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Review Article

# The Oncogenesis of John Cunningham Virus

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**Abstract**

The John Cunningham Virus (JCV) was isolated in culture from the brain of a case of Progressive Multifocal Leukoencephalopathy (PML) complicating Hodgkin's disease. JCV contains icosahedral capsids that are composed of three structural viral proteins and small, circular, double-stranded DNA genomes. JCV is a member of the polyomaviridae family and infects a large proportion of the population worldwide and may cause PML upon immunodeficiency. When the immune system is defective, JCV may be activated. JCV can be found in tonsillar tissue, and the respiratory and digestive tracts are deemed to be the leading sites for JCV to enter human body. Transgenic mouse model showed that T antigen might induce lung and lens tumors with tissue specificity, which is not linked to alternative splicing of its intron. Taken together, T antigen is considered to play a significant role in JCV oncogenesis. In future, we will establish transgenic mice expressing T antigen in various cells using cell-specific promoter and clarify the pathomolecular mechanisms of T-antigen-related tumors and its tissue specificity of oncogenesis.

## Introduction to John Cunningham Virus

John Cunningham Virus (JCV) was for the first time identified in degenerated brain tissue obtained that from a deceased patient who had Progressive Multifocal Leukoencephalopathy (PML) had been fixed in formalin prior to processing by electron microscopy in 1965 by ZuRhein and Chou [1]. In 1971, JCV was isolated in culture from the brain of a case of PML complicating Hodgkin's disease and named using the initials of the first patient, John Cunningham [2].

JCV contains icosahedral capsids that are composed of three structural viral proteins: VP1, VP2, and VP3 and small, circular, double-stranded DNA genomes. The icosahedron consists of 72 pentamers without apparent hexamers, each comprised of five VP1 molecules and one molecule of VP2 or VP3. The virus is composed of 88% protein and 12% DNA, represented by a single copy of super coiled, circular, and double-stranded molecule of almost 5.2 kb, related to cellular histone proteins H2A, H2B, H3, and H4 and packaged into chromatin like cellular genomes. The genome of virus has a bipartite organization and contains two areas of about the same size, known as early and late transcription units, transcribed in opposite directions starting from a common hyper variable Non-Coding Control Region (NCCR), including the origin of DNA replication, the TATA box, cellular transcription factors binding sites, and bidirectional promoters and enhancers for the transcription of early and late genes. Starting from the NCCR, early transcription proceeds in a counterclockwise direction, when late transcription proceeds clockwise on the opposite strand of the DNA [3].

JCV is a member of the polyomaviridae family and ubiquitously infects a large percentage of the adult population. JCV is established as the etiologic agent for GML and a number of malignancies [4-6]. JCV is found in high concentrations in urban sewage worldwide. The observed abundance and wide dissemination of JCV in water environments strongly suggest the need to shed light on the fate of these viruses in water environments and to elucidate their potential for waterborne transmission [7]. When the immune system is defective, JCV may be activated. JCV can be found in tonsillar tissue, and the respiratory and digestive tracts are deemed to be the leading sites for JCV to enter human body. Abundant levels of JCV receptor-type sialic acids are expressed in lung tissue. The JCV receptor-type sialic acids can mediate JCV infection. JCV has been detected in several epithelial malignancies, such as colon, prostate, and esophageal carcinomas. T-antigen is considered to play a significant role in JCV oncogenesis as it interferes with two tumor suppressor proteins, pRb and p53. Both of them can regulate cell-cycle progression [8]. Moreover, the association of T-antigen with a range of tumor signaling molecules, such as β-catenin, which plays a role in the oncogenic function of JCV T-antigen [9].

## JCV in Head and Neck Squamous Cancers

In the tongue, the presence of JCV may be a risk factor of cancer, because its DNA was detected in the nucleus of tongue cancer cells through a large number of cases from Japan [10]. Compared

with non-neoplastic mucosa, pharyngeal carcinoma showed higher JCV copies [11]. The possibility that JCV may play an oncogenetic role can thus not be rejected. Further research therefore appears to be wanted for this possibility.

