Gliomagenesis

Results highlighted the role of PTX3 and TIMP1 which were previously considered in glioma tumorigenesis as well as LTF as a new potential biomarker [1].

Increasing evidence has suggested that microRNAs (MicroRNAs) are critical regulators of tumorigenesis [2].

The induction of Epithelial-mesenchymal-transition (EMT) is important for carcinogenesis and cancer progression.

Survival of patients with glioma remains poor, which is largely attributed to active carcinogenesis.

The Hippo signaling pathway plays a crucial role in suppressing tumorigenesis.

Huang et al. identified differentially expressed genes and Competing endogenous RNA (ceRNA) networks in malignant glioma and then constructed Cox/Lasso regression models to further identify the most valuable genes through stepwise refinement. Top-down comprehensive integrated analysis, including functional enrichment, SNV, immune infiltration, transcription factor binding site, and molecular docking analyses, further revealed the regulatory maps among these genes. The results revealed a novel and accurate model (AUC of 0.91 and C-index of 0.84 in the whole malignant gliomas, AUC of 0.90 and C-index of 0.86 in LGG, and AUC of 0.75 and C-index of 0.69 in Glioblastoma) that includes twelve ncRNAs, 1 MicroRNA, and 6 coding genes. Stepwise logical reasoning based on top-down comprehensive integrated analysis and references revealed crosstalk signaling pathways among these genes that were correlated with the circadian rhythm, tumor immune microenvironment, and cellular senescence pathways. In conclusion, the work reveals a novel model where the newly identified biomarkers may contribute to a precise diagnosis/prognosis and subclassification of malignant glioma, and the identified cross-talk signaling pathways would help to illustrate the noncoding RNA-associated epigenetic regulatory mechanisms of glioma tumorigenesis and aid in targeted therapy [3].

Glioma is a unique neoplastic disease that develops exclusively in the central nervous system (CNS) and rarely metastasizes to other tissues. This feature strongly implicates the tumor-host CNS microenvironment in gliomagenesis and tumor progression.

Certain genotypes of inflammatory gene which associated with asthma and allergic conditions (IL-4R α and IL- 13) are inversely associated with glioma risk.

Gohar et al. studied the relation between allergic conditions and serum level of IgE and glioma risk. They also examined the role of SNP of inflammatory genes Interleukin 4 (IL-4 R) α (rs 1801275) and IL-13 (rs 1800925) in development of glioma and to find out factors which can modify the prognosis of glioblastoma. This study included 98 Egyptian glioma cases and 98 healthy controls. Full history and clinical data were taken; total serum IgE were assayed, genotyping of IL-4 R α (rs 1801275) and IL-13 (rs 1800925) genes was carried out by restriction digestion after genes amplification. In cases group

histopathological examination and tumor grading were done. Past history of allergic condition and elevated serum levels of IgE were more frequent in controls than in cases group (P< 0.05). Genotypes AA and AG of IL- 4R α were significantly frequent in cases and A allele were considered risk factor for glioma OR 2.31(1.53- 3.48), P < 0.001. We also found that C allele of IL-13 is risk factor for glioma susceptibility with p value = 0.006. Longer median survival period in glioblastoma were associated with elevated serum IgE level and who were AA genotypes of IL-4 R α. We conclude an inverse relation between glioma risk, and allergy biomarker IgE and allergy related (IL-4R α; rs 1801275) gene polymorphisms. GBM patients with IL-4Rα AA genotype, have longest survival. Chemotherapy and gross total resection improve GBM prognosis [4)].

Connolly et al. investigated the differences and similarities in glioma biology as conveyed by transcriptomic patterns across four mammalian hosts: rats, mice, dogs, and humans. Given the inherent intra-tumoral molecular heterogeneity of human glioma, we focused this study on tumors with upregulation of the platelet-derived growth factor signaling axis, a common and early alteration in human gliomagenesis. The results reveal core neoplastic alterations in mammalian glioma, as well as unique contributions of the tumor host to neoplastic processes. Notable differences were observed in gene expression patterns as well as related biological pathways and cell populations known to mediate key elements of glioma biology, including angiogenesis, immune evasion, and brain invasion. These data provide new insights regarding mammalian models of human glioma, and how these insights and models relate to our current understanding of the human disease [5)].

Both genetic and environmental factors are thought to be causal in gliomagenesis. Several genes have been implicated in glioma development, but the putative role of a major immunity-related gene complex member.

Although epigenetic alterations play an essential role in gliomagenesis, the relevance of aberrant histone modifications and the respective enzymes has not been clarified.

immunoglobulin heavy chain γ (IGHG) has not been evaluated. Prior observations that IGHG-encoded γ marker (GM) allotypes exhibit differential sensitivity to an immunoevasion strategy of cytomegalovirus, a pathogen implicated as a promoter of gliomagenesis, has lead us to hypothesize that these determinants are risk factors for glioma. To test this hypothesis, we genotyped the IGHG locus comprising the GM alleles, specifically GM alleles 3 and 17, of 120 glioma patients and 133 controls via TaqMan® genotyping assay. To assess the associations between GM genotypes and the risk of glioma, we applied an unconditional multivariate logistic regression analysis adjusted for potential confounding variables. In comparison to subjects who were homozygous for the GM 17 allele, the GM 3 homozygotes were over twice as likely, and the GM 3/17 heterozygotes were over three times as likely, to develop glioma. Similar results were achieved when analyzed by combining the data corresponding to alleles GM 3 and GM 3/17 in a dominant model. The GM 3/17 genotype and the combination of GM 3 and GM 3/17 were found to be further associated with over 3 times increased risk for high-grade astrocytoma (grades III-IV). Allele frequency analyses also showed an increased risk for gliomas and high-grade astrocytoma in association with GM 3. Our findings support the premise that the GM 3 allele may present risk for the development of glioma, possibly by modulating immunity to cytomegalovirus [6)].

Over the past 20 years the cytogenetic and molecular genetic alterations associated with glioma formation and progression have been intensely studied and genetic profiles as additional aids to the

definition of brain tumors have been incorporated in the WHO classification.

In fact, first steps have been undertaken in supplementing classical histopathological diagnosis by the use of molecular tests, such as MGMT promoter hypermethylation in glioblastomas or detection of losses of chromosome arms 1p and 19q in oligodendroglial tumors. The tremendous progress that has been made in the use of array-based profiling techniques will likely contribute to a further molecular refinement of glioma classification and lead to the identification of glioma core pathways that can be specifically targeted by more individualized glioma therapies [7)].

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