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Changes in the Proportions of Peripheral Blood Immune Cell Subsets across Different Stages of Colorectal Cancer

Miao Liu, Chanchan Hu*

The Affiliated Hospital of Chengde Medical University, Chengde, Hebei, 067000, China

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Abstract: Colorectal cancer (CRC) is a highly prevalent malignancy of the digestive system, and its initiation and progression are closely associated with the host immune status. Alterations in the proportions of peripheral blood immune cell subsets can dynamically reflect the level of antitumor immune responses and are of considerable value for the early diagnosis, staging assessment, and prognostic prediction of CRC. This article systematically reviews the characteristics of proportional changes in peripheral blood immune cell subsets-such as T lymphocytes, natural killer (NK) cells, and myeloid-derived suppressor cells (MDSCs)-across different stages of CRC. Current controversies and limitations in existing studies are analyzed, and future directions are proposed, including the standardization of detection methods, expansion of sample sizes, and implementation of multicenter collaborative studies to clarify the associations between immune cell proportions and tumor stage. This review aims to provide a theoretical basis for immune monitoring and individualized treatment of CRC.

1. Introduction

Colorectal cancer could indicate one of the significant leading malignancies worldwide in terms of both the critical incidence rates and the important mortality figures, posing a substantial serious threat to human health overall. Moreover, the tumor development and the progression may suggest these processes depend not only on malignant proliferation of tumor cells but appear closely related to functional status of the host immune system. Given that peripheral blood represents the primary compartment for immune cell circulation, peripheral blood might reflect dynamic changes in immune cell subsets and thereby could mirror the systemic antitumor immune state. However, investigating patterns of change in peripheral blood immune cell subsets among CRC patients at different stages may show great significance for elucidating mechanisms of tumor immune evasion. Thus, this review aims to examine the current research status, existing problems, and potential optimization strategies related to changes in peripheral blood immune cell subsets across different CRC stages[1].

2. Importance of Immune Monitoring in Colorectal Cancer

2.1 Regulatory Role of the Immune System in Tumor Development and Progression

Tumorigenesis appears to demonstrate a complex, multistage process in which the significant immune system could plausibly play a dual role. Given that immune surveillance operates effectively, the immune system may recognize and eliminate these newly transformed malignant cells, constituting the first line of defense against cancer. Moreover, the immune effector cells, such as T lymphocytes and NK cells, might directly kill tumor cells, whereas antigen-presenting cells, including dendritic cells, could initiate and regulate specific immune responses. Furthermore, during immune editing, tumor cells with weak immunogenicity may escape immune attack and proliferate into detectable tumors. Within the tumor microenvironment, cancer cells might induce immune tolerance by upregulating checkpoint molecules and secreting immunosuppressive factors. Nevertheless, this immunosuppressive state may promote tumor growth but also facilitates invasion and metastasis[2].

However, the dynamic balance of the immune system could substantially demonstrate that it directly influences the important tumor progression and outcomes. In light of early-stage CRC presentation, the immune system appears activated and may attempt to restrain tumor growth. Thus, as disease advances, immunosuppressive cell populations-such as MDSCs and regulatory T cells (Tregs)-may expand markedly. These cells might suppress effector T-cell function through multiple mechanisms, leading to diminished antitumor immunity. Additionally, interaction between tumor cells and immune system may determine disease trajectory, making immune status a factor for predicting tumor behavior. Therefore, understanding of immune regulation during tumor progression appears fundamental to development of immunotherapeutic strategies.

2.2 Value of Peripheral Blood Immune Cell Subsets in Reflecting Antitumor Immune Status

Peripheral blood is the primary means by which immune cells circulate and transit, and the cellular composition of peripheral blood directly reflects overall immune status in the body. Sampling of peripheral blood is less invasive and more easily repeated than sampling of tumor tissue, which allows repeated longitudinal sampling. The proportion and absolute count of different immune cell subsets in peripheral blood offer objective indicators for assessing antitumor immune capacity. For instance, effector $CD8^+$ T cells are the primary cytotoxic effector cells that directly kill tumor cells, and the proportion and activation state of $CD8^+$ T cells are closely related to the strength of antitumor immune response. NK cells constitute an important component of the innate antitumor immune response, and the number and cytotoxic activity of NK cells reflect the nonspecific immune surveillance capacity[3].