## JCV in Lung Cancer

JCV may take part in lung carcinogenesis, especially in squamous cell carcinoma, small and large cell carcinomas other than adenocarcinoma. Lung cancer with higher JCV copy numbers shows high proliferation and down-regulation of cell adhesion mediated by membrane β-catenin from clinical cases for lung carcinomas [8]. The JCV genome might be present in cancer cells, and T-antigen may play a role in oncogenesis of lung cancers through inactivation of p53 and dysregulation of the Wnt signaling pathway in roughly half of all Japanese lung carcinomas cases [12]. In transgenic mouse models which can be established through a transgene composed of the K19 promoter, specific to bronchial epithelium with the JCV T-antigen, the lung tumors were driven by the JCV T-antigen. This finding positive shed light on lung carcinogenesis [13]. The molecular mechanisms of oncogenesis of the JCV in the lung cancer need to be elucidated using transgenic mouse model with lung-specific promoter like surfactant protein C.

## JCV in Gastrointestinal Cancer

The association of human polyomaviruses (e.g. JCV) with gastric cancers is emerging. JCV plays a role as cofactor in the pathogenesis of the intestinal type of gastric carcinomas in old people. The multiplication of JCV copies might be a risk factor and a background for gastric carcinogenesis. However, the involvement of JCV in gastric carcinogenesis has been not yet raveled. The detection of viral DNA and its correlation with deviant methylation of multiple tumor suppressor genes raised the possibility that this virus may play a mechanistic role in the development and/or progression of gastric carcinoma [14,15].

JCV can mediate chromosomal instability (CIN) and aberrant methylation in colorectal cancer (CRC). Like other viruses, chronic infection with JCV may induce CRC by variious mechanisms which should be further studied. In Tunisia, the existence of JCV was significantly tied-in with tumor differentiation [16]. Thus, gene promoter methylation induced by JCV may be a very important process in CRC and the adenoma-adenocarcinoma sequence [17,18]. T-antigen overexpression increased the migration and invasion of colorectal cancer cells and T-antigen expression was immunohistochemically observed in primary tumors as well as in their matching liver metastasis, which may partly be mediated through the AKT/MAPK signaling pathway [19].

The T-antigen of JCV may contribute to gastrointestinal carcinogenesis and the gastrointestinal tract that may lead to JCV infection [20]. Possible molecular mechanisms of oncogenesis of the JCV T-antigen in gastrointestinal carcinogenesis and the reasons for high detection rates of JCV genes should be elucidated in the future.

## The Transgenic Mouse Model of JCV T-Antigen Expressing in Epithelial Cells

To clarify the oncogenic role of JCV T-antigen in epithelial cells, we established two transgenic mice of T-antigen using either α-crystallin A (αAT) or cytokeratin 19(KT) promoters. Lens tumors were found in high-copy αAT mice with the immunopositivity of T-antigen. KT7 mice suffered from lung tumor with EGFR mutation although JCV T-antigen was strongly expressed in gastric epithelial cells. Further investigation suggested that T-antigen might induce carcinogenesis at a manner of cell specificity, which is not linked to alternative splicing of its intron [21]. To clarify the oncogenic role and molecular mechanisms of T-antigen, we plan to establish more transgenic mice of T-antigen expressing in intestinal, parietal, chief, pit, type-II alveolar, hepatic and tubular cells using villin, Atp4b, PGC, Capn8, SP-C, albumin or AQ-2 promoters respectively.

## Conclusions

According to the reported results, JCV may cause an opportunistic infection, and JCV has not might be activated until the immune system is defective although JCV can be found in almost every adult people. JCV has been detected in several epithelial malignancies, such as lung cancer, gastric cancer and CRC. The transgenic mice of JCV T-antigen expressing are often used to make the animal models of these cancers to study the pathogenic mechanisms of the cancers. T-antigen is considered to have a significant role in JCV oncogenesis as it interacts with two tumor suppressor proteins, pRb and p53, and tumor signaling molecules, such as β-catenin. JCV may play important roles in cancinomas. However, the mechanisms of oncogenesis induced by JCV remain yet unclear. Altogether the urgent matter is to make clear the pathogenic mechanism, and it is important to find an effective way for treatment of T-antigen-associated cancers.

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