The etiopathogenesis of diffuse low-grade gliomas

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Abstract

The origins of diffuse low-grade gliomas (DLGG) are unknown. Beyond some limited data on their temporal and cellular origins, the mechanisms and risk factors involved are poorly known. First, based on strong relationships between DLGG development and the eloquence of brain regions frequently invaded by these tumors, we propose a “functional theory” to explain the origin of DLGG. Second, the biological pathways involved in DLGG genesis may differ according to tumor location (anatomo-molecular correlations). The cellular and molecular mechanisms of such “molecular theory” will be reviewed. Third, the geographical distribution of diffuse WHO grade II–III gliomas within populations is heterogeneous, suggesting possible environmental risk factors. We will discuss this “environmental theory”. Finally, we will summarize the current knowledge on genetic susceptibility in gliomas (“genetic predisposition theory”).

These crucial issues illustrate the close relationships between the pathophysiology of gliomagenesis, the anatomo-functional organization of the brain, and personalized management of DLGG patients.

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1. Introduction

To date, the origins and etiologic factors of diffuse low-grade gliomas (DLGG) are mostly unknown. There is, however, a few data regarding their temporal origins. Indeed, because the DLGG growth rate is constant during the initial premalignant symptomatic period, it was possible to extrapolate backwards in time, leading to the approximate glioma date of birth in early adulthood (around 20 years of age) (Mandonnet 2003; Duffau et al. 2011; Gerin et al. 2012). This suggests that DLGG arise more likely “ex nihilo” rather than from a preexisting congenital lesion.

Although the causative factors of DLGG are poorly known, it is already noteworthy to mention that the implication of one unique etiologic factor for all DLGG is unlikely, as these tumors represent a heterogeneous entity. Indeed, recent refinement of the biometathematical model, based on a differential equation describing the diffusion–proliferation process, has enabled the identification of two types of DLGG: firstly, very slow-growing tumors that appear during adolescence; secondly, slow-growing tumors that appear later during the young adult period (Gerin et al. 2012). These different DLGG subgroups attest of the heterogeneity among DLGG and of the complexity of DLGG genesis.

The aim of this article is to review the possible mechanisms underlying the genesis of DLGG. One way to better understand these mechanisms is to study their spatial distribution, both within the brain and at the geographical level within populations (at the international and national levels), as some hypothesis regarding the mechanisms may be speculated from these distributions.

Indeed, DLGG have preferential locations within the brain, mostly within the so-called “functional areas”, and these locations are different from that of other gliomas (including glioblastomas) (Duffau and Capelle 2004). This observation leads to consider two hypotheses regarding the DLGG genesis. First, it is possible that the brain microenvironment, shaped by environmental demands and specific regional neuron-microenvironment interactions, might influence the risk of tumor development (“the functional theory”). Second, it can be hypothesized that the biological pathways involved in the DLGG genesis may differ according to the tumor location. Biological differences according to the tumor location have been demonstrated (“the molecular theory”), including for example the mutation of the isocitrater dehydrogenase (IDH) gene that is considered as an early event in the DLGG genesis. We will review the current knowledge on the cellular and molecular origins of DLGG.

Moreover, the geographical distribution of lower-grade gliomas (World Health Organization or WHO diffuse grade II and grade III gliomas) is also heterogeneous. This has been recently demonstrated by our team in a study of 4790 patients with a newly diagnosed, histologically-proven lower-grade glioma (WHO 2007 classification) in metropolitan France (Darlix et al. 2014). This observation raises the question of the role of environmental risk(s) factor(s) (“the environmental theory”), which will also be addressed in this article.

Finally, we will briefly summarize the current knowledge on genetic susceptibility in gliomas.

2. DLGG have preferential brain locations

DLGG have preferential locations within the brain (Duffau and Capelle 2004; Capelle et al. 2013; Parisot et al. 2016). These locations have been reported using various methods: the classical methods based on the lobar anatomy, the voxel-wise methods, and the probabilistic approaches.

