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JC virus infection- a cause of colorectal cancer?

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Polyomavirus infections have been investigated as potential causes of cancer since the discovery of simian virus 40 (SV40) in 1960 (1) and its ability to induce tumors in experimentally infected animals in 1961 (2). Until 2007, the only polyomaviruses known to naturally infect humans were JC virus (JCV) (3) and BK virus (BKV) (4). Three additional human polyomaviruses have since been identified, including KI (5), WU (6) and Merkel cell polyomavirus (MCV) (7). All polyomaviruses encode for the large T-antigen, a non-structural protein that can bind to and inactivate tumor suppressor proteins p53 and pRB (8) as well as interfere with other cell signaling pathways (9-11). Because of their oncogenic potential, the role of polyomavirus infection in human cancer has been the focus of many investigations. With the exception of the emerging evidence linking MCV to Merkel cell carcinoma (12), the associations between the other human polyomaviruses and cancer remain unclear (13-15).

JCV infection was first implicated as a potential risk factor for colorectal cancer (CRC) with the observation by Laghi et al that 96% of 24 CRC tissues investigated contained JCV DNA sequences (16). Since this initial publication, six tumor studies have subsequently been published in which JCV DNA was found in 26-68% of CRC tissues, with sample sizes ranging from 18 to 100 (17-22). In contrast, two large studies of 100 and 233 CRC tumors observed JCV DNA prevalences of 1% and 0%, respectively (23;24). Reasons for the variation in results across studies include differences in assay sensitivity across laboratories, possible laboratory contamination, and differences in patient populations with respect to the prevalence of JCV infection and/or cofactors potentially involved in JCV-associated carcinogenesis.

Although demonstration of the presence of the virus in the tumor is an important step in the characterization of the role of JCV in colorectal carcinogenesis, additional lines of evidence are necessary to establish a causal role (25). First, with respect to the characterization of the virus in the tumor, a causal role for the virus would be supported by the isolation of JCV DNA to the nuclei of tumor cells, presence of viral DNA at high copy number (i.e. at least one viral copy per cell equivalent), and expression of the T-antigen oncoprotein. JCV viral load in the context of CRC has only been investigated in two studies (16;22), and although viral copy numbers were observed to be higher in CRC tumor as compared to adjacent normal tissue, the absolute copy numbers in the tumor tissue were lower than 1 copy per cell (16). Studies have also demonstrated expression of JCV T-antigen in CRC tissues by immunohistochemistry in 32-94% of CRC tissues investigated ranging in sample size from 18-766 tumors (17;18;21; 26-30). Although none of the CRC studies investigated the location of T-antigen staining within

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the cell, a study of 74 adenomas did observe the concentration of T-antigen staining to the nucleus in the 12 JCV T-Ag-positive tissues (31). Furthermore, JCV T-antigen expression has been shown to be statistically significantly associated with several different CRC tumor characteristics, including loss of heterozygosity (19;28;29), p53 expression (28) and gene methylation (19).

Like other virus-associated cancers, if JCV were associated with CRC, one would expect higher incidence rates of JCV-associated CRC among immunosuppressed individuals. Liver transplant recipients (LTRs) experience higher incidence of CRC than healthy individuals (32), and, as such, Selgrad and colleagues investigated the presence of the virus in adenomatous polyps and adjacent normal colonic epithelium obtained from LTRs and normal controls (30). Although JCV DNA was observed in similar proportions of the 26 adenomas in LTRs (62%) and 40 adenomas in normal controls (50%), JCV T-antigen expression was observed in 50% versus 5% of adenomas in LTRs and controls, respectively. In addition, JCV DNA was found in 67% of normal mucosa samples from LTRs compared to 24% of normal mucosa in controls, suggesting that immunosuppression may lead to reactivation of JCV infection in the colon (30).

