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PROTOCOL

The Role of Ubiquitin-specific Peptidases in Colorectal Cancer: A Systematic Review Protocol

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Abstract

Background: This systematic review aims to comprehensively assess and synthesize the current body of evidence regarding the role of ubiquitin-specific peptidases in colorectal cancer. **Methods:** This protocol adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) and was officially registered with the International Prospective Register for Systematic Reviews (PROSPERO) under the registration number CRD42022348183. **Results:** This study will provide a concise summary of the synthesized data from the included studies and will synthesize key findings, explore clinical and therapeutic implications, address limitations and gaps in knowledge, and propose avenues for future research. **Conclusion:** This section will conclude by summarizing the key takeaways from the systematic review and emphasizing the relevance of the findings in advancing our knowledge of the role of USPs in colorectal cancer. It will also underscore the potential implications for clinical practice and future research directions.

Keywords: Colorectal Cancer- Ubiquitin-specific Peptidases- Protocol

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Introduction

Colorectal cancer (CRC) stands as a highly prevalent malignancy on a global scale, casting a substantial weight upon public health. It ranks as the third most frequently diagnosed cancer and is the second primary contributor to cancer-related fatalities worldwide. CRC originates from the epithelial cells lining the colon or rectum, manifesting through a multifaceted interplay of genetic, environmental, and lifestyle influences. Notwithstanding progress made in screening, diagnosis, and therapeutic interventions, CRC persists as a formidable adversary, emphasizing the imperative for a more profound exploration of its molecular underpinnings and potential avenues for therapeutic intervention [1-7].

Recognizing the diverse factors contributing to the

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onset of CRC holds exceptional significance in the pursuit of combating this disease. Among the pivotal aspects in cellular regulation, post-translational protein modifications play a central role, influencing crucial functions such as tumor proliferation and metastasis. This recognition has spurred researchers to delve deeper into these modifications, aiming to uncover insights that could potentially unveil innovative therapeutic avenues. One notable form of post-translational modification is ubiquitination, a reversible process involving the attachment of ubiquitin, a 76-amino-acid protein, to other proteins. Ubiquitination serves as a regulatory mechanism governing numerous cellular processes while upholding overall cellular equilibrium [8-11].

Ubiquitin-specific peptidases (USPs), a subset within the family of deubiquitinating enzymes (DUBs), assume a pivotal role in governing cellular processes through the precise removal of ubiquitin chains from target proteins. This enzymatic function extends its influence across a broad spectrum of vital cellular functions, including the regulation of the cell cycle, facilitation of DNA repair mechanisms, orchestration of programmed cell death (apoptosis), and modulation of intricate signal transduction pathways. Within the realm of cancer research, USPs have garnered notable attention, primarily attributable to their capacity to finely tune the stability and activity levels of oncoproteins as well as tumor suppressors [12-18].

Emerging evidence suggests that dysregulation of USPs may be a key factor in the development and progression of CRC. Several studies have implicated specific USPs in processes crucial to CRC pathogenesis, such as cell proliferation, apoptosis resistance, epithelial-mesenchymal transition (EMT), and metastasis. Moreover, USPs have been linked to the stability and function of proteins with established roles in CRC, including β-catenin, p53, and various growth factor receptors.

Significance of the Systematic Review: A systematic review focused on the role of USPs in CRC is essential for several reasons:

1. Identifying Therapeutic Targets: Understanding the specific USPs involved in CRC can unveil potential therapeutic targets, leading to the development of novel treatment strategies.

2. Prognostic Insights: Investigating the association between USP expression and CRC patient outcomes can provide valuable prognostic information, aiding clinicians in treatment decision-making.

3. Highlighting Knowledge Gaps: A systematic review can identify gaps in the existing literature, paving the way for future research directions and hypotheses.

4. Clinical Translation: Insights gained from this review may ultimately lead to the development of precision medicine approaches tailored to CRC patients based on their USP profiles.

In summary, this systematic review aims to comprehensively assess and synthesize the current body of evidence regarding the role of USPs in colorectal cancer. By doing so, it seeks to shed light on the molecular mechanisms underpinning CRC pathogenesis and potentially pave the way for innovative therapeutic interventions in the fight against this prevalent and deadly malignancy.