At the lobar level, a first report showed a frequent involvement of so-called “functional” areas, namely the supplementary motor area (SMA) (27.3%) and the insula (25%), with a significant difference when compared with de novo glioblastomas, suggesting a possible different origin between these two kinds of gliomas (Duffau and Capelle 2004). This preliminary observation was confirmed by a study demonstrating a higher rate of DLGG in anterior regions of the brain (Lagle-Donadet et al. 2004), and then by a French study on a large 1097 DLGG series in which about 90% of patients had a tumor located in the frontal and/or-temporal and/or-insular regions (Capelle et al. 2013). More recently, in a series of 198 DLGG patients from our team, the tumor distribution was as follows: 31.3% frontal, 23.7% temporo-insular, 20.2% fronto-temporo-insular, 12.1% parietal, 9.1% fronto-insular and 3.5% of other locations.

However, these DLGG spatial classifications based on cerebral lobe or gyri lack accuracy. More recently, two other new approaches, a voxel-wise method and a probabilistic approach, have confirmed this data. Our team used, for the first time, a voxel-wise method to assess the intra-cerebral topography of 198 DLGG patients at diagnosis. As illustrated in Fig. 1, the overlap map of all 198 tumors showed a quite homogeneous and symmetrical distribution of the tumors within the fronto-temporo-insular regions (unpublished data).

The other approach consists in the construction, by means of a novel probabilistic method, of a graph-based spatial positioning (Parisot et al. 2016, 2011). We applied this methodology in a consecutive series of 210 DLGG patients at diagnosis, and confirmed the symmetrical distribution of the tumors and the preferential location within frontal (33%), insular (37%) and temporal (18%) areas (Fig. 2).

Whatever the methodology used to assess the preferential locations for DLGG, two main findings should be highlighted. On one hand, DLGG are preferentially located within the so-called “eloquent” areas, including the insula and the SMA, which are both functional interfaces between the limbic system (mesiotemporal structure and cingulum) and the temporal pole (for the insula) or the prefrontal cortex (for the SMA). On the other hand, there are very few DLGG located in the posterior regions of the brain, including the occipital lobe. In a large consecutive series of DLGG recently reported by the UCSF team, only two out of 281 patients (0.71%) had an occipital tumor involving visual regions (Chang et al. 2011). Similarly, in the French Low-Grade Gliomas Consortium series, only 5 out of 1094 (0.46%) DLGG were occipital (Capelle et al. 2013). The results are almost similar in our consecutive experience with about 400 DLGG, since only six patients (2.0%) had an occipital glioma (Viegas et al. 2011). These findings lead to several biological hypotheses regarding DLGG genesis. First, the cytoarchitectonics of the visual cortex is not the same, since the insula is constituted by a mesocortex, making a link between the allocortex and the neocortex (Duffau and Capelle 2004). Second, from a functional point of view, both the insula and the SMA play a role in the planning of movements and language (Duffau 2009a; Kainik et al. 2003), while the occipital lobe is not involved in planning. It can thus be hypothesized that the risk of DLGG is linked, among other factors, to the eloquence of the area involved and that there may be an impact of the microenvironment on DLGG development (“the functional theory”). Another hypothesis is that differences linked to developmental processes, including the myelination processes, could be involved. Indeed, fronto-temporal areas are among the last myelinated areas during development, the myelination processes occurring until the second decade of life, particularly in the frontal lobe (Paus et al. 1999). In the study published by Paus et al. in 111 children and teenagers (4–17 years old), there was an age-dependent increase in white matter density in several areas including the posterior part of the arcuate fasciculus connecting the frontal and temporal areas and involved in language (Paus et al. 1999). Interestingly, the myelination processes seem
Fig. 1. Tumor overlap map overlaid on a standard Montreal National Institute (MNI) T1 for 198 DLGG patients, presented according to the neurological convention (left to left and right to right). The color range indicates the number of patients for whom the voxel is lesioned. Each brain section is presented with its z-coordinate in the MNI space. Personal unpublished data.

