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EDITORIAL

Colorectal Adenocarcinoma, Not Just One Disease

Colorectal adenocarcinoma is one of the most common cancer diagnoses worldwide and a leading cause of cancer mortality in the United States. Through decades of research there have been multiple routes of colorectal cancer formation identified. The molecular drivers of progression in these pathways are varied and range from genomic, epigenomic, and environmental. The traditional or chromosomal instability pathway, which generally arises from progression of colon adenomas, is thought to stem from loss of *APC* followed by activating mutations in *KRAS* and then alterations in the tumor-suppressor gene *TP53*, leading to chromosomal instability. From a preneoplastic to invasive cancer perspective, the other major pathway is the serrated pathway. It is characterized by serrated preneoplastic lesions and activating mutations in *BRAF*. This pathway is tied closely to hypermethylation of CpG islands or CpG island methylator phenotype (CIMP), leading to inactivation of *MLH1* and thus microsatellite instability. Although these generally are considered the 2 main pathways for colorectal cancer formation, when looking at large molecular characterizations of colorectal cancer, such as The Cancer Genome Atlas (TCGA) or International Cancer Genome Consortium (ICGC) one can clearly identify cancers that do not seem to fit into either pathway. Another example of this is colorectal cancer that arises in the setting of inflammatory bowel disease. These cancers tend to acquire *TP53* mutations very early in the process and often lack alterations in *APC*. Thus, despite all of the past research, there is still a need to better define the different subtypes of colorectal cancer and to identify the key molecular drivers within each.

In an attempt to further classify colorectal cancer, Guinney et al[1] proposed 4 "consensus molecular subtypes" based on transcriptional profiling, providing further evidence for additional types of colorectal cancer. Going further, Hinoue et al[2] previously proposed 4 colorectal cancer subtypes based on methylation analysis using 27k DNA methylation arrays, which interrogate approximately 27,000 CpG dinucleotides. Although somewhat broad in scope, the 27k arrays lack the broad genome-level characterization ability of larger methylation arrays (450k arrays) or whole-genome bisulfite sequencing. In their report, integrative genome-scale DNA methylation analysis of a large and unselected cohort shows 5 distinct subtypes of colorectal adenocarcinomas, Fennell et al[3] further improve our resolution of the different subtypes of colorectal adenocarcinoma through pan-genomic methylation analysis (450k methylation arrays) and paired expression analysis. They show strong evidence for 2 distinct types of CIMP-high cancers. The first is similar to what we traditionally think of as CIMP-high cancer, but also show a second CIMP-high subgroup. Interestingly this group appears to have a unique methylation pattern, with excess areas of both hypermethylation and hypomethylation. The majority of this group previously was lumped into CIMP-low using the 5-marker CIMP panel proposed by Weisenberger et al.[4] However, using the genome-wide approach suggests this is not the case. Because this subgroup had a high frequency of *KRAS* mutations and almost exclusively was microsatellite stable, it is interesting to speculate if these cancers are traditional colorectal cancers that arise in a high-methylation background (hard-to-explain increased levels of hypomethylation), a hybrid pathway between the chromosomal instability and CIMP pathway, or a unique pathway that uses methylation to promote progression in a different manor than traditional CIMP-high cancers (possibly gene body methylation). Regardless, it does appear that there are a subgroup of CIMP-high cancers that are distinctly different from both traditional CIMP-high cancers and the CIMP-low cancers identified in this study.

By showing an increase in mutations within epigenetic regulators (chromatin remodeling genes) in CIMP-high cancers, Fennell and colleagues begin to provide a possible mechanism for this epigenetic dysregulation. Because gene body methylation has been linked to increased gene expression, the significant preference for the methylation of gene bodies of oncogenes as compared with tumor-suppressor genes in CIMP-high cancers raises the possibility of a different route of oncogenic activation in these cancers. If this is the case, one could image targeting epigenetic regulation as a possible mode of therapy.

In this generation of rapidly expanding ability to test clinical samples and with better and more numerous molecularly targeted therapies, having a clear understanding of what is driving an individual cancer is going to become critical. It is this knowledge that will allow us to identify the key vulnerabilities within each cancer. Going further, with improved understanding of the progression process that is tied intimately to the different subtypes of the cancers, future early treatment and preventative measures focused on the process driving an individual's neoplastic disease may be realized. Fennell et al[3] push this understanding of the different subtypes of colorectal cancer forward. However, more work still is needed to further define the differences between the cancer subtypes, to determine how these pathways compare in preneoplastic lesions, and to identify and test possible vulnerabilities within each subtype.

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Conflicts of interest
The author discloses no conflicts.


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