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Role of JCV agnoprotein in DNA repair

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The late region of human neurotropic JC virus (JCV) encodes a small 71 amino acid Agnoprotein that is also found in the polyomaviruses SV40 and BKV. Several functions of Agnoprotein have been identified including roles in regulating viral transcription and virion maturation. Earlier studies showed that Agnoprotein expressed alone induced p21/WAF-1 expression and caused cells to accumulate in the G2/M stage of the cell cycle. Here we report that Agnoprotein expression sensitized cells to the cytotoxic effects of the DNA-damaging agent cisplatin. Agnoprotein reduced the viability of cisplatin-treated cells and increased chromosome fragmentation and micronuclei formation. Whereas cisplatin-treated control cells accumulated in S-phase, cells expressing Agnoprotein did not, instead becoming aneuploid. Agnoprotein expression correlated with impaired double-strand break repair activity in cellular extracts and reduced expression of the Ku70 and Ku80 DNA repair proteins. After Agnoprotein expression, much of the Ku70 was located in the perinuclear space where Agnoprotein was also found. Results from binding studies showed the interaction of Agnoprotein with Ku70 and this was mediated by the N-terminus. The ability of Agnoprotein to inhibit double-strand break repair activity when added to cellular extracts was also N-terminal. We conclude that Agnoprotein inhibits DNA repair after DNA damage and interferes with DNA damage-induced cell cycle regulation. Since Ku70 is a subunit of DNA-dependent protein kinase that is responsible both for double-strand break repair and signaling damage-induced cell cycle arrest, modulation of Ku70/Ku80 by Agnoprotein may represent an important event in the polyomavirus life cycle and in cell transformation.