Summary. Gliomas are the most common intracranial malignant tumors in humans, and high-grade gliomas in particular pose a unique challenge due to their propensity for proliferation and tissue invasion. Our understanding of glioma oncogenesis, proliferation, and invasion has been greatly advanced in the past 10 years as researchers have gained a better understanding of the molecular biology of these tumors. This article highlights glioma histopathology, as well as cytogenetic and molecular alterations associated with the pathogenesis of human gliomas. It is hoped that better understanding of the molecular pathogenesis of gliomas will improve tumor classification as well as lead to novel targets for therapy and prognostic markers.

Key words: Gliomas, Proto-oncogenes, Tumor suppressor genes, Invasion

Introduction

Tumors of the central nervous system (CNS) can be devastating because they are difficult to treat and may cause grave disability or death. CNS gliomas pose particularly difficult problems because of their tendency toward malignancy, rate of tumor spread, and the lack of effective therapy. Gliomas are the most common intracranial malignant tumors in humans. Among astrocytic gliomas, glioblastoma multiforme is the most common and most aggressive type. Glioblastoma multiforme poses a unique challenge because of its propensity for invasion and proliferation. Our understanding of glioma oncogenesis, proliferation, and invasion has been greatly advanced in the past 10 years as researchers have gained a better understanding of the molecular biology of these tumors.

Presently, gliomas are classified according to the cell types, morphology of the cells within the tumors, and associated endothelial proliferation and necrosis within tumor samples. This system provides a scheme for classifying tumors that in most cases correlates with the behavior of these tumors. However, a number of studies have indicated that within each of these grades there may be subtypes that behave differently. This article highlights some of the molecular alterations associated with the pathogenesis of human gliomas.

Grading of gliomas

Astrocytic gliomas are divided into two major classes based on their potential for invasion and progression to more malignant forms. The first major class consists of the diffuse astrocytic tumors. This group is generally characterized by a high capacity for invasion with diffuse infiltration beyond the macroscopic brain-tumor interface and a significant potential for tumor progression (Vandenberg and Lopes, 1999). These tumors are classed as astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), and glioblastoma multiforme (WHO grade IV) (Kleihues et al., 2002). This classification system reflects these two characteristics as well as the degree of anaplasia.

The second class is composed of tumors that have more limited invasion potential and a decreased capacity for malignant transformation. These include juvenile pilocytic astrocytoma (WHO Grade I), pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. Furthermore, three major histopathologic variants are recognized that are not classified according to the degree of anaplasia, these include fibrillary, gemistocytic and protoplasmic. The histopathologic features of these tumors and their limited and less aggressive behavior preclude their classification with other more infiltrative gliomas.

Histopathology of astrocytomas

The purpose of any tumor grading system is to describe histopathologic features of tumors that in some way defines specific tumor types. A number of different criteria have been used to classify astrocytomas (Vandenberg and Lopes, 1999). Recent and widely used criteria involve a three-tiered system corresponding to the WHO classification and are supported by clinical
survival data (Hoshino et al., 1989; Fujimaki et al., 1991; Kim et al., 1991; Salmon et al., 1992). However, weighting of the significance of histopathological features varies somewhat among different institutions. These features include magnitude of cellularity, degree of cellular pleomorphism (cytoplasmic and nuclear), mitotic activity, and prominence of microvascular endothelial and pericytic proliferation and necrosis (Vandenberg and Lopes, 1999). As one might imagine, these classification systems do not take into account (1) sampling error (tumors may have different degrees of malignancy in different areas); nor (2) topography (tumor location may affect clinical behavior).

Criteria separating WHO grade II and grade III astrocytomas include increased magnitude of cellularity and increased cellular atypia. Grade IV tumors, unlike grade III astrocytomas, are characterized by increased cellularity as well as endothelial proliferation and necrosis. These classification systems are described extensively elsewhere (Nelson et al., 1983; Burger et al., 1985; Davis, 1989) and will not be reproduced here. As one might imagine, grading tumors based on the extent of different characteristics allows for a very subjective classification of different tumors.

