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Review Article

Comprehensions Keen on the Biology of Brain Tumors: Possibilities and Challenges

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ABSTRACT

The word "tumor" is a Greek term that refers to a swelling or a lump. In modern medical terms, a tumor is usually an abnormal mass of cells and tissues which grows due to the abnormal division of cells. The unnatural division of cells occurs due to the cancerous nature of these cells, which no longer obey standard checkpoints that prevent healthy or non-cancerous cells from uncontrolled cell divisions. Tumors may be circumscribed or diffuse depending on whether they remain localized to a part of the brain or spread to other parts aggressively by metastasis; in 2016, WHO has classified tumors of the brain or central nervous system by taking into account the latest molecular genetic data along with classic histopathological features characteristic of each kind of tumor. The new classification system makes diagnosis more precise, but a better prognosis analysis is now possible since genotype is far more determinative and accurate than histological phenotype. Modern technologies like high throughput gene sequencing, CRISPR-Cas9 gene editing, and personalized medicine approaches have improved the prognosis of brain tumor patients. They have also revolutionized our understanding of the biology of brain tumors and how they are now being treated. In this review, we will discuss the latest knowledge about the biology of brain tumors and how modern technologies are helping to understand the molecular basis of these pathologies and develop better treatment options to improve patient survival.

Keywords: Brain tumors, Pathologies, Checkpoints, Sequencing, CRISPR-Cas9.

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INTRODUCTION

Cells are structural and functional units that create the human body. Cancer begins when genetic variations interfere with this organized process. Cells start to grow nonstop and form a mass called a tumor. Commonly tumors are divided into three groups 1. Benign Tumor, 2. Premalignant Tumor, 3. Malignant Tumor.[1,2] Benign Tumor: These tumors are circumscribed and do not metastasize or spread to other tissues. They do not return once after being removed. In other words, such tumors are not usually harmful unless their unrestricted growth can lead to large tumors that can exert pressure on neighboring tissues, including blood vessels and nerves, and cause pain and malfunction of organs. Some benign tumors are adenomas, fibrosis or fibroids, hemangiomas, lipomas, etc.[3,4] Premalignant Tumor: A premalignant tumor does not have hallmark features of cancer or malignancy but has the potential to transform into a malignant or cancerous one. Only appropriate laboratory and clinical tests can detect the premalignant tumor while still in a stage of premalignancy. Given the potential of premalignant tumors to develop into cancerous forms, it is recommended that a premalignant tumor be monitored closely over time to ensure timely intervention. Some well-studied examples of premalignant tumors are actinic keratosis, cervical dysplasia, metaplasia of the lung, leukoplakia, etc.[4-8] Malignant Tumor: The word malignant is Latin for "badly born."

Malignant tumors are cancerous. They can grow and spread aggressively and pervasively to other healthy tissues by a process known as metastasis, leading to death by multiple organ failure. In malignancy, cancerous cells increase faster and fail to die at a normal rate, but the hallmark feature of malignancy is the ability to invade neighboring healthy tissues and spread throughout. Such tumors can multiply uncontrollably to metastasize or spread to various body parts and invade surrounding tissues.[4,9-13]

Brain tumors can be cancerous (malignant) or non-cancerous. When the tumors (Benign or malignant) develop in the brain, they can cause an increase in pressure inside the limited space of the skull. As a result, the affected parts of the brain can undergo irreversible damage and may be life-threatening. The brain is a privileged organ in many ways. The brain is a significant consumer of glucose and oxygen and consumes almost 20% of total glucose consumed in a day by our bodies. The brain has its delicate internal biochemical milieu, maintained by the blood-brain barrier. The blood-brain barrier (BBB) is a static lining that separates the brain from systemic circulation. Still, now more and more neurobiologists believe that the blood-brain wall is an organ in itself.

Moreover, it has a much-defined arrangement of cells; endothelial cells and pericytes. The blood-brain barrier cells maintain tight junctions to prevent seepage of the unwanted chemical into the brain. Moreover, cells use molecular pumps to efflux any unwanted molecules that may cross BBB and reach the brain. Because of this highly selective nature of BBB, it becomes challenging to get anti-tumor drugs across it and run the brain. Nevertheless, cancer cells can still make their way to the brain.[14]

The brain is primarily composed of neurons and glial cells. Glial cells are a crucial component of the brain because they serve so many purposes that highly specialized neuron cells cannot perform independently. There are several types of glial cells such as astrocytes which maintain delicate chemical balance so that neurons can function; oligodendrocytes that perform myelination of neurons; and ependymal cells that are secretory and contribute to fluids in brain cavities; microglial cells are phagocytic

cells that act as immune cells of the brain. Optimal brain function is not possible without glial cells. Most commonly, brain tumors occur in glial cells.[15]

