

# Novel Insights into the Colon Polyp-to-Cancer Sequence

June 16, 2014

VA Morris

Colorectal cancer is the second leading cause of cancer-related deaths in the United States, and the third most common cancer worldwide. Noncancerous colon polyps, which include benign adenomas and serrated polyps, originate from the epithelial cells of the colon and can progress to malignancies via the accumulation of genetic and epigenetic changes. The number of gene mutations found in adenomas is significantly smaller than those seen in colorectal cancers, which typically have hundreds of mutations as a result of genomic instability. Epigenetic changes, such as aberrant DNA methylation, are found in the polyps and normal tissues of people predisposed to colorectal cancer, suggesting DNA methylation could be an early molecular event in the formation of colorectal cancer. In an exciting set of studies, lead author Dr. Yanxin Luo and colleagues in the laboratory of Dr. William Grady (Clinical Research Division) assessed the methylome of colon polyps and cancers and identified unique polyp subgroups that may be the precursors for specific molecular subtypes of colorectal cancer. Their findings were published in the journal *Gastroenterology*.

The researchers conducted genome-wide analysis of DNA methylation changes in 41 normal colon tissues, 42 adenomas, and 64 cancers. Luo and colleagues used cluster analysis of the DNA methylation patterns in the cancer samples to identify three subtypes of colorectal cancers. The high methylation subset was enriched for two subtypes of colorectal cancers: the CpG Island Methylator Phenotype (CIMPs), characterized by excessive DNA methylation changes; and the microsatellite instability (MSI) subtype, which results from defects in DNA mismatch repair machinery causing the expansion or contraction of DNA repeats throughout the genome. The intermediate methylation subset corresponded to CIMP2 or CIMP-low colorectal cancers. The third subset comprised of low DNA methylation changes was enriched for non-CIMP cancers. The researchers examined gene mutations in these subtypes, and found that the high methylation subset lacked *APC* mutations, suggesting these cancers may arise independent of the WNT pathway, which is a key signaling pathway commonly altered in colorectal cancers. Importantly, these heterogeneous molecular changes in different colorectal cancers reflect different pathways leading to tumor formation.

Similarly, the researchers performed cluster analysis of DNA methylation patterns in the adenoma samples. They found a low-methylator adenoma subtype that appears similar to normal mucosa,

and may identify the 90% of adenomas that do not progress to colorectal cancer. A second subset included high-methylator adenomas, which have a DNA methylation pattern similar to CIMP-negative colorectal cancers. Over half of these polyps possessed *KRAS* gene mutations, with smaller subsets containing mutations in *APC*, *BRAF* and *PIK3CA* genes. Finally, not studied in this body of work, but shown by a team of investigators led by Dr's. Andrea Burnett-Hartman and Polly Newcomb in the Public Health Sciences Division, there is a third group of polyps that have a serrated morphology and unique epigenetic changes. These serrated polyps appear to be the precursors for CIMP and MSI colorectal cancer. Importantly, the authors confirmed these findings in a separate collection of 24 adenomas.

The researchers found that the majority of changes involved hypermethylation in the promoters of genes, which can lead to decreased gene expression. As such, the researchers confirmed that 55% of the hypermethylated regions were in loci commonly bound by Polycomb group proteins, which repress gene transcription. In addition, DNA methylation changes were evident in the non-tumor colon mucosa surrounding the tubular adenomas and cancers. The researchers compared the DNA methylation patterns in normal tissue from people with and without colorectal cancer, and were able to find changes in 65 different genomic loci in the normal colon of people with colon cancer. The authors state that these changes could contribute to a process known as field cancerization, where specific molecular changes may provide a growth advantage to histologically normal cells that can then expand into a field or patch of cells. These altered fields of cells may predispose a person to acquire additional molecular changes to promote polyp and subsequent cancer formation (Luo, Yu, and Grady, 2014). Building upon these results, future studies are warranted to determine if methylation patterns in the normal colon can predict the risk for developing colorectal cancer.

These results not only provide new insight into the polyp to cancer progression but also suggest new ways to prevent colorectal cancer. Dr. Grady states, "This study identifies novel molecular subgroups of colon polyps that may be the adenomas with very low malignant potential or the adenomas with high potential to progress to microsatellite stable colorectal cancers." Furthermore, Dr. Grady suggests these results have "the potential to lead to more precise risk stratification methods which could improve the cost effective delivery of colorectal cancer screening."

[Luo Y, Wong CJ, Kaz AM, Dzieciatkowski S, Carter KT, Morris SM, Wang J, Willis JE, Makar KW, Ulrich CM, Lutterbaugh JD, Shrubsole MJ, Zheng W, Markowitz SD, Grady WM.](#) 2014. Differences in DNA Methylation Signatures Reveal Multiple Pathways of Progression from Adenoma to Colorectal Cancer. *Gastroenterology* Epub ahead of print, doi: 10.1053/j.gastro.2014.04.039.

See also: [Luo Y, Yu M, Grady WM](#). 2014. Field cancerization in the colon: a role for aberrant DNA methylation? *Gastroenterol Rep (Oxf)* 2:16-20.

### Novel insights into the polyp → cancer sequence

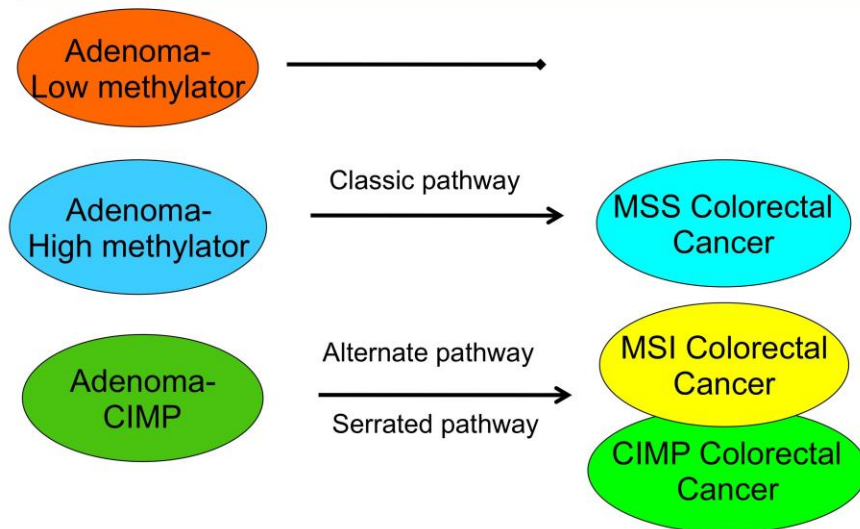


Image provided by Dr. William Grady

The DNA methylome of colon polyps and cancers classify unique polyp subgroups that appear to be the precursors for specific molecular subtypes of colorectal cancer. A low-methylator polyp subtype appears similar to normal mucosa, which could account for up to 90% of polyps that do not progress to cancer. A second set of polyps has a high methylator phenotype similar to microsatellite stable (MSS) colorectal cancer. Finally, there is a group of polyps with serrated morphology that appear to be the precursors for CpG Island Methylator Phenotype (CIMPs) and microsatellite instability (MSI) colorectal cancer.