One system that attempts to provide a more reproducible classification of astrocytomas with prognostic significance is the St. Anne-Mayo system (Daumas-Duport et al., 1988, Kim et al., 1991). This system is based on the presence or absence of four criteria: (1) nuclear atypia, (2) mitosis (regardless of normal or abnormal configuration), (3) endothelial proliferation (in which vascular lumina are surrounded by “piled up” endothelial cells instead of a single layer), and (4) necrosis. Tumor grade is then determined by the number of these criteria (Grade I, 0 criteria; Grade II, 1 criterion; Grade III, 2 criteria; Grade IV, 3 or 4 criteria). The occurrence of these features appear in a predictable sequence with nuclear atypia occurring in all Grade II tumors, mitotic activity seen in 92% of Grade III tumors, and with necrosis and endothelial proliferation seen almost exclusively in Grade IV tumors. Median survival given these grades were less than 1 year for Grade IV, 1.6 years for Grade III, 4 years for Grade II, and greater than 8 years for Grade I.

The criteria used in these grading systems rely on histopathology alone. In the past 10 years, advances in molecular biology have provided an increasingly precise description of chromosomal abnormalities and genetic mutations within these tumors. These more objective molecular descriptions of tumors may allow for a more detailed classification system based on the genetic features of these tumors.

Chromosomal abnormalities in human gliomas

The development of many cancers has been directly attributed to genetic mutations including loss of function of tumor suppressor genes and mutations in proto-oncogenes. An increasing body of evidence suggests that progression of low-grade astrocytomas to glioblastoma multiforme involves the progressive loss of genes responsible for the control of cell proliferation, apoptosis, and/or cell migration (Collins, 1998). The genetic changes involved in these tumors are often reflected as gains or losses of different chromosomes. The study of chromosomal amplifications and deletions has increased our understanding of the individual genes involved in glioma tumorigenesis.

The genetic alterations most often reported in astrocytic tumors are mutation or alteration of the p53 tumor suppressor gene (Fults et al., 1989, 1991; Mashiyama et al., 1991; Frankel et al., 1992, 1994), loss of heterozygosity for chromosome 17p (James et al., 1988; Fults et al., 1989, 1990, 1992, Frankel et al., 1992), for chromosome 10 (James et al., 1988; Fujimoto et al., 1989; Fults et al., 1989, 1992; Bigner and Vogelstein, 1990; von Deimling et al., 1992, 1993), for chromosome 9p (James et al., 1991), or for chromosome 19q (von Deimling et al., 1992); amplification and rearrangement of the epidermal growth factor receptor gene (EGFR) (Ekstrand et al., 1991, 1992; Collins and James, 1993; Riemenschneider et al., 1999); amplification and rearrangement of the MDM2 gene (Riemenschneider et al., 1999); and amplification of the oncogenes N-myc, e-myc, N-ras, K-ras, and platelet-derived growth factor receptor A (PDGF-RA) (Kinzler et al., 1987; Bigner and Vogelstein, 1990; Collins and James, 1993).

Low-grade astrocytomas have been less thoroughly studied than their higher grade counterparts, however a number of well-defined regions have been found to have loss of alleles in these tumors. The most frequently found regions include 13q, 17p and 22q (el-Azouzi et al., 1989; James et al., 1989; Fults et al., 1990; von Deimling et al., 1992; Wu and Darras, 1992; Ohgaki et al., 1993; Kraus et al., 1994; Liang et al., 1994; Rasheed et al., 1994). Both 13q and 22p are lost in 20% of low grade astrocytomas and losses of 17p occur in nearly 30% of these tumors (James et al., 1989). Little is known about the relationship of these genetic abnormalities and tumor behavior. For a more complete review, including relationship of these genetic changes to tumor resistance to radiotherapy and chemotherapy, see recent review by Smits (Smits, 2002). The data on anaplastic astrocytomas show that they also have losses in 13q, 17p and 22p at rates similar to the low-grade astrocytomas (Weber et al., 1996). In addition, anaplastic astrocytomas have amplification of 12q and new sites of allele loss at 9p.

Glioblastoma multiforme is the best studied of the astrocytomas and demonstrates the greatest number of genetic abnormalities. Cytogenetically, glioblastoma multiforme has losses in portions of chromosomes 1, 6, 9, 10, 13, 17, 22 and Y and amplification or gain of material on chromosomes 7, 12, and 19 (Rey et al., 1987; Bigner et al., 1988; Jenkins et al., 1989; Collins, 1998). A number of the relevant genes involved have been identified and include growth factor receptors.
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EGFR (Collins, 1993), components of the cell cycle machinery (Rb, cdk4, and p16) and regulators of apoptosis (p53, mdm2, ARF, and PTEN) (see below). Studies into the molecular biology of tumorigenesis in glioblastoma multiforme show that there may be distinct variants based on the profile of mutated genes (Lang et al., 1994).

