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Effect of hypoxic microenvironment on expression of stem cell marker (nestin) in astrocytic tumors

Introduction: Gliomas account for 40% of the primary central nervous system tumors in western countries, and for about one-third (37.3%) in Egypt. Identification of the cellular origin of gliomas presents an opportunity for improving the treatment strategies. It has been postulated that astrocytomas may be originated from neural stem cells. Hypoxia-inducible factor-1a (HIF-1a) is considered one of the key hypoxia regulatory factors. Hypoxia may be a critical component of a stem cell niche and contributes to the tumor initiation and maintenance of cancer stem cells (CSCs). In the present study, we hypothesized that the expression of stem cell marker (nestin) and hypoxia marker (HIF-1a) may be upregulated with increasing grades of astrocytomas. In addition, there is a correlation between hypoxia and stem cell marker in all grades of astrocytomas in both tumor cells (TRCs) and vascular endothelial cells (VECs). To explore our hypothesis, this study was organized into specific aims: (a) analysis of the immunohistochemical expression of nestin and HIF-1a in different grades of astrocytomas and (b) analysis of the correlation between nestin and HIF-1a in different grades of astrocytomas.

Materials and methods: Paraffin-embedded sections of 43 specimens of astrocytic tumors (nine pilocytic astrocytoma, 13 diffuse astrocytomas, seven anaplastic astrocytomas, and 14 glioblastoma multiforme) and six normal brain tissue (as a control) were stained with nestin and HIF-1a using standard immunohistochemical approaches. The immunoreactivity for nestin and HIF-1a in both TRCs and VECs was evaluated. Correlation between nestin and HIF-1a expression was also studied.

Results: The expression of nestin in TRCs was present in 88.4% of patients. As compared with normal brain tissue, there was statistically significant ($P < 0.01$) gradual increase in the mean of nestin immunoreactivity score with increasing grade of the studied astrocytomas (I–IV) (0.0 ± 0.0, 1.7 ± 1.8, 2.5 ± 1.6, 5.7 ±3.2, and 7.8± 2.5, respectively). The expression of HIF-1a was seen in 65.1% of studied patients. The immunoreactivity score of HIF-1a showed significant ($P < 0.001$) difference between low-grade astrocytomas (pilocytic astrocytoma and diffuse astrocytomas) and high-grade astrocytomas (anaplastic astrocytomas and glioblastoma multiforme). There was statistically significant positive correlation between expression of nestin and HIF-1a in both TRCs and VECs ($r = 0.71$ and 0.47, respectively, and $P < 0.001$ for both).

Conclusion: Restricted oxygen conditions increase the CSC fraction. Determining the cross-talk between hypoxia and CSCs will enhance the understanding of tumorigenesis and may provide new therapeutic strategy. Intense expression of nestin in high-grade astrocytomas may be helpful in their diagnosis especially in small biopsy.

Speaker Biography

Ahmed A S Elhakeem is working as a lecturer at the Department of Pathology of Assiut University in Egypt. His professional affiliation entails being a member of the International Society of Neuropathology, Egyptian society of Pathology and Egyptian society of progenitor cell research. He excels in the subspecialty of Neuropathology with over 10 years of experience in the diagnosis of brain and spinal lesions. His research interest also covers cancer stem cells.

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