Journal of Pharmaceutical Sciences & Emerging Drugs

Perspective A SCITECHNOL JOURNAL

The Role of Antibody-Drug Conjugates in Immuno-Oncology: Combination Approaches for Improved Responses

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Received date: 22 May, 2023, Manuscript No. JPSED-23-106515;

Editor assigned date: 24 May, 2023, Pre QC. JPSED-23-106515(PQ);

Reviewed date: 15 June, 2023, QC No. JPSED-23-106515;

Revised date: 22 June, 2023, Manuscript No. JPSED-23-106515(R);

Published date: 29 June, 2023, DOI: 10.4172/2380-9477.1000148.

Description

Antibody-Drug Conjugates (ADCs) have emerged as a promising class of therapeutics in immuno-oncology, combining the targeting specificity of monoclonal antibodies with the cytotoxic potency of small-molecule drugs. This brief study explores the role of ADCs in immuno-oncology, focusing on their potential for combination approaches to enhance therapeutic responses. By leveraging the unique characteristics of ADCs and synergizing with other immuno-oncology modalities, such as immune checkpoint inhibitors and adoptive cell therapies, ADCs hold the promise of improving outcomes for cancer patients.

Mechanisms of action of antibody-drug conjugates

ADCs consist of three main components: a monoclonal antibody, a cytotoxic drug payload, and a linker that connects the two. The monoclonal antibody specifically binds to cancer cell surface antigens, allowing for selective targeting. Upon binding, the ADC is internalized, and the cytotoxic drug payload is released within the cancer cell, leading to cell death.

Combination approaches with ADCs

Immune checkpoint inhibitors: Immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, have revolutionized cancer treatment by restoring antitumor immune responses. Combining ADCs with immune checkpoint inhibitors can enhance therapeutic responses. ADCs can induce immunogenic cell death, releasing tumor antigens and activating immune responses. Additionally, ADCs targeting immune checkpoint molecules can enhance the blockade of inhibitory pathways, further promoting immune activation.

Adoptive cell therapies: Adoptive cell therapies, such as Chimeric Antigen Receptor (CAR) T-cell therapy, have demonstrated remarkable efficacy in certain cancers. Combining ADCs with adoptive cell therapies can address challenges like antigen heterogeneity and tumor escape mechanisms. ADCs can selectively eliminate antigen-positive tumor cells, reducing the antigen-negative tumor burden and enhancing the effectiveness of adoptive cell therapies.

Radiotherapy: Radiation therapy is a cornerstone of cancer treatment. Combining ADCs with radiation therapy can exploit the synergistic effects between the two modalities. Radiation can enhance the antigenicity of tumor cells, making them more susceptible to ADC-mediated killing. Moreover, radiation can improve tumor vascular permeability, facilitating ADC penetration into the tumor microenvironment.

Targeted therapies: Targeted therapies, such as small-molecule kinase inhibitors, have shown efficacy in specific cancer subtypes. Combining ADCs with targeted therapies can overcome resistance mechanisms and broaden the therapeutic window. ADCs can target antigen-positive subpopulations within tumors, while targeted therapies can address resistant clones or downstream signaling pathways, leading to improved responses.

Combination ADCs: Dual-targeting or multi-targeting ADCs can be developed to address tumor heterogeneity and overcome escape mechanisms. By simultaneously targeting different antigens or pathways, combination ADCs can enhance therapeutic efficacy and reduce the likelihood of resistance development.

Challenges and future perspectives

The development of ADCs in combination approaches faces several challenges. Optimal sequencing, dosing, and timing of combination therapies need to be determined to maximize therapeutic benefit. Additionally, the selection of appropriate targets and understanding their expression patterns in different tumor types is essential. Overcoming the limitations of tumor antigen heterogeneity and acquired resistance remains a significant challenge.

Future perspectives include the exploration of novel ADC formats, such as bispecific or trispecific antibodies, to enhance tumor targeting and immune activation. Advances in payload selection, linker technologies, and conjugation methods are expected to improve the therapeutic index and reduce off-target toxicities. Furthermore, the use of predictive biomarkers and companion diagnostics can aid in patient selection and treatment stratification.

Conclusion

ADCs have demonstrated promise in immuno-oncology, offering targeted and cytotoxic effects against cancer cells. Combining ADCs with other immuno-oncology modalities holds great potential for synergistic therapeutic responses. Overcoming challenges related to target selection, tumor heterogeneity, and resistance mechanisms will be essential for the successful integration of ADCs in combination approaches. By leveraging the strengths of ADCs and capitalizing on the multifaceted nature of immuno-oncology, researchers aim to improve treatment outcomes and advance the field of cancer therapy.

Citation: *Zahra A (2023) The Role of Antibody-Drug Conjugates in Immuno-Oncology: Combination Approaches for Improved Responses. J Pharm Sci Emerg Drugs 11:3.*