Genes mutated in gliomas

Unchecked cellular proliferation is an important feature in the development of brain tumors. There are a number of regulatory pathways that ensure that cellular proliferation is in balance with cell death. Control of the cell cycle is critical in determining the rate of proliferation within tissues of all types. Cyclins, cyclin-dependent kinases (CDK), and cyclin-dependent kinase inhibitors (CDKI) play in important role in the cell-intrinsic regulation of the cell cycle (Dirs and Rutka, 1997) whereas growth factors and extracellular matrix proteins constitute important stimuli for cell proliferation.

Enhanced cellular survival is a key feature in the development of tumors. Apoptosis, or programmed cell death, acts to ensure control of cell numbers during development and in normal tissues in adults. Apoptosis, like cellular proliferation, is under very tight genetic controls. The loss of normal regulation of apoptosis has been implicated in the development and progression of gliomas in a number of studies (Alderson, 1995; Sano et al., 1999; Rodriguez-Pereira, 2001; Chakravarti, 2002). We shall briefly discuss some of genes found to be implicated in the control of cellular proliferation and apoptosis in human gliomas.

EGFR

EGFR is a transmembrane glycoprotein that binds to EGF and a number other ligands including transforming growth factor-α (TGF-α) (Marguardt et al., 1983), amphiregulin (Shoyab et al., 1988), heparin-binding EGF-like growth factor (HB-EGF) (Margolis et al., 1990; Shing et al., 1993), and betacellulin (BTC) (Alimandi et al., 1997). The activation of EGFR leads to the stimulation of tyrosine kinase activity leading to activation of phospholipase C-γ (PLC-γ), mitogen-activated protein kinase (MAPK) and the ras GTPase-activating protein (GAP), with the ultimate effects of increased DNA synthesis and cell division (Maruno, 1991; Tang, 1997). After activation of EGFR, the receptor/ligand complex is endocytosed and degraded within lysosomes or recycled to the plasma membrane. This endocytosis and degradation is the major mechanism for down-regulation of the growth factor induced signal.

Amplification of the EGFR gene was among the first to be linked to GBM (Libermann et al., 1985). EGFR amplifications occur in 40-50% of glioblastomas and result in elevated levels of EGFR expression. Sequencing of EGFR in high-grade gliomas indicated that these genes may have mutations that result in deletions of parts of the extracellular domain required for ligand binding (Ekstrand et al., 1992; Wong et al., 1992), and in some cases may have constitutive tyrosine kinase activity (Ekstrand et al., 1994; Hoi Sang et al., 1995). There are at least three different types of deletions in the extracellular domain of EGFR (Voldborg et al., 1997). One of these types causes constitutive activation of EGFR (EGFRvI) (Humphrey et al., 1988); one type has a deletion that does not seem influence the malignant phenotype of GBM, but is a result of gene amplification (EGFRvII) (Humphrey et al., 1991); and another type that has deletions that lead to decreased endocytosis and overrepresentation at the cell surface (EGFRvIII) (Bigner et al., 1990; Wikstrand et al., 1995). Of these types, EGFRvIII is the best described and the type most commonly found in human gliomas. EGFRvIII is present on more than 50% of high- and low-grade gliomas (Garcia de Palazzo et al., 1993). Given the amplification and mutations in EGFR and the presence of its ligands, EGFR may promote proliferation of gliomas through both autocrine and paracrine mechanisms.

p53

The CDKIs play an integral role in inhibiting cell-cycle progression by inhibiting the formation of the cyclin-CDK complexes. p53 is a cellular phosphoprotein that is a transcriptional activator of p21Cip1, a potent CKPI (Dulic et al., 1994). Through p21Cip1, p53 causes G1 cell cycle arrest, providing an important checkpoint for the cell cycle (Fig. 1), p53 responds to DNA damage and allows cells to control proliferation by either causing arrest of the cell cycle or apoptosis (Bates and Vousden, 1996; Chen et al., 1996; Amundson et al., 1998; Albrechtsen et al., 1999; Andoh, 2000). Mutations in p53 are particularly detrimental because they remove the normal mechanism for cell-cycle regulation in the face of genetic instability. This accounts for the importance of p53 in cancer in general and gliomas in particular.