In CRC patients, changes in the number of peripheral blood immune cell subsets have clinical significance. Many researchers have reported abnormal $CD4^+/CD8^+$ T-cell ratios and significantly increased proportions of Tregs, suggesting an immunosuppressive state. The expansion of MDSCs in peripheral blood is associated with increasing tumor burden and disease progression. High-throughput flow cytometry can be used for immunophenotyping of peripheral blood immune cells to profile the immune landscape of patients comprehensively. Blood-based immune analysis enhances our understanding of tumor immune escape mechanisms and helps to find noninvasive immune biomarkers.

2.3 Significance of Immune Cell Proportion Changes in CRC Staging Assessment

Clinical staging of CRC is critically important for treatment decision and prognosis evaluation.

These different clinical stages present large variations in local invasion depth, lymph node involvement and distant metastasis, and will inevitably induce different immune responses. The changes in immune cell proportions are closely associated with tumor stage. In early-stage CRC, with relatively low tumor burden, immune homeostasis is generally well-maintained or partially compensated in certain subsets. While advanced-stage tumor exhibits broadly activated immunosuppressive processes and pronounced proportions changes of multiple effector T-cell exhaustion and immunosuppressive cells in peripheral blood.

Characterizing the proportions of various immune cell subsets in the peripheral blood of patients with different stages of CRC may help to construct auxiliary staging systems for CRC, which may provide additional information in addition to conventional imaging and pathological staging. Some proportions of immune cells have been reported to be potential biomarkers for distinguishing early and advanced stages of CRC. For example, several groups reported that the proportion of Treg in the peripheral blood of advanced stage CRC patients was significantly higher than that in early stage CRC patients. Combining the information of clinical staging parameters and immune cell proportion is of clinical significance for more comprehensive evaluation of the stage of disease and immune function in different stages of CRC, which is clinically meaningful for treatment response, recurrence risk assessment and individualized immunotherapy.

3. Existing Problems in Immune Research across Different CRC Stages

3.1 Insufficient Understanding of Dynamic Changes in Peripheral Blood Immune Cell Subsets

Current studies might not provide systematic depiction of the significant dynamic changes in peripheral blood immune cell subsets during CRC progression. Moreover, research examines one or few cell types-such as $CD4^+$ or $CD8^+$ T cells or Tregs-without comprehensive coverage of NK cells, B cells, MDSCs, neutrophils, and key subsets. This fragmented approach could hinder construction of complete immune network map. Nevertheless, isolated indicators may not capture overall trajectory of immune evolution. Given that functional subtypes within subsets-such as effector memory, central memory, and exhausted T cells-remain scarce, understanding of fine immune regulatory mechanisms appears limited[4].

Methodological heterogeneity might further obscure recognition of the important consistent patterns. However, variations in sample processing, antibody clone selection, flow cytometry gating strategies, and lack of standardized protocols could impede data comparability across studies. Factors such as sampling time points, pre-treatment intervals, and comorbidities may not be adequately controlled. Furthermore, inconsistent criteria for selecting healthy controls-particularly regarding age and sex matching-add complexity. These methodological discrepancies could undermine generalizability of findings and impede consensus on immune changes during CRC progression.

3.2 Inconsistent Results Regarding Immune Differences among Stages

The significant discrepancies may indicate that studies examining immune differences across CRC stages demonstrate considerable methodological variation. Moreover, some research could suggest markedly reduced $CD8^+$ T-cell proportions and elevated $CD4^+/CD8^+$ ratios in the advanced-stage patients, potentially indicating intensified immunosuppression. However, others show no significant changes or even increased proportions of specific subsets, such as effector memory $CD8^+$ T cells. Given that most studies indicate elevated Treg proportions in advanced disease, the magnitude of increase varies widely, and some research might show no statistical significance. Nevertheless, NK cell proportion and activity changes appear inconsistently reported,

undermining reliability as staging indicators.

The significant inconsistencies could demonstrate that multiple factors related to study design and population characteristics substantially influence the observed results. Furthermore, the patient heterogeneity-including ethnicity, age, sex, tumor location, and molecular subtype-may significantly influence immune responses, yet stratified analyses appear lacking. Moreover, small sample sizes limit statistical power, especially for subgroup analyses. Additionally, variability in staging assessments across centers might misclassify patients in transitional immune states. Thus, failure to exclude confounding factors such as neoadjuvant therapy, infections, or autoimmune diseases may exacerbate heterogeneity.

3.3 Limited Research on the Association between Immune Cell Proportions and Clinical Stage

Most studies may demonstrate that differences in immune cell proportions exist between the stage groups, without examining that these continuous relationships between the important immune parameters and the critical clinical stage could reveal significant patterns. Moreover, given that staging appears to be an ordinal variable from stage I to IV, immune changes might indicate linear or nonlinear trends. Furthermore, the absence of trend analyses could preclude identification of dose–response relationships or critical transition points in immune status. However, within-stage heterogeneity-such as varying lymph node involvement in stage III-has been examined in relation to immune gradients.

