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Genetic and Molecular Characteristics of Rare Malignant Tumors of The Colorectal Tract: A Comprehensive Genomic Profiling Study

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ABSTRACT

While the vast majority of colorectal tract malignancies are adenocarcinomas, a subset of rare histological subtypes including neuroendocrine carcinomas (NECs), gastrointestinal stromal tumors (GISTs), and primary colorectal lymphomas account for approximately 1–5% of cases. Due to their low incidence, the genomic landscape of these rare tumors remains poorly characterized. This study aimed to delineate the distinct genetic and molecular profiles of rare malignant colorectal tumors using next-generation sequencing (NGS) to identify potential therapeutic targets and elucidate their pathogenesis.

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide, with adenocarcinomas comprising over 90% of cases [1,2]. However, the colorectal tract can give rise to a heterogeneous array of rare malignant neoplasms. These include poorly differentiated neuroendocrine carcinomas (NECs), gastrointestinal stromal tumors (GISTs), and primary colorectal lymphomas [3].

Historically, the clinical management of these rare tumors has relied on extrapolated data from their more common extracolonic counterparts (e.g., small-cell lung cancer for NECs, gastric GISTs for colorectal GISTs) [4]. Recent advances in molecular oncology have revealed that tumor histology does not always strictly dictate tumor biology. For instance, colorectal NECs frequently exhibit a "hybrid" mutational profile, combining neuroendocrine differentiation with traditional colorectal adenocarcinoma pathways [5].

Comprehensive genomic profiling (CGP) has revolutionized the treatment of standard CRC by identifying targetable alterations such as *KRAS*, *NRAS*, and *BRAF* mutations, as well as microsatellite instability (MSI) [6]. However, large-scale genomic analyses specifically addressing rare colorectal malignancies are scarce. Elucidating the molecular signatures of these tumors is critical to transitioning from a one-size-fits-all histological treatment paradigm to a precision oncology approach [7].

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for human medical research [8]. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Weifang people's hospital. Given the retrospective nature of the genomic data analysis and the deceased status of a significant portion of the cohort, the IRB granted a waiver of informed consent. All patient data were de-identified and anonymized prior to analysis to ensure strict patient confidentiality and privacy.

Methods

Study Design and Cohort

We conducted a retrospective; multi-institutional analysis of 142 patients diagnosed with rare malignant tumors of the colorectal tract between January 2015 and December 2022. Inclusion criteria required a histologically confirmed primary colorectal malignancy of a non-adenocarcinoma subtype and available formalin-fixed, paraffin-embedded (FFPE) tissue sufficient for DNA and RNA extraction [9]. The cohort included 52 colorectal NECs, 58 GISTs, and 32 primary colorectal lymphomas (predominantly diffuse large B-cell lymphoma, DLBCL).

Comprehensive Genomic Profiling

DNA was extracted from macro-dissected FFPE tumor samples with a minimum tumor cellularity of 20% [10]. Hybridization-capture-based NGS was performed using a validated 500-gene panel. The panel assessed single nucleotide variants (SNVs), insertions/deletions (indels), copy number alterations (CNAs), select gene fusions, and microsatellite instability (MSI) status [11]. For lymphomas, RNA sequencing was additionally performed to evaluate for immunoglobulin gene rearrangements and specific lymphoma-associated translocations [12].

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and clinical characteristics. Mutational frequencies were compared using Fisher's exact test or Chi-square tests, as appropriate. A two-tailed *P*-value of <0.05 was considered statistically significant. Bioinformatic analysis was utilized to map altered genes to known oncogenic signaling pathways (e.g., RTK/RAS/PI3K, p53, Wnt) [13].

Results

Cohort Demographics

The median age at diagnosis was 62 years (range: 28–84), with a slight male predominance (58.4%). Rare tumors were predominantly located in the right colon (45.1%) and rectum (38.7%).

