing infectious diseases, polarized vaccines enhance effective antigenicity by increasing epitopes favorable to humoral immunity or decreasing those favorable to cellular immunity. Conversely, for therapeutic vaccines targeting cancer and chronic infections, polarized vaccines boost antigenicity by increasing epitopes favorable to cellular immunity or decreasing those favorable to humoral immunity. This approach maximizes the antigenicity and durability of the vaccine while minimizing potential side effects at the molecular level.

There are at least two advantages of polarized vaccines in regulating vaccine antigenicity over other methods. Firstly, changes in amino acid sequences ensure that epitopes similar to those in human tissues are absent, preventing corresponding autoimmune diseases. This could potentially address issues like myocarditis in young people vaccinated with mRNA COVID vaccines. Secondly, other methods, such as adjuvants, may cause side effects and limit vaccine dosage. In contrast, with more than 20 amino acid substitutes and approximately 10 amino acids in an epitope, there are many opportunities to avoid sequences that cause significant side effects.

However, there are concerns about polarized vaccines. One concern is whether amino acid sequence changes in epitopes affect vaccine antigenicity and specificity. Although antigenicity may change for specific epitopes, the overall vaccine maintains its antigenicity and specificity since B cell and T cell epitopes do not share the same molecules. Another concern is the difficulty in determining which epitopes and amino acids should be modified to enhance vaccine efficacy. Previously, this required extensive experimentation, but advancements in artificial intelligence and the analysis of replaceable amino acids (RAA) have simplified this process [111].

Another notable technology is epitope vaccines which use epitope peptides as vaccines and can select specific epitopes for targeted immunization. For example, selecting B cell epitopes for preventing infectious diseases and CD8+ T cell epitopes for therapeutic vaccines to treat cancer and chronic infections resembles the approach of polarized vaccines. However, a challenge with epitope vaccines is the weak immunogenicity of epitope peptides, even with adjuvants. Adding cytokine-stimulating epitopes may significantly improve immunogenicity [112-117].

In sum, effective regulation of cellular immune responses in vaccine development requires a comprehensive understanding of the complex interplay between vaccine components, immune cells, and host factors. Advances in immunology, systems biology, and vaccinology continue to inform and refine strategies for optimizing cellular immune responses, paving the way for the next generation of vaccines that harness the full potential of the immune system.

Conclusion

In conclusion, vaccines represent a vital tool in the global effort to combat infectious diseases, offering protection through the induction of robust and durable immune responses. While traditional vaccines have primarily focused on eliciting humoral immunity, the pivotal role of cellular immune responses in mediating effective and long-lasting immunity is increasingly recognized. Understanding the mechanisms by which cellular immune responses are regulated, optimized, and harnessed in vaccine development holds the promise of advancing vaccine efficacy, safety, and applicability across diverse infectious diseases and other pathological conditions, including cancers and chronic viral infections.

Future research endeavors will continue to elucidate the intricate interplay between vaccine components, immune cells, and host factors, informing the rational design of next-generation vaccines that maximize the benefits of cellular immunity. By leveraging advances in antigen discovery, adjuvant formulation, vaccine delivery platforms, and dosing strategies, the field of vaccinology is poised to deliver innovative solutions that address the challenges of emerging pathogens, vaccine-resistant strains, and complex diseases, ultimately contributing to improved global health and disease prevention.

Through the concerted efforts of researchers, clinicians, and public health professionals, the continued development and optimization of vaccines, especially with careful management and regulation of side effects related to cellular immune response elicited by vaccine, will remain a cornerstone of preventive medicine, safeguarding populations and fostering a healthier and more resilient world.

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