Objective

To systematically review the existing literature to determine the role of ubiquitin-specific peptidases in the development, progression, and treatment of colorectal cancer.

Methods

This protocol adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) [19] and was officially registered with the International Prospective Register for Systematic Reviews (PROSPERO) under the registration number CRD42022348183.

2.1. Eligibility Criteria

2.1.1 Population

This systematic review will encompass studies involving human subjects who have been diagnosed with colorectal cancer (CRC). Studies focusing on both newly diagnosed and recurrent cases of CRC will be considered. There will be no restrictions based on age, gender, ethnicity, or geographical location.

2.1.2 Intervention/Exposure

Studies eligible for inclusion will investigate the expression, activity, or any other relevant aspects of ubiquitin-specific peptidases (USPs) in the context of colorectal cancer. These investigations may involve various types of interventions or exposures, such as:

- Assessment of USP expression levels in CRC tissues or cells.
- Examination of USP enzymatic activity in CRC.
- Studies involving genetic or pharmacological modulation of USPs and their effects on CRC.

2.1.3 Comparator/Control

Given the nature of the research question, this systematic review does not require a specific comparator or control group. Studies that investigate USPs in CRC without direct comparison to a control group will be included.

2.1.4 Outcomes

Eligible studies should report outcomes related to the role of USPs in colorectal cancer. These outcomes may encompass, but are not limited to:

- Tumor growth and proliferation.
- Metastatic potential and invasion.
- Response to therapy or treatment resistance.
- Prognostic markers for CRC.
- Molecular mechanisms involving USPs in CRC progression.

2.1.5 Study Designs

To comprehensively address the research question, a

wide range of study designs will be considered, including:

• Observational studies: Cohort studies, case-control studies, cross-sectional studies, and longitudinal studies that investigate USP involvement in CRC.

• Experimental studies: In vitro and in vivo experiments exploring USP functions in CRC.

• Clinical trials: Studies assessing the impact of USP-targeted interventions on CRC outcomes.

2.1.6 Exclusion Criteria

Studies will be excluded if they do not meet the inclusion criteria outlined above. Additionally, studies not published in English or those without full-text availability will be excluded.

2.2 Study Selection

2.2.1 Screening Process

The study selection process will be carried out in a two-stage approach, including an initial screening of titles and abstracts followed by a full-text assessment. The screening will be performed independently by two reviewers. Any discrepancies or disagreements regarding study eligibility will be resolved through discussion, involving a third reviewer if necessary. Transparency and consistency in decision-making will be ensured throughout this process.

2.2.2 Inclusion Criteria Refinement

During the full-text assessment, each study's eligibility will be reevaluated against the predefined inclusion criteria, with a particular focus on the following aspects:

• The relevance of the study's population, intervention/exposure, outcomes, and study design to the research question.

• The provision of sufficient data to extract relevant information regarding USPs and their role in colorectal cancer.

2.2.3 Handling of Duplicate Publications

In cases where multiple publications exist for a single study (e.g., conference abstracts, full-length articles, supplemental materials), the most comprehensive and up-to-date source of data will be selected for inclusion. If there are uncertainties or discrepancies between sources, the authors will be contacted for clarification.

3. Data Extraction

3.1 Data Items

Data extraction will involve systematic collection of relevant information from eligible studies. The following data items will be extracted:

• Study characteristics: Author(s), publication year, study design, location, and funding source.

• Participant demographics: Age, gender, ethnicity, and relevant clinical characteristics (e.g., cancer stage, treatment status).

• Intervention/exposure details: Description of USP-related interventions or exposures, including specific USP isoforms or proteins studied.

• Outcomes: Key findings related to USPs in colorectal cancer, including quantitative data (e.g., effect sizes, hazard ratios) and qualitative descriptions.

• Methodological details: Information on study methodologies, including assay techniques for assessing USP expression or activity, sample sources, and any potential sources of bias.

3.2 Data Extraction Tool

A standardized data extraction form will be developed and utilized by reviewers to ensure consistency and accuracy in data collection. This form will be pilot-tested on a subset of included studies to refine data extraction procedures.

3.3 Data Verification and Quality Control

To enhance data reliability, a random sample of extracted data will be independently cross-verified by a second reviewer. Any discrepancies will be resolved through discussion, involving a third reviewer if needed. Quality control measures will be implemented to maintain data accuracy throughout the extraction process.