Fig. 2. 3D-representation of the complete clustered graph superimposed to the mean registered image. The numbers of nodes in each cluster are reported. From Parisot et al., PLoS One 2016.
to occur earlier in the posterior regions of the brain (including the occipital lobe), which are only rarely affected by DLGG. It could thus be hypothesized that these temporal differences between regions myelinated at varied periods in the development could participate in the differences in terms of risk of DLGG according to the location. Finally, tumors of different locations could arise from different molecular pathways (“the molecular hypothesis”, see below). Indeed, differences in terms of molecular markers, including the mutation of the IDH gene and the 1p19q codeletion, have been reported by several studies (Laigle-Donadey et al., 2004; Zlatescu et al., 2001; Mueller et al., 2002; Huang et al., 2008; Gozé et al., 2009; Metellus et al., 2010; Stockhammer et al., 2012; Ren et al., 2012; Leeper et al., 2015; Brat et al., 2015), and further confirmed by a recent work by our team.

3. The functional theory

The functional theory relates to the impact of the microenvironment or stroma on the tumor development. This hypothesis may be considered to interpret the reasons for the preferential brain locations of DLGG. It could be hypothesized that interactions between neurons and glia are different in the SMA and insula compared with those in the occipital lobe. Indeed, glial cells are known to play a role (1) in neuronal migration, which may explain the existence of migration disorders in some cortical epilepsy, including the extra-temporal epilepsy that often originates from the SMA and insula — but rarely from the occipital region; (2) in the regulation of synaptic transmission; (3) in the control of synapse numbers; and (4) in the energy metabolism of the neuron, explaining the neurovascular and metabolic decoupling in gliomas (Pellerin and Magistretti, 1994; Ullian et al., 2001). Therefore, if we consider that the insula/SMA and the occipital lobe have different structural and functional profiles, repercussions concerning the biologic behavior of the local glial cells are likely.

Arguments for an influence of functional parameters linked to the subject’s activities on the glial cells can be found in the literature on training-induced macrosopic structural changes (of both white and grey matter) in human and animals. A number of neuroimaging studies in healthy volunteers showed that learning could generate a significant increase of gray matter volume in areas specifically involved in tasks extensively repeated (Draganski et al., 2004). The microscopic mechanisms involved will be discussed farther in this article. Interestingly, an implication of the glial cells has been suggested (Blumenfeld-Katzir et al., 2011; Sagi et al., 2012; Anderson et al., 1994; Demerens et al., 1996). Thus, we might suppose that such modifications in the local glial properties may favor or prevent DLGG development in some specific brain locations.

