International Journal Of Bilogical Sciences

Interferon-Gamma-Induced Nitric Oxide Inhibits the Proliferation of Murine Renal Cell Carcinoma Cells

David J. Tate Jr.1, John R. Patterson1, Cruz Velasco-Gonzalez2, Emily N. Carroll3, Janie Trinh1, Daniel Edwards1, Ashok Aiyar1,4, Beatriz Finkel-Jimenez1, Arnold H. Zea1,4, 5,?

1. Stanley S. Scott Cancer Center, LSUHSC, New Orleans, LA, 70112; 2. Department of Public Health, LSUHSC, New Orleans, LA, 70112; 3. Ohio State University-College of Medicine, LSUHSC, New Orleans, LA, 70112; 4. Microbiology Immunology and Parasitology, LSUHSC, New Orleans, LA, 70112; 5. Section of Pulmonary and Critical Care Medicine, LSUHSC, New Orleans, LA, 70112.

Abstarc :

Renal cell carcinoma (RCC) remains one of the most resistant tumors to systemic chemotherapy, radiotherapy, and immunotherapy. Despite great progress in understanding the basic biology of RCC, the rate of responses in animal models and clinical trials using interferons (IFNs) has not improved significantly. It is likely that the lack of responses can be due to the tumor's ability to develop tumor escape strategies. Currently, the use of targeted therapies has improved the clinical outcomes of patients with RCC and is associated with an increase of Th1-cytokine responses (IFN?), indicating the importance of IFN? in inhibiting tumor proliferation. Thus, the present study was designed to investigate a new mechanism by which IFN? mediates direct anti-proliferative effects against murine renal cell carcinoma cell lines. When cultured RCC cell lines were exposed to murine recombinant IFN?, a dose dependent growth inhibition in CL-2 and CL-19 cells was observed; this effect was not observed in Renca cells. Growth inhibition in CL-2 and CL-19 cell lines was associated with the intracellular induction of nitric oxide synthase (iNOS) protein, resulting in a sustained elevation of nitric oxide (NO) and citrulline, and a decrease in arginase activity. The inhibition of cell proliferation appears to be due to an arrest in the cell cycle. The results indicate that in certain RCC cell lines, IFN? modulates L-arginine metabolism by shifting from arginase to iNOS activity, thereby developing a potent inhibitory mechanism to encumber tumor cell proliferation and survival. Elucidating the cellular events triggered by IFN? in murine RCC cell lines will permit anti-tumor effects to be exploited in the development of new combination therapies that interfere with L-arginine metabolism to effectively combat RCC in patients.

Key Word :
nitric oxide, Interferon-gamma, nitric oxide synthase, renal cell carcinoma, arginase 2, polyamines, L-arginine, cell proliferation.

Volume 8, Number 8, - 2012 , ISSN 1545-1003