Results

4.1 Search Results

In this section, we will provide an overview of the initial search results. It will include the number of records identified through the search strategy, along with the sources and databases from which these records were retrieved. A flow diagram, following PRISMA guidelines, will be presented to illustrate the progression from initial search to the final selection of studies for inclusion.

4.2 Study Selection

This subsection will detail the study selection process, including the number of studies screened at each stage (title and abstract screening, full-text assessment) and the reasons for exclusions. The final number of studies meeting the inclusion criteria will be reported.

4.3 Characteristics of Included Studies

Here, we will present a summary of the characteristics of the included studies. This will encompass essential information such as the publication year, study design, location, sample size, and key findings related to the role of ubiquitin-specific peptidases (USPs) in colorectal cancer (CRC).

4.4 Data Synthesis and Summary

This subsection will provide a concise summary of the synthesized data from the included studies. It will highlight the main findings and trends observed in relation to USPs and CRC. Depending on the nature of the included studies, this section may incorporate quantitative data, such as effect sizes, as well as qualitative descriptions of USP involvement in CRC.

4.5 Subgroup Analyses (if applicable)

If subgroup analyses were conducted based on predefined criteria (e.g., cancer stage, USP isoforms), this subsection will present the results of these analyses. It will discuss any variations or patterns identified across different subgroups.

4.6 Quality Assessment

Summarize the results of the quality assessment of included studies, addressing any potential biases or methodological limitations identified during the review process. This will provide context for interpreting the reliability of the findings.

4.7 Additional Analyses (if applicable)

If any additional analyses or sensitivity analyses were performed, such as assessing publication bias or exploring heterogeneity between studies, these results will be presented and discussed.

4.8 Data Availability and Reporting Bias

Discuss any challenges or limitations encountered in accessing data or potential reporting biases identified during the review process.

Discussion

5.1 Synthesis of Key Findings

In this section, we will synthesize and discuss the key findings derived from the selected studies regarding the role of ubiquitin-specific peptidases (USPs) in colorectal cancer (CRC). This synthesis will involve an in-depth analysis of the evidence presented in the reviewed studies, focusing on the following aspects:

• The influence of USPs on CRC progression, including their impact on tumor growth, metastasis, and invasion.

• The association between USP expression or activity and CRC patient outcomes, such as survival and disease recurrence.

• The potential implications of USPs in CRC therapy, including their involvement in treatment resistance or sensitivity.

5.2 Clinical and Therapeutic Implications

This section will explore the clinical and therapeutic implications of the findings. We will discuss how a deeper understanding of USPs in CRC could inform clinical practice and therapeutic strategies. Specifically, we will consider:

• The potential of USPs as prognostic markers for CRC, aiding in patient risk stratification.

• The prospects of USPs as therapeutic targets for CRC, including the development of USP-specific inhibitors or activators.

• The role of USPs in personalized medicine approaches for CRC treatment.

5.3 Limitations and Gaps in Knowledge

An essential aspect of the discussion will involve an honest appraisal of the limitations and gaps in the existing literature. We will address methodological limitations in the reviewed studies and potential sources of bias. Additionally, we will highlight areas where further research is needed to deepen our understanding of the role of USPs in CRC. These gaps may include:

• The need for more comprehensive and standardized methodologies for assessing USP expression or activity.

• The necessity of larger and more diverse patient cohorts to establish robust associations.

• The exploration of specific USP isoforms or subtypes in CRC, which may have distinct roles.

5.4 Future Directions

Building on the identified limitations and gaps, this section will propose avenues for future research in the field of USPs and CRC. We will outline potential research questions and directions that may contribute to a more comprehensive understanding of the topic. These could involve:

• Exploring the mechanistic underpinnings of USPs in CRC through in vitro and in vivo studies.

• Conducting prospective studies to validate the prognostic and predictive value of specific USPs in CRC.

• Investigating the therapeutic potential of USP-targeted interventions in preclinical and clinical settings.

In conclusion, the "Discussion" section will conclude by summarizing the key takeaways from the systematic review and emphasizing the relevance of the findings in advancing our knowledge of the role of USPs in colorectal cancer. It will also underscore the potential implications for clinical practice and future research directions.

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Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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