Early studies from the 60’s have suggested a link between the environmental demands and the brain structure in animals (Rosenzweig et al., 1962; Walsh et al., 1963). In the past fifteen years, a number of in vivo studies in human have been performed thanks to new imaging techniques, mostly magnetic resonance imaging (MRI) (Draganski et al., 2004). With these techniques, both the grey (“voxel-based morphometry”, or VBM, based on a 3D and T1-weighted sequence (Ashburner, 2009)) and the white matters (“diffusion-tensor imaging”, or DTI) were explored. Beyond these morphological parameters, the changes in the functional connectivity induced by training have also been studied using “resting-state” methods, as it can be modulated by the expertise of the subject for a task (see for example the study by Fauvel et al. (Fauvel et al., 2014)). Using these techniques, the macroscopic changes induced by various tasks or activities have been studied in human, from navigation skills in London licensed taxi-drivers (Maguire et al., 2000) to cognitive training tasks in students (Draganski et al., 2006) or visuo-spatial tasks with varying complexity (i.e., juggling (Draganski et al., 2004)). These macroscopic changes constitute a powerful phenomenon. They have been reported for a high number of tasks (motor tasks (Draganski et al., 2004; Boyke et al., 2008; Jäncke et al., 2009; Granert et al., 2011), pure visual or visuospatial tasks (Ditwe et al., 2013), spatial memory and navigation (Maguire et al., 2000), memory tasks (Draganski et al., 2005), linguistic tasks (Mechelli et al., 2004), calculation (Aydin et al., 2007), reasoning tasks (Mackey et al., 2012), creative and “artistic” tasks (Takeuchi et al., 2010), and music (Herholz and Zatorre, 2012); from simple tasks (Granert et al., 2011) or more complex tasks (visuo-motor tasks such as juggling, golf, dance…); on healthy brain (most studies are performed on healthy voluntary subjects) or on damaged brain (i.e., after stroke (Wan et al., 2014)); in young subjects (Draganski et al., 2004) (including children (Hyde et al., 2009)) or elderly subjects (Boyke et al., 2008; Bezzola et al., 2011); with controlled tasks or in “ecological” conditions (i.e., uncontrolled leisure activities (Bezzola et al., 2011)); in the long term (i.e., London licensed taxi drivers (Maguire et al., 2000)) or in the short term (Draganski et al., 2004; May et al., 2007); for over-training or for suppression of a task (the withdrawal of the task, even short, is associated with a focal reduction of the grey matter in the corresponding areas (Takeuchi et al., 2010)); and for both the grey and white matter. However, this phenomenon also seems reversible, with a possible regression of the macroscopic changes after a period of training withdrawal (Draganski et al., 2004), even though a more persistent effect is possible (Draganski et al., 2006). Therefore, in the case of an impact of the subject’s activities on the genesis of DLGG, it could only concern regular activities, such as professional activities, but probably not activities performed punctually. Moreover, it is not completely clear yet whether the morphological changes are linked to a skill itself, or to the fact of learning a new skill. Indeed, correlations between the intensity of the macroscopic changes in MRI and the subject’s performance at the task are inconsistently found (Draganski et al., 2004; Ditwe et al., 2013). Moreover, some studies have reported a regression of the morphological changes without concomitant decrease in the subject’s performance at the task (Draganski et al., 2004; Ditwe et al., 2013), suggesting that these macroscopic changes reflect the fact of learning more than the skill itself. This would explain that, in human, there is no significant modification of the brain volume in relation with developing new skills or performing a higher number of activities. However, some discordant data have been reported in animals, among which an increased brain volume and weight in rats placed in an enriched environment (Rosenzweig et al., 1962). In human, the correlations between the subject’s activities and brain volume have also been studied in non-demented healthy subjects, with inconsistent results (Solé-Padullés et al., 2009; Foubert-Samier et al., 2012). Finally, if the macroscopic changes visible in MRI are in relation with the learning of a task rather than with the skill/the expertise itself, how could we explain the differences between expert groups and novices in cross-sectional studies? One hypothesis is that expert subjects constantly learn and improve their skills: new streets, new traffic rules etc. for London licensed taxi drivers, new dance steps or choreographies for dancers, for example, which is less true for novice subjects.

To date, the microscopic changes underlying the macroscopic changes induced by training are still uncertain (Zatorre et al., 2012). These changes most probably not only affect one isolated area but rather the whole functional network involved in the task. Microscopically, they probably occur both in the grey and white matter. Microscopic data in humans is lacking and most of it comes from animal studies (Blumenfeld-Katzir et al., 2011; Zatorre et al., 2012). Various mechanisms are currently suspected: neurogenesis (Pereira et al., 2007), gliogenesis (Blumenfeld-Katzir et al., 2011; Rosenzweig et al., 1962), glial hypertrophy (possi-
bly mediated by the interactions between astrocytes and neurons; a recent study on cerebellar cortex in mice suggested that the molecular and functional profiles of astrocytes are regulated by the neurons, through the "sonic hedgehog" pathway (Farmer et al., 2016) (Sagi et al., 2012; Anderson et al., 1994), and synaptogenesis (mediated by astrocytes) (Anderson et al., 1994) for the grey matter changes and increased glial cells density, increased myelination (mediated by oligodendrocytes) (Blumenfeld-Katzir et al., 2011; Anderson et al., 1994) or axonal sprouting (possibly involving NogoA which is mainly expressed by the oligodendrocytes (Delkate et al., 2011)) (Pereira et al., 2007) for the white matter changes. Training-induced vascular changes (that is, changes in blood-flow) represent another candidate mechanism to account for grey matter as well as white matter macroscopic changes (Zatorre et al., 2012). Indeed, an increased rCBV (relative cerebral blood volume) was found in the dentate gyrus of both mice and humans following physical training in a study published by Pereira et al. (Pereira et al., 2007). Overall, glial cells seem involved in training-induced macroscopic changes, either directly (gliogenesis and glial hypertrophy) or indirectly, through the regulation of synapses, axonal sprouting or myelination. It can be hypothesized that these changes could impact DLGG genesis.

