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Rheumatology: Current Research

Opinion Article

Enhancing Immune Checkpoint Inhibitor Safety and Efficacy: Toward Smarter Local Delivery Strategies

Heraian Scop*

Department of Bioengineering, Rice University, USA.

DESCRIPTION

Immune Checkpoint Inhibitors (ICIs) have significantly transformed the oncology landscape by mobilizing the body's own immune system to identify and destroy cancer cells. Unlike traditional therapies such as chemotherapy and radiation which often indiscriminately target healthy and malignant tissues ICIs provide a more targeted approach by reactivating immune responses suppressed by tumors. This paradigm shift has brought unprecedented therapeutic benefits, particularly in cancers that were previously unresponsive or resistant to conventional treatments.

A revolution in cancer treatment comes with complications

Since the first FDA approval of an ICI targeting CTLA-4 in 2011, ICIs against PD-1 and PD-L1 have followed, rapidly expanding their clinical applications. These therapies now span multiple cancer types, offering improved median overall survival and, in some cases, the only viable path forward for patients with advanced or refractory disease. As a result, over half of cancer patients in the United States are now eligible for treatment with ICIs, a dramatic increase from just over 1% a decade ago.

However, this revolution comes at a cost. ICIs are not effective for all patients many experience little to no benefit and the occurrence of Immune-Related Adverse Events (irAEs) remains alarmingly high, affecting up to 89% of patients. These irAEs stem from the systemic activation of the immune system, leading to inflammation and tissue damage in healthy organs such as the lungs, liver, intestines and endocrine glands. Even though these drugs are designed to activate immune responses locally, their long biological half-life and rapid systemic distribution after administration result in unintended widespread immune activity.

To address this, researchers have turned to local delivery strategies such as intratumoral and peritumoral injections to increase the concentration of ICIs in tumor tissues while minimizing systemic exposure. Preclinical models have shown that local administration not only enhances therapeutic efficacy but also reduces irAE incidence. Yet, the problem of rapid systemic leakage persists, limiting the full potential of this approach. ICIs, due to their protein structure and long systemic half-life, continue to circulate and act on non-target tissues even after local delivery. Thus, a major challenge remains: how can we better localize ICIs at the tumor site for sustained action without triggering harmful systemic immune responses?

Engineered biomaterials: A smart solution for smarter immunotherapy

One of the most promising strategies to improve local ICI delivery lies in the use of engineered biomaterials. These materials can be tailored to control drug release kinetics, enhance retention at the tumor site and even respond to tumor-specific signals to release their payload only in the desired microenvironment. Such precision may be the key to enhancing ICI efficacy while minimizing toxicity.

For example, hydrogels and nanoparticles are being developed to form depots that slowly release ICIs over days or weeks at the tumor site. These systems can act as reservoirs, dramatically improving drug retention and reducing the need for repeated injections. Furthermore, some delivery vehicles are designed to respond to changes in pH, enzyme activity, or temperature features often unique to the tumor microenvironment. These "sense-and-respond" materials release ICIs only when triggered by these conditions, ensuring minimal impact on surrounding healthy tissues.

In another innovative approach, antibody-mediated targeting strategies have been incorporated into delivery systems, enabling ICIs to bind directly to tumor-associated antigens. This allows for a more selective engagement with cancer cells or tumor-infiltrating immune cells. Alternatively, biomaterial systems can be engineered to interact with endogenous immune cell trafficking. By presenting ICIs in a form that attracts and

Correspondence to: Heraian Scop, Department of Bioengineering, Rice University, USA. Email: scoh@gmail.com

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activates immune cells locally, the therapeutic payload becomes more effective and localized.

Additionally, biodegradable carriers are under exploration to further reduce systemic exposure. These carriers degrade into non-toxic components after releasing the drug, minimizing long-term risks and side effects. Some systems even utilize cell-based carriers such as macrophages or dendritic cells engineered to deliver ICIs to the tumor site, leveraging their natural homing abilities.

CONCLUSION

As the clinical use of ICIs continues to expand, the need to overcome challenges related to safety and efficacy becomes more urgent. Local administration has demonstrated great promise in addressing some of these challenges, but rapid systemic dispersion remains a significant barrier. Engineered biomaterials offer a transformative solution by allowing for controlled, site-specific delivery of ICIs with fewer side effects and better outcomes.

The future of cancer immunotherapy will likely depend on the convergence of immunology and material science. Ultimately, enhancing how ICIs are delivered may be just as important as what they target. As researchers and clinicians collaborate across disciplines, precision delivery of immunotherapies will become not just a possibility but a new standard in oncology care.