Potential Mechanisms for the Generation of Chromosome Aneuploidy and DNA Damage in Human Cancer and Disease

Presenter: John M. Lehman, Brody School of Medicine, East Carolina University, Greenville, NC

John M. Lehman is Professor of Pathology and Laboratory Medicine and Director of Cancer Research at the Brody School of Medicine at Eastern Carolina University. His research has focused primarily on the interaction of the SV40 virus large T antigen and small t antigen with cell cycle regulatory proteins and how these proteins are involved in cell transformation and cell cycle dysregulation. These studies will form a basis for understanding the regulation of the G2 and S phase of the cell cycle and how the SV40 antigens (T and t) modulate this regulation, leading to the stimulation of cell DNA synthesis, a block to mitosis and a second S phase (tetraploidy-polyploidy). Recently his laboratory has begun to assay the regulation of DNA synthesis following infection with the human polyomaviruses, BK, JC and MC.

Abstract

The polyomaviruses have attracted increasing attention recently, due to the recognition of a number of human polyomaviruses associated with human disease and cancer. The JC and BK viruses (BKV) isolated in 1971 are associated with progressive multifocal leukoencephalopathy and hemorrhagic cystitis. Within the last three years, two human polyomaviruses, KI and WU viruses, were isolated from upper respiratory infections and MC virus was isolated from Merkel Cell Carcinomas, and presumably is the causative agent of this highly malignant tumor. The Simian virus 40 isolated in 1960 has served as a model for this group of viruses and has provided a significant amount of information regarding the molecular events in virus replication and cell transformation, which include the induction and synthesis of both cellular and viral DNA in the permissive infection. One of the unique events in SV40 infection is the induction of multiple rounds of cellular DNA synthesis (rereplication) that has been assayed utilizing multiparameter laser scanning cytometry (iCys® Research Imaging Cytometer). Potential mechanisms related to the development of neoplasia following polyomavirus infection will be discussed.

BKV has attracted interest due to the association of this virus in kidney transplant patients with nephropathy as a result of virus activation and replication leading to increased graft loss. The studies reported have followed the infection of human renal proximal tubule epithelial cells (RPTEC) with BKV utilizing the multiparameter capabilities of the iCys instrument to assay infection including T antigen, V antigen, DNA synthesis (viral and cellular) and the activation of DNA damage pathways. The infection was efficient with the generation of cells with the accumulation of T- and V-positive infected cells within three to four days post-infection and the accumulation of cells with greater than 16C DNA content. Further, the phosphorylation of Chk1 was demonstrated and the phosphorylation of ATM at ser 1981, suggesting that the activation of DNA damage pathways may allow optimal viral DNA replication and therefore providing an opportunity for antiviral therapy and prevention of rejection.

John M. Lehman[1], Ralph L. Smith[1] and Thomas D. Friedrich[2], [1]Brody School of Medicine, East Carolina University, Greenville, NC, [2] Albany Medical College, Albany, NY