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Inflammation and Cancer: Is AID aiding?

S. Perwez Hussain, Ph.D.

Laboratory of Human Carcinogenesis, CCR, NCI, NIH, Bethesda, MD 20892

The concept of an association between inflammation and cancer is more than a century old, however, the possible mechanisms linking the two events have recently started to be deciphered by the scientists around the world^{1–3}. Infection and chronic inflammation are implicated in about one-fourth of all human cancers worldwide and, therefore, can be prevented by controlling and targeting the inflammatory pathways that are responsible for perturbing the normal cellular homeostasis. Patients with cancer-prone chronic inflammatory and oxy-overload diseases e.g., ulcerative colitis (UC), pancreatitis, hepatitis, hemochromatosis and Wilson disease carry a several-fold higher risk of developing cancer³. Inflammation in general is an important mechanism that safeguards the body against infection or injury by launching a well-coordinated immune response involving both innate and adaptive immune systems. Following the elimination of the invading pathogen and wound healing, inflammation subsides. However, an unresolved inflammation due to any failure in the precise control of immune response can continue to perturb the cellular microenvironment, thereby leading to the alterations in cancer-related genes and post-translational modification in crucial cellular proteins involved in DNA repair, apoptosis and cell cycle.

Evidence supports the role of a number of components including cytokines, chemokines, inducible nitric oxide synthase (NOS2), reactive nitrogen (RNS) and oxygen species (ROS), cyclooxygenase type-2 (COX2), hypoxia inducible factor-1 α (HIF1- α), signal transducer and activators of transcription 3 (STAT3), matrix metalloproteases (MMPs) in inflammation-associated cancer. An increase in the generation of reactive oxygen and nitrogen species has been implicated in the DNA alteration including point mutations in the cancer-related genes either directly or indirectly through lipid peroxidation and generation of reactive aldehyde for e.g., 4-hydroxynonenal (4-HNE) or malondialdehyde (M₁G). A high p53 mutation-load in the inflamed lesion area of the colon is correlated with an increased NOS2 activity in the patients with ulcerative colitis indicating the involvement of nitric oxide (NO^{*}) or RNS⁴.

The risk of colorectal cancer in the patients with UC increases with the duration of the disease with a cumulative risk of 18% after 30 years. A number of genetic alterations including microsatellite instability and mutation in TP53 tumor suppressor gene are frequently found in UC-associated colorectal cancer. However, in contrast to sporadic CRC, mutation in TP53 occurs in early stages of cancer development in UC. Further support and understanding for an association between inflammation and cancer in patients with UC comes from the accompanying study by Endo et. al., providing evidence supporting the role of activation-induced cytidine deaminase (AID) as a link between inflammation and ulcerative colitis-associated colorectal cancer⁵. Activation-induced cytidine deaminase (AID) was discovered

Address Correspondence to: S. Perwez Hussain, Ph.D., Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, NIH, Bldg 37, Room 3060D, 37 Convent Drive, Bethesda, MD 20892, Phone: 301-402-3431, Fax: 301-496-0497, Email: hussainp@mail.nih.gov.

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about 9 years ago and characterized as a key molecule that is required for immunoglobulin class switch recombination (CSR) and somatic hypermutation (SHM) of immunoglobulin genes in order to produce high affinity antibodies for specific antigens⁶. However, AID over-expression can also have deleterious effects including the targeting of protooncogenes, including BCL6 and cMYC, leading to the mutations and translocations that are associated with lymphomas⁷ (also reviewed in⁸). AID-transgenic mice are prone to lymphomas⁹. Interestingly, AID has been associated recently with inflammation-associated cancer^{10, 11}. The findings of the study by Endo et. al., highlights three major points: 1) Th2 cytokines IL-4 and IL-13 can induce aberrant AID expression in human colon cells 2) an increased AID expression in UC-associated colorectal cancer 3) an association between aberrant AID expression and preferential mutation in p53 tumor suppressor gene in human colonic cells.

So, can we benefit from these findings in diagnosis, prevention and therapy of ulcerative-colitis associated colorectal cancer? A number of issues have to be addressed to get the answer by designing studies based on the current findings. Most importantly, a prospective study is needed to test the hypothesis that aberrant AID expression increases the risk of CRC in patients with UC. Furthermore, it is critical to decipher the mechanism underlying the associations between Th2 cytokines, aberrant AID expression and p53 mutations to identify molecular targets for clinical intervention. It would be interesting to investigate if AID-deficient mice are resistant to colitis-associated colon cancer for example in the model using dextran sodium sulphate (DSS) and azoxymethane (AOM). Similar questions should be asked in mice deficient in IL-4 and IL-13. Chronic inflammation involves the generation of free radicals including NO[•] and as mentioned earlier an increased number of p53 mutant cells in inflamed area of colon correlates with the NOS2 activity in UC. This leads to the question, whether NO[•] modulates AID expression. Another interesting observation of this study is the tissue specificity for targets of AID-related mutagenicity as the mutations in *APC*, *K-ras* and *c-myc* genes occurred at much lower frequency as compared with *TP53* in colon cells. In order to address this issue further studies are warranted to determine the mechanism of AID-associated off-target mutations.

Most recently, it is reported that AID expression is regulated by microRNA (miR)-155 resulting in the suppression of AID-mediated Myc-Igh translocation in murine B lymphocytes¹². These translocations are crucial events in the development of Burkitt's lymphomas that are also deficient in miR-155¹³. Interestingly, miR-155 is upregulated by inflammatory mediators including IFN γ and TNF α and described as an oncogene in a number of different cancers^{14, 15}. A number of miRs, other than miR-155, including miR-146, miR-Let-7 and mir-21 are also regulated by inflammatory mediators. In view of these findings it is important to investigate the possible regulation of AID by miR-155 or other miRs in the colon tissue of the patients with UC.

The inflammation-AID-p53 mutation sequence in UC-associated colon cancer is novel, attractive and promising (Figure 1). However, the validation of the role of AID in UC, the mechanism of AID-associated p53 mutation, and the strategy to control its optimal level without any deleterious effect on host immune response requires further studies based on mechanistic approach before we can, for sure, say "Yes, AID is aiding".

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Figure 1.

Cytokine mediated increase in AID expression in ulcerative colitis, a cancer prone chronic inflammatory disease, may induce p53 mutation increasing the risk of developing colorectal cancer. Inflammation-induced increase in cancer-related miRNA expression can also regulate AID. The interaction of cytokines, free radicals, miRNA, and AID and its association with p53 mutation provide clues for future studies to understand and intervene the development of colorectal cancer in patients with ulcerative colitis.