Perspective

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Enzyme Targeted Prodrugs: Precision Strategies for Controlled Drug Activation

Omar Khoury*

Dept. of Medicinal Chemistry, Levant Univ, Lebanon

*Author for correspondence: okhoury@levantuniv.lb

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Introduction

Enzyme-targeted prodrugs are an innovative approach in modern pharmacology, designed to improve the efficacy, specificity, and safety of therapeutic agents. Prodrugs are inactive or less active precursors that are converted into their active form in vivo, and when coupled with enzyme-targeting strategies, they allow selective activation in diseased tissues or specific cellular environments [1,2]. This method minimizes systemic toxicity, enhances bioavailability, and offers precise temporal and spatial control over drug activity, making it particularly valuable in oncology, infectious diseases, and metabolic disorders.

Discussion

The design of enzyme-targeted prodrugs relies on exploiting differences in enzyme expression or activity between healthy and diseased tissues. For example, tumor-associated enzymes such as beta-glucuronidase, matrix metalloproteinases (MMPs), or certain proteases are overexpressed in cancer cells, providing a trigger for localized prodrug activation. By linking a cytotoxic drug to a cleavable moiety recognized by these enzymes, the prodrug remains inactive in circulation but releases the active drug specifically at the target site, thereby reducing off-target effects [3-5].

Several classes of enzyme-targeted prodrugs have been developed. Anticancer therapies often utilize peptide-linked prodrugs activated by tumor-specific proteases. Antibiotics have been engineered as prodrugs that are converted into active agents by bacterial enzymes, enhancing selectivity and reducing resistance. Similarly, enzyme-targeted antiviral prodrugs exploit viral or host enzymes to achieve site-specific drug activation, increasing therapeutic effectiveness while minimizing systemic exposure.

Advantages of enzyme-targeted prodrugs include improved pharmacokinetics, increased therapeutic window, and the potential to overcome drug resistance. By releasing drugs only at sites of elevated enzymatic activity, these systems reduce cumulative toxicity and enhance drug concentration in target tissues. Additionally, prodrugs can be designed to improve solubility, stability, or cellular uptake, addressing common limitations of parent drugs.

Challenges remain, such as variability in enzyme expression among patients, potential premature activation, and ensuring adequate prodrug delivery to the target site. Advances in molecular engineering, computational modeling, and enzyme profiling are improving prodrug design, enhancing selectivity, and predicting patient-specific responses.

Conclusion

Enzyme-targeted prodrugs represent a sophisticated and highly selective strategy for controlled drug activation. By leveraging tissue- or disease-specific enzymatic activity, these prodrugs enhance efficacy, reduce systemic toxicity, and improve pharmacokinetic profiles. Ongoing innovations in enzyme targeting, prodrug chemistry, and personalized

medicine are poised to expand the therapeutic applications of this approach, offering safer and more effective treatments across cancer, infectious diseases, and other complex disorders.

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