Malignant tumors of the brain can be further divided into two types primary and secondary. Primary tumors start within the brain, and secondary tumors are the ones that originated in some other tissue but spread to brain tissue by metastasis.[4,9] All brain tumors produce various symptoms that may depend on the brain's part; they may cause headaches, seizures, vision problems, mental changes, and vomiting.[4] Other symptoms such as walking difficulties speaking may also occur as the disease increases and may even lead to loss of consciousness.[9]

Tumors may be symptomatic or asymptomatic, i.e., they may indicate their presence by symptoms or may not do so. Most often, tumors are discovered because the patient has symptoms, and some show up through medical investigations, i.e., autopsy and image scanning.[9] In 1993 according to the world health organization, the tumor's grading of the central nervous was as follows.

PRIMARY TUMORS OF BRAIN

The four most common brain tumors are:

Gliomas: It is a kind of tumor that begins in the glial cell of the brain or spine.[14,16] Gliomas account for about 30% of focal sensory system tumors and a wide range of cerebrum tumors, and 80% of all malignant brain tumors. Normal glial cells can produce tumors, such as oligodendrocytes, astrocytes, and ependymal cells. Tumors that display a mixture of these cells are called mixed gliomas.[17]

Meningiomas: Meningiomas are typically slow-growing tumors originating from the meninges; meninges are the membranous layers surrounding the brain and spinal cord. Meningiomas are also known as meningeal tumors.[18] Symptoms depend on the occurrence resulting from the tumor pressing on nearby tissues.[19] Generally, symptoms of meningiomas are seizures, talking trouble, vision problems; risk factors are exposure to ionizing radiation during radiation therapy, neurofibromatosis type2, and the family history of a patient.[20,21] Women are likely to be affected about twice as much as men.[21]

Pituitary adenomas: Pituitary adenomas are those tumors that are present in the pituitary gland. Generally, these are divided into a benign adenoma, invasive adenoma, and carcinomas. Moreover, pituitary tumors can cause over-secretion of hormones, such as over-secretion of growth hormone that can cause pituitary gigantism in younger patients and acromegaly in adult patients where the epiphysis has fused, and diaphysis elongation is no longer possible by growth hormones.[22,23]

Pituitary adenomas are the maximum not unusual place form of pituitary disorder. They are benign neoplasms that account for 10% to 15% of all intracranial masses. Few considerable research has delineated the precise occurrence; however, the latest look at the population of a network withinside the United Kingdom located the public event to be better than formerly reported, at 77.6 in keeping with 100,000 persons. Although post-mortem and radiologic research suggest that the superiority can be as excessive as 20%, the bulk of those tumors is incidentalomas without scientific significance.[24-28]

Nerve sheath tumor: It is the type of tumor of the nervous system (nervous system neoplasm) that is made up of primarily of the myelin surrounding nerves. A peripheral nerve sheath tumor (PNST) is a nerve sheath tumor, which is present in the peripheral nervous system. Benign outer nerve sheath consists of schwannomas and neurofibromas. A malignant peripheral nerve sheath tumor (MPNST) is a cancerous nerve sheath tumor.

The nerve sheath is a layer of myelin and connective tissue surrounding and insulating nerve fibers. A nerve sheath tumor is a boom in the cells of this covering. Some humans with nerve sheath tumors do now no longer enjoy symptoms; however, others might also additionally notice: pain, numbness, tingling, itching or a burning sensation, weakness, and a mass that the character can see or feel.[29,30]

SECONDARY TUMORS

Secondary varieties of tumors are metastatic brain tumors that start in any other part of the frame; however, which has to unfold to the brain; because of this that cancerous cells have to seep out from the number one tumor and pass in withinside the lymphatic implement and blood vessels after which circulated over the bloodstream and colonized withinside the brain.[31]

Metastatic tumors of brain tumors are prevalent in patients with terminal phases of incurable metastasized cancer. The most common types of cancer that bring secondary brain tumors are lung cancer, breast cancer, malignant melanoma, and kidney and colon cancer. Secondary types of brain tumors are a more common brain tumor category than primary tumors. A survey of the United States of America indicated about 170,000 new cases of brain tumors each year. The structure of skull bone can also be subject to a neoplasm; due to its nature, the intracranial cavity volume reduces and may damage the brain.[32]

