

Brain cancer essay

[Science](#), [Genetics](#)



The article under study is Expression of mutant p53 proteins implicates a lineage relationship between neural stem cells and malignant astrocytic glioma in a murine model.

Glioblastoma is referred to as the most cancerous type of astrocytic gliomas and the most commonly occurring chief brain cancer in adults. Due to the weak prognosis of glioblastoma, there is an urgent need for a better and profound understanding of disease pathogenesis. The article presents a demonstration of the fact that p53 deficiency is capable of cooperating with various mitogenic signalling pathways for inducing malignant glioma. As an example, it is not necessary to deactivate the Nf1 tumor suppressor, or activate phosphatidylinositol-3-OH kinase pathways, or activate the mitogen-activated protein kinase. However, they may elevate the formation of p53-mediated glioma. Further, the mutant p53 protein expression is determined as a depiction for glioma cell in every stage. Examination study of brain cells by means of a detectable level of mutant p53 expression is said to offer crucial information on the role of neural stem cells as well as transit-amplifying progenitors within p53-mediated gliomagenesis.

Latest research studies have discovered core pathways and genes that are modified within human glioblastoma. Nevertheless, the processes through which changes of these glioblastoma genes separately transform brain cells have not been correctly understood. Moreover, the root of glioblastoma is greatly elusive. The current article tries to address these issues (Wang et al.). The researchers of this article have targeted a p53 in-frame deletion mutation to the brain as an attempt to demonstrate that deficiency in p53 does not offer any substantial growth benefits to adult brain cells. However,

p53 deficiency is likely to induce pleiotropic accumulation of conjunctive oncogenic alterations that drive gliomagenesis. Findings from the study reveal that the first occurrence of a detectable level of mutant p53 proteins accumulation is seen within neural stem cells within the SVZ or subventricular zone, and the initiation of glioma formation is triggered by the subsequent expansion of mutant p53-expressing cells identical to transit-amplifying progenitor cells in the SVZ-related areas.

The article focuses on Glioblastoma which is Grade IV malignant astrocytic glioma also termed as glioblastoma multiforme (long for GBM). Glioblastoma is the most common and aggressive neoplasm seen in human primary brain tumours. Two subtypes are associated with GBM.

1. Primary GBM is one which develops from the beginning with no accurate evidence of pre-existent lesions
2. Secondary GBM is one that is produced from lower-grade gliomas, even though malignant, i. e. Grade II or III gliomas.

Irrespective of typical medical courses and varying molecular lesions, both primary as well as secondary GBMs are known to share similar histopathological and medical characteristics, in particular a high tendency of disseminating penetrating the normal brain parenchyma and immune towards virtually every therapy. Accordingly, the article claims GBM to be among the most deadly human tumours with an average survival that has persisted at one year for over the past 20 years (Wang et al.). Among several studies conducted on the subject of brain cancer, some of the more recent studies have found core pathways and genes which are altered in human

GBM. It was also found that in most of the human primary GBM, mutation in the elements of the p53 tumour suppressor pathways have been determined, as much as 30% to 40% of which have mutations within the p53 gene. Moreover, the studies revealed that frequencies of p53 mutation are higher and same as that of lower-grade cancerous gliomas and secondary GBMS, thereby proposing a pivotal role of p53 gene defects during early stages of glioma growth. Researchers also confirmed that patients with Li-Fraumeni syndrome, carrying germline p53 mutations, have been seen as predisposed to growth of astrocytic gliomas. Yet, the mechanisms through which p53 deficiency transforms normal brain cells still lack clear interpretations.

One important challenge encountered in the understanding of GBM pathogenesis is the identification of the cell-of-origin of this deadly disease. In majority of human cancers, the cell-of-origin remains unidentified until the human tumour is shown at the terminal stages of the disease and therefore do not give a window of study for addressing this crucial question. It has also been illustrated that several forms of brain cancers, including GBM, are controlled and sustained by a subtype of cells similar to stem cells that depict the cellular features of normal stem cells, such as characteristics of multi-potency and self-renewal. Even so, whether a normal stem cell, a fully differentiated cell, or a progenitor cell, is the cell-of-origin for glioma stem cells stays greatly unidentified (Wang et al.). In an adult human brain, progenitor and multipotent neural stem cells are spatially confined to two stem cell categories, namely:

1. The Subventricular Zone of the lateral ventricle
2. The Subgranular Zone of the hippocampal dentate gyrus.

Previous literature on genetic studies also concludes that the use of murine glioma models and imaging analysis from a clinical field gives evidence that a few GBMs might be produced from the SVZ stem cell niche. Seen at the cellular level are the neural stem cells in the adult SVZ (type B cells or SVZ-B) giving rise to an extremely multiplying cell population, i. e. transit-amplifying progenitor cells subsequently differentiating into two lineage-constrained progenitor cells called neuroblasts or SVZ-A cells, along with oligodendrocyte precursor cells or SVZ-OPC (Wang et al.). The fact is made evident that due to the deficiency in reliable markers for glioma cells, mainly during early stages of tumour maturation, the purpose of several SVZ cell populations in gliomagenesis continues to be unknown. The study devises a murine glioma framework wherein an in-frame p53 deletion mutation is particularly directed into the human brain nervous system and uses it to investigate the purpose of neural stem cells as well as transit-amplifying progenitors within p53-mediated gliomagenesis. Specifically, in a bid to study the role of p53 in gliomagenesis, study researchers applied two transgenic mouse strains to target a p53 mutation inside the nervous system.

The first strain showed Cre being controlled by the human glial fibrillary acidic protein or GFAP promoter (read hGFAP-cre). Specifically, the hGFAP-cre gene is presented in radial glial cells all the way through embryonic development and in fully grown astrocytes of the postnatal brain. The study

also found that as radial glial cells are the chief multi-potent neural stem/progenitor cell populations within the developing human brain, hGFAP-cre-mediated transgene deletion will be channelled to all the descendants of radial glial cells such as neurons, glia, and adult neural stem cells. Therefore, the inactivation of the hGFAP-cre-mediated neural-specific transgene enables the assessment of the related tumour susceptibility or “tumour competence” of neural stem and progenitor cells, and glia in the adult brain.

Lastly, the second strain harboured a p53 conditional allele (p53flox). Cre-mediated recombining of this p53flox allele leads to an in-frame deletion of exons 5 and 6 through which a substantial portion of the p53 DNA binding domain (DBD) is encoded.

Works Cited

Wang, Yuan, Yang Jiong, Zheng Huarui, Tomasek Gerald J., Zhang Peng, McKeever Paul

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