In addition to its role in control of the cell cycle, p53 plays an important role in the control of apoptosis. The interleukin-1β-converting enzyme (ICE) is a cysteine protease that has been found to activate apoptosis. The Bcl-2 protein blocks ICE-induced apoptosis and the bcl-2 gene belongs to a family of genes with anti-apoptotic effects. Other genes, such as bax, bad, bak, and bcl-xs increase sensitivity to apoptotic stimuli (Boise et al., 1993; Olvai et al., 1993; Chittenden et al., 1995; Yang et al., 1995). p53 acts as a transcriptional activator of the bax gene and may act to enhance sensitivity to apoptosis (Miyashita and Reed, 1995). Thus, mutations in p53 may cause tumors to be less sensitive to apoptotic stimuli.

p53 plays a fundamental role in at least one molecular pathway of glioblastoma tumorigenesis (Lang et al., 1994). In this model, termed the “progression pathway,” p53 mutation is an early event and is thus
found in lower grade tumors (Fig. 2). Progressive loss of heterozygosity of other chromosomes as well as amplification of EGFR leads to further tumor progression. However, studies have not shown p53 to be an independent predictor of patient outcome in gliomas (Alleyne et al., 1999; Kirla et al., 2000). This may be accounted for by the fundamental role of p53 mutations in these lower-grade lesions.

Glioblastomas with p53 mutations may represent tumors that progress from low-grade astrocytomas. This particular variant is more likely to have a loss of chromosome 17p than tumors without p53 alterations (Lang et al., 1994). The loss of chromosome 10 is associated with progression from anaplastic astrocytoma to glioblastoma multiforme in some tumors (Fig. 1). In this variant, amplification of EGFR is a late and rare event in tumor progression. Another variant of GBM most likely represents clinically de novo high grade tumors. These tumors show EGFR amplification more often than tumors with p53 mutation (Lang et al., 1994). Roughly 60% of these tumors with EGFR amplification also showed loss of chromosome 10, and loss of chromosome 17p is infrequent in this variant. These findings suggest that glioblastomas are heterogeneous tumors that may arise from multiple genetic pathways and have a biological basis for behaving differently. These data are strongly supported by studies that show that p53 mutations do not play a major role in high-grade astrocytomas in the pediatric population, who have de novo tumors (Litofsky et al., 1994).

**PTEN**

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a gene isolated from chromosome 10q23.3, one of the areas deleted in glioblastomas as well as breast tumors and prostate cancer (Steck et al., 1999) that is believed to affect apoptosis. PTEN is a lipid phosphatase and has been shown to catalyze the conversion of phosphatidylinositol (3,4,5)-triphosphate (PIP3) to phosphatidylinositol (4,5)-biphosphate (PIP2) (Maehama and Dixon, 1998; Myers et al., 1998). This conversion is important in the pathway linking growth factor and extracellular matrix signaling to cell survival (Wechsler-Reya and Scott, 2001). Growth factors activate phosphatidylinositol-3’ kinase (PI3K) which increases cellular levels of PIP3. PIP3 then serves as a second messenger that attracts proteins containing the pleckstrin homology domains to the plasma membrane. Akt is a serine-threonine kinase which binds to PIP3 and becomes activated. Akt then phosphorylates and inactivates a number of proteins involved in apoptosis including Bad and Caspase-9, thereby supporting cell survival (Wechsler-Reya and Scott, 2001). The activity of PTEN reduces the level of PIP3, thus loss of this gene ultimately supports cell survival.

PTEN alterations occur in 41-63% of glioma cell lines and 17-44% of primary glioblastomas and are rare in low-grade gliomas (Liu et al., 1997; Rasheed et al., 1997; Wang et al., 1997; Duerr et al., 1998). Furthermore, studies show that the growth of glioma cells could be suppressed by the transfer of the wild-type PTEN gene *in vitro* and *in vivo* (Furnari et al., 1997; Cheney et al., 1998). In a recent study, the absence of PTEN was associated with increased tumor malignancy in gliomas, whereas increased PTEN was a positive prognostic factor for patient survival (James et al., 1991; Alleyne et al., 1999; Sano et al., 1999). These findings indicate that PTEN may play an important role in tumor progression.

