Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Biochemistry

Peptide-Based Therapeutic Strategies in Colorectal Cancer: Emerging Horizons and Clinical Challenges

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DOI: https://doi.org/10.36347/sjams.2025.v13i12.002 | **Received:** 09.10.2025 | **Accepted:** 03.12.2025 | **Published:** 06.12.2025

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Abstract Editorial

Colorectal cancer (CRC) remains a major global health burden, with standard treatments often limited by toxicity, resistance, and poor targeting. Peptide-based therapies offer a compelling alternative due to their high specificity, modifiability, and favorable pharmacokinetic profiles. This editorial discusses recent advances in peptide applications for CRC, including diagnostic peptides, tumor-targeting peptides, cell-penetrating peptides (CPPs), and peptide vaccines. Key preclinical and early clinical studies are highlighted, mechanisms of action are elucidated, and challenges such as stability, delivery, and immunogenicity are examined. Finally, future directions to accelerate translation of peptide-based CRC therapies, emphasizing rational design, bioinformatics, and personalized medicine are proposed.

Keywords: Colorectal cancer, colorectal cancer peptides, Peptide vaccine, tumor-targeting peptides, cell-penetrating peptides, anticancer peptides, peptide-based therapy, peptide immunotherapy, therapeutic peptides.

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INTRODUCTION

Colorectal cancer (CRC) continues to impose a significant burden on global health, being among the most common malignancies and accounting for high morbidity and mortality [1, 2]. Despite improvements in surgical, chemotherapeutic, and immunotherapeutic regimens, limitations remain—particularly off-target toxicities, resistance, and the inability to eradicate micrometastases. In this context, peptide-based therapies emerge as a promising frontier, combining molecular precision with tunable pharmacology.

Why peptides? Advantages in CRC therapy

Peptides offer multiple advantages over conventional small molecules or biologics. They are relatively easy and rapid to synthesize, can be chemically modified to improve stability, and often have low immunogenicity [3]. Their small size and modularity enable them to act as cytotoxic agents, targeting ligands, or vaccine epitopes. Moreover, they can be engineered to recognize and bind CRC-specific targets, thus improving selectivity and reducing systemic toxicity [4, 5].

Tumor-targeting and diagnostic peptides in CRC

One of the well-established roles of peptides in CRC is as targeting agents. Peptides selected via phage-display or computational design can home to tumor cells by binding overexpressed molecules. For example, Shapira and colleagues outlined how peptides can be developed to carry cytotoxins, radioisotopes, or imaging agents directly to CRC cells, thereby enhancing both therapy and diagnosis [6]. These tumor-homing peptides improve selective delivery, reducing damage to healthy tissue.

Bioinformatic approaches have also been used to design anticancer peptides (ACPs) targeting key CRC receptors such as EGFR and VEGFR. For instance, Gallocin-derived engineered peptides, modeled in silico, have shown promising predicted interactions with these receptors, suggesting a future path for highly specific peptide therapeutics [7].

Cell-penetrating peptides (CPPs) and intracellular delivery

CPPs are another vibrant area of peptide-based therapy. These peptides can translocate across cell membranes, facilitating the intracellular delivery of therapeutic cargoes. In CRC, CPPs have been explored to shuttle drugs, siRNAs, or other biologically active molecules into tumor cells, enhancing therapeutic efficacy [8]. Their modular nature and ability to penetrate cells make them ideal vectors for hard-to-reach intracellular targets.

Peptide-based vaccines and immunotherapy

Beyond direct cytotoxicity or targeting, peptides have become cornerstones in immunotherapeutic strategies. Personalized peptide-based vaccination has garnered attention in CRC: by selecting patient-specific tumor antigens, vaccines can trigger cytotoxic T-cell responses and potentially eradicate micrometastatic disease [5, 9]. Clinical early-phase trials using multi-epitope peptide cocktails, including oncogenic and angiogenesis-related peptides, have demonstrated safety and immunogenicity in metastatic CRC, although clinical efficacy remains to be established [10].

Moreover, the peptide vaccine landscape in CRC includes epitopes derived from tumor-associated antigens such as carcinoembryonic antigen (CEA), MUC-1, and survivin [11]. As immunologic monitoring technologies improve, the rational design of vaccine regimens tailored to individual tumor antigenicity becomes increasingly feasible.

Biological and mechanistic underpinnings

Mechanistically, the antitumor efficacy of peptides can be mediated by multiple routes. Some peptides directly exert cytotoxic effects, whereby they disrupt tumor cell membranes, inducing apoptosis, or interfering with receptor signaling. Others function as delivery vehicles or immunomodulatory agents. Importantly, the design of these peptides increasingly relies on bioinformatics, molecular docking, and in silico prediction of anticancer potential [7, 12].

Emerging research also underscores the role of antimicrobial peptides with dual anticancer activity. These peptides not only kill microbes but can disrupt cancer cell membranes or modulate intracellular pathways, thereby adding another layer to peptide-based CRC therapy [13].

Challenges and barriers to translation

Despite tremendous promise, several hurdles impede the clinical translation of peptide-based therapies in CRC:

Stability and degradation:

Peptides are susceptible to proteolytic degradation in vivo, reducing their half-life and efficacy. Chemical modifications like cyclization, N-terminal protection, or use of non-natural amino acids can help but may complicate manufacturing and increase cost.

Delivery and pharmacokinetics:

Achieving optimal biodistribution and tumor penetration is nontrivial. While CPPs and homing peptides help, off-target uptake and renal clearance remain concerns.

Immunogenicity:

Though generally low, peptide therapies, especially vaccines, must balance immune activation with safety.

Manufacturing and scale-up:

Producing peptides at pharmaceutical grade, with reproducible quality and reasonable cost, is a non-trivial engineering challenge. This is especially so in resource limited settings where investment in pharmaceutical manufacturing is not proportional to the rate of prevalence of various cancers. For instance, prevalence of cancer has been noted to be on the rise in Kenya, occasioned by recent changes in the lifestyles of the population [14].

Regulatory pathways:

Peptide therapies, particularly novel vaccine constructs, face regulatory hurdles related to validation, safety, and consistent immunogenicity.

Future directions and perspectives

To realize the full potential of peptide-based CRC therapies, concerted efforts are needed:

Rational design and bioinformatics integration:

Leveraging machine learning, molecular dynamics, and structure-based design can accelerate the identification of high-affinity, stable peptides.

Combination strategies:

Peptides could complement existing therapies (chemotherapy, monoclonal antibodies, immune checkpoint inhibitors), enhance efficacy while reducing side effects.

Personalization:

Tumor antigen profiling and neoepitope mapping should inform personalized vaccine development.

Advanced delivery platforms:

Formulations such as nanoparticle-peptide conjugates, PEGylation, or sustained-release systems may enhance pharmacokinetics and tumor targeting.

Robust clinical trials:

Early-phase trials must rigorously assess not only safety and immunogenicity but also downstream clinical endpoints like recurrence and survival.

In light of the foregoing discussion, it can be seen that peptide-based therapies offer a versatile, precise, and increasingly mature toolkit in the fight against colorectal cancer. While challenges remain, the confluence of bioinformatics, molecular engineering, and immunology holds promise for a new era of peptide-driven CRC interventions. Prioritizing translational efforts will be key to turning preclinical promise into patient benefit.

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