In addition to investigating JCV DNA and T-antigen protein expression in tumor tissues, other biomarkers of JCV infection can be used to further characterize the full signature of the virus in CRC patients (33), such as circulating antibodies to JCV. In the current issue of *Journal of Clinical Gastroenterology*, Niv and colleagues present findings from a cross-sectional study of patients undergoing colonoscopy in Israel, the first study to compare JCV seroreactivity in patients with prevalent CRC or adenomas to normal controls (34). In this study, they observe a statistically significantly higher mean titer of JCV antibodies in those with advanced adenomatous polyp or CRC compared to those with normal colonoscopy findings. In addition, the percentage of patients with JCV antibody titers falling into the fourth quartile increased with disease severity (29% of 41 patients with normal colonoscopy results, 42% of 19 patients with “simple” adenomas, 67% of 12 patients with advanced adenomas and 72% of 25 patients with CRC). Colon tissues were only available for 7 advanced adenomas and 11 CRC tissues, of which JCV DNA was found in 29% and 36%, respectively. The authors concluded that their findings indicate JCV may play an early role in CRC carcinogenesis.

This study is the first report of JCV seroreactivity measured in small numbers of patients with prevalent adenomas and CRC. Therefore, the results should be interpreted with caution, as they are based on limited sample size. Importantly, there was no correlation observed between JCV T-antigen expression in the colon tissues and JCV seroreactivity. The authors state that this discordance could be due to small sample size, although it may also be due to a lack of specificity. JCV seroreactivity to VP1, the capsid protein, is a marker of past exposure to JCV, which is highly prevalent in the general population. Antibodies directed against JCV T-antigen, the oncoprotein, may be a more specific marker of JCV-associated colon disease and better correlated with T-antigen expression in the colon tissues. Alternatively, the lack of concordance between T-antigen expression in the tumor and seroreactivity may reflect the lack of an underlying association between JCV and CRC.

In contrast to the conclusion drawn by the authors, the observation that JCV antibody levels were higher among individuals with more advanced disease (advanced adenomas and CRC versus simple adenomas and normal colon tissue) could also suggest either that individuals with more advanced disease may be immunosuppressed and experience reactivation of JCV infection or that JCV infection is somehow involved in the promotion of disease progression. In fact, the role of JCV in carcinogenesis has been postulated to range from an initiator acting directly through a T-antigen-driven hit-and-run mechanism (35) to a promoter acting indirectly through the provision of cytokine rich microenvironment (36). Additional studies with large

numbers of individuals with normal colon, early adenomas, advanced adenomas and CRC are needed to further characterize the full signature of JCV virus infection across the entire disease spectrum.

In addition to large studies of patients with adenomas and CRC that incorporate multiple markers of JCV infection, alternative study designs are also needed to provide information on the temporal relationship between JCV infection and disease. For example, two case-control studies nested within cohorts have examined the association between baseline antibodies to JCV and subsequent development of CRC (37;38). Although neither study observed a positive association between the two, the study that included adenoma cases did observe a statistically significant two-fold increased risk of adenomas associated with baseline JCV seropositivity among men (38). While these prospective studies were able to establish that JCV seroreactivity preceded the development of disease, they relied on JCV capsid antibodies for exposure assessment. As described above, other markers of JCV infection, such as antibodies directed against JCV T-antigen, may be more specific for JCV-associated carcinogenesis (39). In addition to serologic markers, future epidemiologic studies could include viral shedding in the urine (40) or feces (41) as markers of reactivated JCV infection, although if colon carcinogenesis is associated with nonpermissive JCV infections (42;43), active viral replication and subsequent shedding may not be occurring. Ideally, the association between JCV infection and CRC should be investigated in the context of a cohort of individuals undergoing colonoscopy at multiple timepoints, with biopsies of colon tissue and collection of blood, urine and feces. Within such a study, multiple markers of JCV infection could be assessed over time, prior to the development of disease, and correlated with the expression of JCV proteins in and molecular characteristics of subsequent adenoma and CRC. In parallel, ongoing molecular biology studies should continue to elucidate the mechanisms of JCV oncogenesis so that additional markers can be incorporated into human studies. In light of the gaps in our current knowledge, the question of whether JCV causes colorectal cancer remains unanswered.

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