![Fig. 1. Genetic pathways leading to glioblastoma multiforme. As described by Lang et al., 1994. The progression of astrocytomas to GBM may be divided into a p53 dependent and p53 independent pathway. These differences account for the tumor variants that occur de novo versus tumors that transition through increasingly malignant grades. The loss of heterozygosity (LOH) of a number of chromosomes is important in all the pathways described.](image1)

![Fig. 2. The role of p53 in regulating the cell cycle. The cell cycle is composed of a sequences of phases that are under the control of a number of molecular mechanisms. When DNA is damaged p53 causes an arrest of the cell cycle at G1 by acting as the transcriptional activator of p21Cip1. This provides an important checkpoint in the cell cycle.](image2)
Molecular biology of glioma invasion

Local tissue invasion is the crucial cytologic attribute that distinguishes high-grade gliomas and makes efforts at resection often futile (Giese and Westphal, 1996). Furthermore, morbidity and mortality from high-grade gliomas is directly related to their ability to invade and infiltrate surrounding tissue (Salcman, 1995). Microscopic evidence of malignant cells can be found well beyond the gross radiographic margins of the tumor (Burger, 1983).

Tumor invasion consists of several discrete steps, including tumor cell interaction with extracellular matrix (ECM) ligands, hydrolytic destruction of the matrix by release of proteolytic enzymes, and subsequent migration of the tumor cells through the area of destruction. What are the proteases involved in ECM digestion? CNS tissue contains three major groups of proteases and their inhibitors: (1) matrix metalloproteases and tissue inhibitors of matrix metalloproteases (TIMPs); (2) serine proteases, including urokinase, tissue plasminogen activator (tPA) and plasminogen activator inhibitors (PAIs); and (3) cysteine proteases, recently implicated in apoptosis (programmed cell death). Of these groups, by far the most is known about the role of matrix metalloproteases in tumor invasion.

Matrix metalloproteases (MMPs) are a multigene family of Zn$^{2+}$-dependent enzymes that degrade a variety of ECM molecules such as proteoglycans, glycoproteins, and types of collagen (Matrisian, 1992). In 1980, Liotta and colleagues (Liotta et al., 1980) were the first to demonstrate elevated expression of MMPs in melanoma cells with metastatic/invasive potential. Since then, the central role of proteases in tumor invasion has been amply demonstrated (Mignatti and Rifkin, 1993; Nakagawa et al., 1994; MacDougall and Matrisian, 1995; Nakano et al., 1995; Uhm et al., 1997). For gliomas, immunohistochemical studies have shown that high-grade human gliomas (GBMs and anaplastic astrocytomas) express MMPs, whereas non-invasive low-grade astrocytomas and normal brain do not (Nakagawa et al., 1994). In addition, abundant evidence indicates that in high-grade gliomas proteolytic activity appears to be strongly correlated with destructive and invasive properties in vitro and in vivo (Paganetti et al., 1988; Humphrey et al., 1991; Vaithilingam et al., 1992; Rao et al., 1993, 1994; Sato et al., 1994; Sawaya et al., 1996). The member of the MMP family most central in glioma invasiveness is MMP-2 (72 kDa-type IV collagenase). In vitro studies reveal that inhibitors of MMP-2 block glioma invasion, whereas increasing MMP-2 activity increases glioma invasiveness (Abe et al., 1994; Uhm et al., 1996). Recently, ex vivo studies demonstrate increased MMP-2 activity in resected glioblastoma specimens compared to normal brain or low-grade glioma (Sawaya et al., 1996). Furthermore, MMP-2 has been shown to be activated by an integral plasma membrane-bound protease termed MT1-MMP (membrane type 1 MMP) (Nakagawa et al., 1994; Sato and Seiki, 1996). MT1-MMP is also upregulated in human gliomas (Sawaya et al., 1996), and serves to concentrate the activation of MMP-2 activity at the cell surface, presumably to facilitate ECM digestion and thus invasion locally at the tumor margin.

