Journal of NeuroVirology, 10(suppl. 2): 22–23, 2004

ISSN: 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280490469662

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JC virus small tumor antigen promotes S phase entry

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A number of studies revealed the detection of human polyomavirus, JC virus (JCV), in a variety of human tumors. Viral large tumor antigen (T-Ag) is known to play a major role in cell proliferation and transformation but the role of JCV small t-Ag in such processes remains completely unknown. Several studies from monkey polyomavirus, SV40, small tumor antigen (t-Ag) suggest that it significantly contributes to the large T-Ag-mediated cell transformation. Here, we investigated the effects of JCV small t-Ag on cell cycle progression and cell proliferation. Examination of subcellular distribution of small t-Ag by means of immunocytochemistry demonstrated that it mostly localizes to the cytoplasmic compartment of the cell. Cell cycle progression analysis of a human glioblastoma cell line, U-87MG, demonstrated that small t-Ag expressing cells enter S phase of the cell cycle at a significantly higher rate than controls when released from G0/G1 arrest. In addition, the growth rate of these cells is consistent with the rate of cell cycle progression and is significantly enhanced compared to controls. Moreover, analysis of the mechanism through which small t-Ag accelerates the cell cycle progression showed that JCV small t-Ag targets a major serine/threonine phosphatase, PP2A, and its interaction domain with this enzyme is mapped toward the middle portion of the protein, residues 82 to 124. Furthermore, examination of the cell cycle stage specific expression profiles of selected cyclins and cyclin-dependent kinases, particularly those active in G1/S and G2/M transition states demonstrated that the rate of the appearance of cyclin E, cyclin B, and cyclin E-dependent kinase 2 (Cdk2) substantially increased in small t-Ag positive cells as compared to controls when the cells were released from G0/G1 arrest. In parallel, in vitro analysis of cyclin E-associated H1 kinase activity of clones demonstrated that small t-Ag positive clones exhibited significantly higher activity than controls. Additionally, results from reporter gene assays showed that small t-Ag has the ability to activate the cyclin E promoter which is consistent

with the results from cell cycle profiles of the clones. Collectively, our results demonstrate that JCV small t-Ag has the ability to facilitate cell cycle progression and such an effect may have implications in JCV-induced cell transformation. This work was supported by NINDS grants awarded to KK and MS.