MODERN CLASSIFICATION OF BRAIN TUMORS

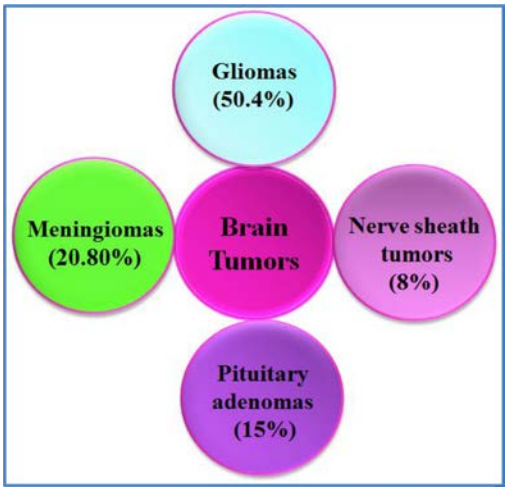
Before 2016 gliomas were studied and differentiated based on histology alone. For example, grade 1 tumors were distinguished by their circumscribed nature; grade 2 brain tumors were determined by nuclear atypia, Oligodendroglioma. Pathologists diagnosed a grade 2 tumor by 'fried egg appearance' of cells under the microscope because of the unusual size of their nuclei. Nevertheless, the histopathological diagnosis of brain cancers was often vogue, and as a result, diagnosis by pathologists varied a lot depending on their experience and judgment. In 2016, the WHO reconstructed CNS or central nervous system tumors classification. The breakthrough in the new system has been to incorporate molecular genetic information available about tumors into classic histology. The inclusion of molecular genetic data has become increasingly important because molecular parameters give a greater degree of precision in the diagnosis. Prognosis of disease, but the rapidly changing field of precision medicine demands a piece of very detailed information about molecular details of cancer in a given patient to choose the most appropriate anti-cancer treatment for the patient.

Moreover, the genotype is considered more informative and deterministic than the phenotype. The discussion of a complicated classification system is beyond the scope of this review. The following are critical molecular features that can now be reliably used for diagnostic purposes.[15,18]

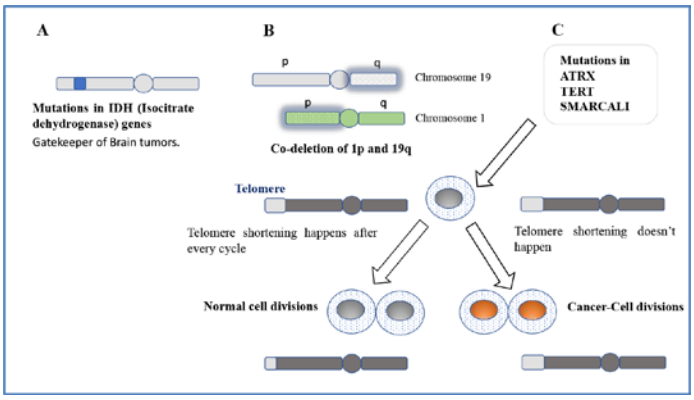
Mutations in genes IDH1 and IDH2 are commonly found in low-grade gliomas. IDH genes encode for isocitrate dehydrogenase enzymes. Gain of function mutations in IDH genes leads to IDH enzymes that convert citrate to metabolite 2-hydroxyglutarate or 2-HG. It is believed that 2-HG concentrations are abnormally high in the tumor, and 2-HG drives the proliferation of cancer cells by interfering with epigenetic mechanisms responsible for switching on and off the genes. IDH is believed to be the gatekeeper gene of brain tumors.

Loss of chromosome arms 1p and 19q combines with the Loss of both IDH genes. In brain cancer known as Oligodendroglioma, one can invariably find the Loss of chromosome arms 1p and 19q and mutations in IDH genes. It is worth noting that patients with brain tumors with IDH mutations or co-deletion of 1p and 19q have better chances of survival than the patients that do not have them.

Mutations in TP53 and ATRX characterize astrocytoma. TP53 encodes for a tumor suppressor protein which prevents cells from going



Types of Primary Tumors.