Histopathologically, the most common pattern of spread of malignant glioma cells is along the path of the deep white matter tracts, in particular the corpus callosum, producing the so-called ‘butterfly glioma’ (Burger, 1990; Schiffer, 1991). How these cells can do this at all is of interest since CNS myelin contains proteins inhibitory to migration of most cell types. However, two recent studies shed light on this issue. First, white matter microglia have been shown to express high levels of MT1-MMP (Yamada et al., 1995), and perhaps could activate MMPs secreted by invading glioma cells thus providing a permissive substrate for infiltration (Uhm et al., 1997). Second, C6 glioma cells and human glioblastoma cells themselves express MT1-MMP, and this appears to be required for migration through CNS white matter (Belièen et al., 1999). In support of this contention is the observation from the same study that transfection of naïve rat 3T3 fibroblasts with MT1-MMP bestows the ability to migrate on the (previously) nonpermissive myelin substrate and invade adult rat optic nerve explants (Belièen et al., 1999).

One mechanism of regulation of MMP activity is post-translational interactions with naturally-occurring tissue inhibitors of metalloproteinases (TIMPs) (TIMP-1 through TIMP-4) (Brew et al., 2000). These proteins bind to MMPs and abrogate their proteolytic activity (Boone et al., 1990; Matrisian, 1992). Thus, the net invasiveness of any tumor is thought to rely on the protease/antiprotease balance of tissue activity rather than absolute levels of protease gene expression. Indeed, as expected, potent anti-invasive activities of TIMPs have been amply demonstrated in multiple in vitro cancer models (DeClerck and Imren, 1994). Transfection of cells and glioma cell lines with TIMPs greatly reduces local tumor invasiveness in vitro (DeClerck et al., 1992; Matsuzawa et al., 1996). In contrast, ex vivo data from glial tumor specimens show that TIMP levels correlate negatively with invasiveness (lowest for glioblastomas, higher for lower-grade gliomas and normal brain) (Nakagawa et al., 1994; Mohanam et al., 1995). In other words, just those molecules (TIMPs) expected to limit invasiveness by neutralizing MMPs are underexpressed in high-grade glial tumors. Whether and how TIMPs are coordinately regulated in glial tumors along with MMPs remains to be investigated.

Prognosis and genetic markers

One of the most clinically relevant goals of the study of gliomas is to understand which particular molecular alterations affect patient prognosis. Our understanding of the molecular markers that are relevant for patient treatment and survival is still in its infancy. As
summarized above, p53 mutations are found in GBMs that arise from low-grade gliomas and have a more protracted course. Also, GBMs that arise primarily usually do not harbor p53 mutations, have EGFR mutations, and have shorter survival times. However, there are conflicting results from studies that evaluate these genetic mutations as independent prognostic indicators. Two studies have shown no correlation between p53 mutations and patient survival (Cunningham et al., 1997; Rainov et al., 1997), while other studies show an unfavorable correlation between p53 mutations and patient survival (Muhammad et al., 1997; Peraud et al., 1997; Pollack et al., 1997; Korkolopoulou et al., 1998). Additionally, some studies suggest a negative correlation between EGFR amplification and patient survival (Zhu et al., 1996; Leenstra et al., 1998), while others show no independent relationship (Waha et al., 1996; Olson et al., 1998).

Studies involving PTEN mostly show that the presence of PTEN is a good prognostic factor. Loss of heterozygosity of chromosome 10 at PTEN has been shown to be a significantly poor prognostic factor in patients with anaplastic astrocytomas (Lin et al., 1998) and GBM (Lin et al., 1998, Tada et al., 2001). And as mentioned above, expression of PTEN in patients with malignant glioma is associated with better prognosis. One may only conclude that as our knowledge base of genes involved in glioma tumorigenesis grows, so will our ability to predict and improve patient outcomes.

Conclusions

Presently, gliomas are classified by histopathology. As we learn more about the molecular biology of these tumors, it becomes clear that within these histological classes, there may be subtypes of tumors that have different molecular characteristics that affect tumor behavior and patient prognosis. An evolving molecular classification of gliomas may allow us to better predict the progression of these tumors as well as their potential response to different therapies. What also becomes apparent is that creating such a molecular classification will require years of research and correlation of different genetic subtypes with individual patient outcomes.

References


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