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IMMUNE ENVIRONMENT IN COLORECTAL ADENOMAS: a systematic review

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 July 2024 and was last updated on 30 July 2024.

INTRODUCTION

Review question / Objective We aim to provide an overview of the current research examining the immune environment in both early and advanced colorectal adenomas, as well as the regulatory factors influencing immune infiltration.

Condition being studied For over fifty years, cancer development has been linked to the adenoma-carcinoma sequence. It is well-established that colorectal carcinoma (CRC) typically arises from colorectal mucosal epithelial cells of the glands or glandular structure. It is known that only small proportion of small adenomas progress to large adenomas and cancer. Immune response and immune infiltration may be responsible for this. Loss of immune control may lead to tumor progression. Immune response to CRC has been widely studied, with significant implications on prognosis and treatment. Colorectal adenoma is much less extensively studied compared to carcinoma and is the condition studied in this systematic review.

METHODS

Search strategy The present systematic review was performed according to the PRISMA guidelines 2020. The systematic review included human and experimental studies investigating the correlation between colorectal adenoma and its immune microenvironment characteristics. All years of publication were eligible until 2024 January. The selected studies had to be written in English. Inclusion criteria were not limited to human studies, as research involving rodents and organoids was also incorporated. All types of studies were eligible for inclusion, although only articles with full text available were included in the systemic analysis. The PubMed database was used for the literature search concerning colorectal adenoma. The last search was conducted in 2024 January. An additional 7 external articles were included. The advanced search function in

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PubMed was used in the literature search for this systematic review. The search was carried out using 3 entered keywords: “immune infiltration” and “adenoma” and “colorectal”. No filters were applied within this database. After obtaining search results, two independent reviewers read titles and abstracts of provided studies. If more clarity was required, the full article was thoroughly examined. In case of a disagreement among the initial reviewers, the third reviewer-consultant was asked to look at the debatable full article text. His/Her decision was final and undisputable. We extracted various data points including titles, authors' names, years of publication, methodological details, sample sizes of participants/subjects, and key findings, and organized them into a Microsoft Excel spreadsheet for comprehensive analysis.

Participant or population In this review, all patients were included regardless of their age, sex, origin, or ethnicity.

Intervention No interventions were conducted for this review. This review focuses on analyzing existing literature analyzing the immune environment of early and advanced colorectal adenomas and the known regulatory factors for immune infiltration.

Comparator No comparative intervention was applied to the patients.

Study designs to be included All studies regardless of their design were included in the review.

Eligibility criteria All inclusion or exclusion criteria were defined in the PICOS.

Information sources The PubMed database was used for the literature search concerning colorectal adenoma. The last search was conducted in 2024 January. An additional 7 external articles were included.

Main outcome(s) The data on the CD4+ T cell infiltration is controversial: some authors suggest that CD4+ concentration decreases going through adenoma-carcinoma sequence, however others show that CD4+ concentration increases through different stages of the CRC development. A third suggestion is that CD4+ concentration is similar in small adenomas and normal mucosa but there is a decreased infiltration CRC.
The levels of cytotoxic CD8+ T lymphocytes vary across studies examining the colorectal adenoma-carcinoma sequence. Decrease of CD8+ T cells was noticed in adenoma to carcinoma development). The opposite opinion exists as well, showing that CD8+ T cells increase as the histology of the lesion evolves throughout adenoma-carcinoma sequence.
CD68 expression rises as the level of dysplasia increases. CD68+ cells were detected in healthy tissue-ulcerative colitis-adenoma-adenocarcinoma sequence, as well as, macrophages were noticed in LGD-HGD-invasive adenocarcinoma pathway.
There are evidence that counts of eosinophils decrease as the adenoma development progresses. In tubular adenomas with low-grade dysplasia, a notable presence of infiltrating eosinophils was observed, whereas fewer eosinophils were noted in cases of adenomas with high-grade dysplasia. Adenocarcinoma cases showed only minimal eosinophil infiltration. A statistically significant decrease in tissue eosinophil count was found as malignancy potential increased. However, there was no statistically significant difference in the degree of tissue eosinophilia between cases of low-grade and high-grade dysplasia. Another study reports, that an inverse relationship was observed between the invasiveness of carcinoma and the intensity of stromal eosinophilia.

Quality assessment / Risk of bias analysis Newcastle-Ottawa assesment was performed for all publications.

Strategy of data synthesis The present systematic review was performed according to the PRISMA guidelines 2020. The PubMed database was used for the literature search concerning colorectal adenoma. The last search was conducted in 2024 January. An additional 7 external articles were included. The advanced search function in PubMed was used in the literature search for this systematic review. The search was carried out using 3 entered keywords: “immune infiltration” and “adenoma” and “colorectal”. No filters were applied within this database. After obtaining search results, two independent reviewers read titles and abstracts of provided studies. If more clarity was required, the full article was thoroughly examined. In case of a disagreement among the initial reviewers, the third reviewer-consultant was asked to look at the debatable full article text. His/Her decision was final and undisputable. We extracted various data points including titles, authors' names, years of publication, methodological details, sample sizes of participants/subjects, and key findings, and organized them into a Microsoft Excel spreadsheet for comprehensive analysis.

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Subgroup analysis No subgrouping was performed.

Sensitivity analysis Not applicable.

Language restriction Due to language limitations, only studies authored in English were examined and included into the research.

Country(ies) involved Lithuania.

Keywords adenoma, carcinoma, adenoma-carcinoma sequence, CD4+, CD8+, immune infiltration.

Contributions of each author

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