Thus, translational research on clinical utility of immune–stage associations may remain limited. Nevertheless, studies assess diagnostic accuracy metrics, such as sensitivity and specificity, or establish clinically applicable cutoff values. Additionally, combined analyses integrating immune indicators with traditional staging markers appear scarce. Given that evidence linking immune cell proportions to prognosis-progression-free or overall survival-across different stages seems insufficient, this could limit application as prognostic biomarkers.

4. Optimization Strategies for CRC Immune Research

4.1 Systematic Analysis of Peripheral Blood Immune Cell Subsets across Stages

The standardized multiparameter flow cytometry protocols could indicate that systematic analysis of the peripheral blood samples from these CRC patients and the healthy controls may establish comprehensive immune profiling frameworks. Moreover, the protocols may encompass the major immune subsets-including the T cells, the B cells, the NK cells, and the MDSCs-and the relevant functional subtypes, such as the helper and the regulatory $CD4^+$ T cells and the effector and the central memory $CD8^+$ T cells. Additionally, uniform sample handling procedures, including anticoagulant selection, transport conditions, and pre-staining processing, might ensure data comparability. However, large-scale sample collection may facilitate construction of stage-specific immune cell proportion databases. Thus, dynamic profiles from stage I to IV could enable identification of key transition points.

Given that single-cell sequencing technologies provide unprecedented resolution, integration of these approaches might further elucidate immune cell heterogeneity and the association with tumor stage. Nevertheless, single-cell data may enable discovery of novel subsets and subtle changes undetectable by conventional flow cytometry. However, combining transcriptomic profiles with surface marker expression could allow functional state assessment. Furthermore, integrative multi-omics approaches might offer insights into immune response complexity. Therefore, these methodologies may reveal patterns across CRC stages.

4.2 Clarifying the Relationship between Immune Cell Proportions and Tumor Stage

Multivariate statistical analyses may demonstrate that adjustments for the significant confounding factors, including age, sex, tumor location, and molecular subtype, could enable assessment of the independent associations between these immune cell proportions and stage. Moreover, generalized linear models might analyze trends across stages and identify threshold effects. Given that correlated immune indicators require integration, multivariate techniques such as principal component analysis could incorporate these indicators into composite immune scores and enhance assessment accuracy[5].

However, receiver operating characteristic curve analyses may evaluate discriminative ability of immune indicators and composite scores for staging differentiation. Additionally, optimal cutoff values, sensitivities, and specificities should be determined, and cross-validation might assess model robustness. Nevertheless, analyses quantify diagnostic value of immune indicators and support clinical applicability.

4.3 Exploring Clinical Applications of Immune Indicators in CRC Staging

Given that these findings indicate important relationships, machine learning algorithms could be used to develop predictive models that integrate the significant immune indicators with the relevant clinicopathological features. Moreover, combining immune cell proportions and immune scores with conventional markers-such as carcinoembryonic antigen levels, imaging features, and pathological grade-may improve staging accuracy, particularly in ambiguous cases. Prospective cohort studies appear required to validate model performance in real-world settings.

However, the potential value of immune indicators in treatment decision-making and prognosis might also be evaluated. Differences in therapeutic response to chemotherapy, targeted therapy, and immune checkpoint inhibitors across immune profiles warrant investigation. Nevertheless, associations between immune cell proportions and survival outcomes should be explored to identify prognostic biomarkers. Furthermore, incorporating immune monitoring into disease management could enable dynamic assessment of treatment response and recurrence risk. Thus, this approach may facilitate translation of immune research into precision oncology.

5. Conclusion

The proportional distribution of peripheral blood immune cell subsets may provide a critical window for reflecting the systemic immune status of patients with colorectal cancer (CRC). However, a comprehensive and systematic characterization of the important immune profiles across different disease stages, and clarification of the significant associations with tumor staging, could yield novel insights and robust evidence for immune surveillance, staging assessment, and development of stage-adapted therapeutic strategies in CRC. Moreover, future investigations might prioritize standardization of detection and analytical protocols. Additionally, expansion of sample sizes could enhance statistical power. Nevertheless, validation of findings through multicenter collaborative studies may ensure reproducibility and generalizability. In light of these methodological considerations, such efforts could prove instrumental in facilitating translational integration of immune-related biomarkers into routine clinical decision-making and precision management of CRC.

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