Molecular Variances Between Rectal and Left Sided Colon Cancers

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Abstract

Background: Retrospective analysis of CALGB 80405 showed that left sided colon cancer tumors had different genetic profiles compared with right-sided tumors, likely due to molecular differences. Molecular variations between LT and rectal tumors remain undefined. Herein, we report our exploration of these variations.

Methods: Tumors with origins clearly defined as splenic flexure to descending colon (SFT), sigmoid colon (SgT), or rectum (RT) were included. Protein expression, gene amplification and NextGen sequencing was performed.

Microsatellite instability (MSI) was measured by PCR. Tumor mutational load (TML) was calculated using only somatic nonsynonymous missense mutations. Chi-square tests were used for comparative analyses.

Results: In total, 1,657 primary tumors (SFT 125; SgT 460; RT 872) were examined. When compared with SFT, RT had a higher frequency of TP53 (17% vs. 37%, p = 0.03) and APC (66% vs. 49%, p = 0.01); a lower frequency of PIK3CA (15% vs. 22%, p = 0.02); BRAF (15% vs. 15% p = 0.0001); GNAS (0.9% vs. 4%, p = 0.04); HNFA4 (4% vs. 12%, p = 0.001); and CTNNB1(12% vs. 4%, p = 0.003); and a higher expression of TOP2A (52% vs. 31%; p = 0.01), ERCC1 (29% vs. 15%, p = 0.03), and MGMT (64% vs. 53%, p = 0.048). When compared with SgT, RT had higher expression of TLE (9% vs. 23%, p = 0.003), TOP2A (52% vs. 35%, p = 0.001), TUBB (41% vs. 28%, p = 0.003), and MGMT (64% vs. 56%, p = 0.003). There were no differences between SFT, SgT, and RT in the frequency of PD-L1 expression (5%, 2%, and 0%) on tumor cells, PD-1 expression on tumor-infiltrating lymphocytes (4%, 42%, and 42%), or Her2 expression (1%, 3%, and 3%) and amplification (1%, 3%, and 5%). MSI was seen in 27% of SFT, 4% of SgT, and 0.7% of RT (total CT vs. RT, p = 0.001). Mean TMB was 23.6, and 5.9 mutations/megabase for the two groups, and the portion of tumors carrying a TML of >17 mutations/megabase was 9%, 3%, and 4% for SFT, SgT, and RT, respectively. In all 3 cohorts, a TML > 17 mutations/megabase was highly concordant with MSI. There was a correlation between PD-1 and TML in RT (p = 0.04) but not in SFT or SgT. There were no correlations between PD-L1 and TML.

Conclusions: Tumors arising in the rectum may carry genetic alterations that are distinct from IBD. A better understanding of disease biology may help to identify therapeutic targets and advance precision medicine.

Results

1. Consort Diagram

2. Frequency of protein overexpression by immunohistochemistry (connective lines indicate statistical significance, p < 0.05)

3. Frequency of gene mutations by NextSeq (connective lines indicate statistical significance, p < 0.05)

4. Frequency of (A) Her2 overexpression (IHC) and amplification (CISH); and (C) MSI in right colon, splenic flexure/descending, and rectal cohorts (connective lines indicate significance when right colon tumors are compared to splenic flexure/descending or colon rectal tumors.

5. Tumor mutation burden (TMB) in the three cohorts. (A) Mean TMB, error bars indicate standard errors; (B) % of tumors carrying TMB >= 17 mutations/megabase.

6. Comparison of (A) NextSeq, (B) Her2 overexpression (IHC) and amplification (CISH); and (C) MSI in right colon, splenic flexure/descending, and rectal cohorts (connective lines indicate significance when right colon tumors are compared to splenic flexure/descending or colon rectal tumors.

Conclusions

• Rectal cancers carry molecular features that are different from left-sided colon tumors.
• CRCs carry a continuous spectrum of genetic alterations from right-sided to left-sided tumors, which can show a clear difference between sides.
• Randomized trials must be stratified based on the location of the primary tumor as well as other molecular features.
• Low frequency mutations exist in several druggable genes (e.g., MSI, Her2, BRAF, PIK3CA, and PTEN)—this may provide therapeutic opportunities.

Future directions

• More comprehensive molecular testing is needed to better stratify patients, which might enable us to further tailor therapy for our patients.
• To carry out prospective clinical trials of treatments tailored to patient-specific molecular targets (gene mutations) to show improved clinical outcomes.
• Collaborative efforts involving multiple cancer centers/institutions.
• Effective data sharing in the research community to promote advances in molecularly classified therapy.

References