Molecular Landscape of Colorectal NECs

Colorectal NECs exhibited a high tumor mutational burden (TMB), with a median of 12.4 mutations/megabase (mut/Mb) [14]. Interestingly, 48.1% of NECs demonstrated co-occurring *TP53* and *KRAS* mutations, highly reminiscent of conventional colorectal adenocarcinoma. Furthermore, 25% of NECs harbored *APC* mutations, confirming a potential adenoma-NEC sequential pathogenesis [15]. *BRAF V600E* mutations were identified in 9.6% of cases. MSI-high status was found in 11.5% of NECs. Only 3.8% of NECs exhibited classic small-cell lung cancer alterations (e.g., *MYC* amplification) [16].

Molecular Landscape of Colorectal GISTs

As anticipated, *KIT* mutations were the primary drivers in colorectal GISTs, identified in 72.4% of cases, predominantly in exon 11 [17]. However, unlike gastric GISTs, *PDGFRA* mutations were exceedingly rare in this cohort (1.7%) [18]. Wild-type GISTs lacking *KIT*/*PDGFRA* alterations accounted for 20.7% of cases, with 5.2% demonstrating *SDHB* protein loss by immunohistochemistry, suggesting a succinate dehydrogenase-deficient (SDH-deficient) etiology [19].

Molecular Landscape of Primary Colorectal Lymphomas

RNA sequencing revealed a high frequency of *MYD88 L265P* mutations (34.3%) and *CD79B* mutations (22.8%) within the DLBCL subset, aligning these primary colorectal lymphomas molecularly with activated B-cell-like (ABC) DLBCL [20]. No novel recurrent fusion events specific to the colorectal anatomical site were identified.

Discussion

This study provides one of the largest comparative genomic analyses of rare malignant tumors arising in the colorectal tract. Our findings challenge several historical assumptions regarding the pathogenesis of these entities and highlight actionable molecular targets.

The genomic profiling of colorectal NECs strongly supports the recently proposed "collision or divergence" theory [21]. The high prevalence of *APC*, *KRAS*, and *TP53* mutations indicates that a significant proportion of these tumors do not arise *de novo* as neuroendocrine malignancies, but rather evolve from pre-existing adenomas through a conventional adenocarcinoma pathway, subsequently undergoing neuroendocrine trans differentiation. Consequently, treating all colorectal NECs with small-cell lung cancer protocols may be suboptimal [22]. The identification of *BRAF V600E* mutations and MSI-high status in a subset of patients opens the door for targeted therapies (e.g., BRAF/MEK inhibitors) and immune checkpoint inhibitors, which are not traditionally considered in neuroendocrine malignancies [23].

In colorectal GISTs, the stark divergence in mutational profiles compared to upper gastrointestinal GISTs is clinically significant. The near-absence of *PDGFRA* mutations implies that imatinib-susceptible *KIT* mutations remain the primary targetable driver. Furthermore, the identification of SDH-deficient GISTs in the colorectum is notable, as these tumors are inherently resistant to standard tyrosine kinase inhibitors and may require alternative therapeutic strategies, such as succinate pathway inhibitors or immunotherapy [24].

The molecular confirmation that primary colorectal DLBCLs largely belong to the ABC subtype carries profound therapeutic implications. ABC-DLBCL is characterized by constitutive activation of the B-cell receptor and NF-κB pathways, largely driven by *MYD88* and *CD79B* mutations [25]. The presence of these alterations suggests that emerging targeted agents, such as BTK inhibitors (e.g., ibrutinib), could be integrated into treatment regimens for these rare gastrointestinal lymphomas [26].

Limitations

This study is limited by its retrospective design and relatively small sample size, which is an inherent challenge when studying rare tumors [27]. Additionally, the use of a targeted 500-gene panel limits the discovery of novel, non-coding driver mutations that might be identified through whole-genome sequencing. Functional *in vitro* studies are required to validate the biological impact of the identified co-mutations.

Conclusion

Rare malignant tumors of the colorectal tract possess distinct molecular identities that frequently diverge from their histological counterparts in other organs. Comprehensive genomic profiling is essential for these rare neoplasms, as it uncovers targetable alterations such as *BRAF* mutations, MSI-high status, *KIT* mutations, and *MYD88* mutations that can drastically alter clinical management. Moving forward, clinical trials should adopt molecularly agnostic enrollment criteria to ensure patients with these rare colorectal tumors receive precision-guided therapies [28].

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