Various genetic mutations and mechanisms that lead to brain tumors.

cancerous. ATRX, in particular, is attractive and has been known to play an essential role in conserving telomeres of chromosomes of cancer cells by mechanisms of alternative lengthening of telomeres. It is important to recall that telomeres shorten with each cycle of chromosomal duplication, limiting the number of processes of mitotic divisions that normal cells can undergo. In cancer cells, this limit is circumvented by mechanisms that either promote telomere lengthening or preserve the telomeres despite uncontrolled cell division. Grade 3 tumors have a very high rate of mitosis because of such mutations.[18]

Genes TERT, EFGR, and PTEN are commonly converted in gliomas and are very useful in differentiating the grade and biology of tumors.[33] TERT, like ATRX, is responsible for telomere maintenance. EFGR is accountable for angiogenesis, or the formation of blood vessels to supply blood to growing cancer. PTEN encodes for a phosphatase that regulates cellular apoptosis and plays a significant role in keeping healthy cells from becoming cancerous. Mutations in IDH, TP53, and ATRX lead to diffuse astrocytoma. Grade 4 tumors are characterized by microvasculature proliferation and necrosis.

INHERITANCE AND GENETICS IN BRAIN TUMORS

Brain tumors do have a familial basis. Someone who has a parent or a sibling with glioma is more likely to be affected by glioma. 5-8% of gliomas are domestic. The mutations and the genes responsible for tumors are being identified at an unprecedented pace because of the revolution in high throughput sequencing technologies. It is now becoming a consensus that each tumor is unique and requires a detailed mapping of its molecular biology to find the most suitable course of treatment for a given patient.

CRISPR-Cas9 technology has been used to create mouse models of tumors by introducing desired mutations in some genes. The genetic basis of brain tumors is complex. For example, it has been found that different mutations in the same gene may have different outcomes in terms of how cancer may become malignant.[14]

CHEMOTHERAPY FOR BRAIN TUMORS

The waterproof nature of the blood-brain barrier (BBB) makes brain cancers one of the most challenging kinds of cancers for chemotherapy. In fact, for pharmacologists developing a drug against brain cancer, one of the most important criteria is its ability to cross the blood-brain barrier. A hallmark of brain tumors is their ability to alter the integrity of BBB. Lately, the use of ultrasound waves to transiently increase the permeability of BBB at the time of administration of a bolus of anti-tumor drugs to patients is gaining much medical attention. Similarly, much research is also going on to produce nanoparticle-based delivery systems that can carry drugs and cross the BBB to deliver the drugs to the tumor site.[34]

Pharmacists are developing smart drugs that can naturally cross BBB to combat the most virulent forms of brain tumors. The latest example of such a drug is modified trastuzumab and a monoclonal antibody targeting HER2 breast cancers. Scientists at Bioasis company have developed an understanding of trastuzumab that can cross BBB to target a HER2 expressing brain tumor that has metastasized to the brain by conjugating this monoclonal antibody with a fragment of iron transporting protein. This complex can naturally cross BBB and reach tumors to kill cancer cells.[34]

EPIDEMIOLOGY

Epidemiology of brain cancer shows a significant difference between developed and developing countries; the results show that the less developed countries have lower incidences of brain tumors.[34,35] This could be possible because of undiagnosed tumor-related deaths. Most patients in developing countries do not get the opportunity to have their tumors diagnosed due to the scarcity of modern facilities to diagnose brain tumors. Interestingly, certain forms of primary tumors are statistically more prevalent amongst specific populations, suggesting a solid ethnic and genetic background.[36]

CONCLUSION

2016 WHO classification has been a breakthrough in brain tumor oncology and clinical practice. The key thrust is to shift the paradigm from the old approach of histopathological interpretations to diagnose brain cancers to relate each cancer to its distinct molecular signature at the genetic level. This has made diagnostic more accurate and treatment more custom-tailored to a given cancer type and has also ushered in an era where clinicians are urged to understand the molecular basis of cancers in more detail. Each cancer is unique in its genetic component, and therefore precision medicine appears to be the most reasonable methodology to diagnose and treat cancers.

Primary brain cancers are either circumscribed or diffuse; each type has its characteristic molecular markers. The circumscribed tumors or the benign tumors are curable by surgery. They do not have IDH mutations. Instead, they seem to have BRAF mutations or fusions. Diffuse tumors can have an entire spectrum of pathological manifestations. They may

have either mutation in IDH, codeletion of chromosome 1p and 19q, ATRX and TP53 mutations such as in diffuse forms of astrocytoma. IDH mutation appears to be the gatekeeper of brain tumor pathogenesis. A more virulent form of tumors may have mutations in genes required for apoptosis, cell cycle regulations, and microvascular proliferation. CRISPR-Cas9 gene editing is now being used to make murine models of human cancers and study their progress and pathogenesis. More and more advances are being made in making anti-tumor drugs that can cross the blood-brain barrier and have good pharmacokinetic properties.

Overall, it can be concluded that a molecular understanding of the origin and propagation of brain tumors has revolutionized the diagnosis and treatment and course of biomedical research.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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