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EDITORIAL

FOXO3 Loss Drives Inflammation-Associated CRC: The Consequences of Being (Knock)Out-FOX'd

Colorectal cancer (CRC) is the third most common cancer diagnosed worldwide and the third leading cause of all cancer deaths. Although surgical resection of the primary tumor often is possible with early detection and can be associated with greater than 90% 5-year survival, overall 5-year survival is only 65%. The etiology of CRC is multifaceted with genetic, environmental, and inflammatory factors driving the transformation of normal epithelium of the colon or rectum to benign adenoma and ultimately adenocarcinoma.

Local chronic injury and inflammation, such as that observed in ulcerative colitis (UC) patients, is associated with a heightened risk of CRC. In the tumor microenvironment, inflammation promotes tumorigenesis on several levels, influencing cellular proliferation, survival, angiogenesis, metastasis, and reduced responsiveness to chemotherapeutic agents.[1] The range of molecular pathways linking inflammation and CRC are only beginning to be unravelled.

Forkhead box O3 (FOXO3), a member of the FOXO family, has been implicated in several key pathways involved in tumorigenesis and CRC, including proliferation, apoptosis, and cell metabolism. FOXO3 is a transcriptional activator that triggers apoptosis in the absence of survival factors and plays a key role in protein turnover.[2] Similar to other FOXO proteins, FOXO3 is phosphorylated to induce nuclear export, where it is targeted for ubiquitination and proteosomal degradation. More recently, FOXO3 activity has been implicated in the maintenance of immune progenitor cell homeostasis, and FOXO3 deficiency enhances lymphocyte activity during infection.[3] Loss of FOXO3 has been identified in CRC cancer tissues and inflammatory diseases including inflammatory bowel disease, and is associated with deficiencies in apoptosis and cell-cycle progression.

Although previous studies have identified that FOXO3 loss drives inflammation and increases cellular proliferation in CRC , the underlying mechanisms driving these pathologies are largely undefined.[4] In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Penrose et al[5] reported their use of transcriptomic profiling to examine the consequences of *Foxo3* gene deletion in a mouse model of inflammation-associated CRC. They identified novel Foxo3-dependent changes in immune cell recruitment and downstream inflammatory and proliferative pathways associated with tumorigenesis.

Foxo3 knockout mice subjected to the Azoxymethane (AOM)/Dextran sodium sulfate (DSS) model of inflammation-associated CRC showed enhanced intestinal tumorigenesis, with significant increases in tumor number and volume. Transcriptomic analysis showed similar gene expression profiles to transcripts from UC patients with CRC, including microsatellite instability and an inflammatory tumor microenvironment. Tumors in *Foxo3*-deficient animals also showed an increased inflammatory microenvironment with significantly greater infiltration by macrophages, neutrophils, and B cells with reduced natural killer cell infiltration. Similar changes were associated with UC-associated CRC.

Transcriptomic analysis of Foxo3 knockout colons and tumors identified potential roles for novel transcripts that have established links with inflammation, tumorigenesis, and host-microbe signaling. Molecular approaches validated increased expression of transcripts for α2 integrin (*Itga2*) and A disintegrin and metalloproteinase with thrombospondin motifs 12 (*Adamts12*), both key proteins in cellular adhesion and migration. A decrease in the expression of ST8 α-N-acetyl-neuraminide α-2,8-sialyltransferase 5 (*St8sia5*) transcript also was observed, which may facilitate synthesis of specific gangliosides favorable to cancer cell growth. In primary inflammatory bowel disease and CRC tissues, *FOXO3* loss in human tumors was similarly associated with altered expression of *ITGA2*, *ADAMTS12*, and *ST8SIA5* and correlated with poor patient outcomes, inferring a potential mechanistic pathway in the pathogenesis of both UC and CRC. Similar changes in expression of *ITGA2*, *ADAMTS12*, and *ST8SIA5* were observed in esophagus, stomach, liver, lung, kidney, breast, and prostate cancer, suggesting a broader role for FOXO3 in other human malignancies.

Inflammation is an important aspect of tumorigenesis and cancer progression yet the mechanisms by which inflammation promotes tumor growth are poorly understood. Transcriptome profiling approaches, such as those performed by Penrose et al,[5] offer the opportunity to identify novel gene associations and pathways to tease out these mechanisms. Although these studies do not provide evidence of causality, they do reinforce the importance of previously identified gene associations and offer insight into potential avenues for both mechanistic studies and systems biology approaches to understanding inflammation-associated colorectal cancers.

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Conflicts of interest
The authors disclose no conflicts.


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