As DLGG have preferential locations in « functional » areas (Fig. 1), and macroscopic white matter and grey matter changes, possibly mediated by glial cells, can occur after training at a task, it can be hypothesized that an over-solicitation of a functional network by a task or a specific environmental demand may impact DLGG genesis. This hypothesis was named the “functional theory”, on the basis of the eloquence of the cerebral regions involved in DLGG. In a recently published study, mice exposed to an enriched environment for over three weeks showed a higher resistance to glioma development after being brain-transplanted with glioma cell lines (glioma development occurred in 73.5% of the transplanted mice from the enriched environment group compared to 96.5% from the standard environment group), suggesting a link between glioma development and the amount of brain solicitations (Garofalo et al., 2015). Mice submitted to the enriched environment also showed smaller tumor sizes and reduced proliferation rates. In human, only few studies have investigated the links between the subject’s activities and the risk of glioma so far. A small number of studies have reported conflicting results regarding the correlation between the education level and the risk of glioma (Wigertz et al., 2010; Scheurer et al., 2008; Cabaniols et al., 2011). A Swedish population-based case-control study in 494 glioma patients (and 321 meningioma patients) and 955 controls reported no correlation between the risk of glioma and the education level (Wigertz et al., 2010). In a North-American study, the education level of 600 controls was higher than that of 325 glioma patients (for example, advanced degree in 26% of controls and 18% of cases) (Scheurer et al., 2008). However, a French case-control study including 122 glioma patients (43 DLGG) found that an education level considered as “moderate” was significantly associated with a decreased risk of glioma (OR = 0.35, IC95%: 0.16–0.77) compared to subjects with no education (Cabaniols et al., 2011). As such association was not found in subjects with a “high” education level, this result must be considered with caution. In the same vein, a recent cohort study found an increased risk of glioma in highly educated people (≥3 years university education) compared to those with primary education (Khanolkar et al., 2016). In this study, men and women with an intermediate or high non-manual occupation had a significantly increased risk of glioma. Regarding DLGGs specifically, a hospital-based case-control study in 135 low-grade gliomas (but including gangliogliomas) found no association with education (Insip et al., 2003). Finally in a pooled analysis of seven case-control studies including 617 WHO grade II and III oligodendrogliomas and oligoastrocytomas and 1260 controls, 16.2% of cases compared with 17.6% of controls had a higher education level (McCarthy et al., 2011).

To date, there is no demonstrated association between professional activities and the risk of DLGG or, more generally, of glioma. A few professions have been inconsistently associated with the risk of brain tumors: health professions (Krishnan et al., 2003; Ohgaki, 2009), electricity workers (Preston-Martin et al., 1989), agriculture workers (Zheng et al., 2001), industrial workers in petrochemical refineries (Navas-Acien et al., 2002), rubber industries (Monson and Fine, 1978), polyvinyl chloride industries (Preston-Martin et al., 1989), chemical industries (Ohgaki, 2009) or nuclear plants; and various other professions such as teachers (Pan et al., 2005), architects (Pan et al., 2005; Ruder et al., 2012), butchers (Ruder et al., 2012), salesmen and waiters (Zheng et al., 2001), servicemen (Zheng et al., 2001). However these associations are inconsistently found and must be considered with great caution as they could be due to chance only, since many of these studies conducted multiple comparisons. Moreover, due to the lack of “functional” classification of the activities, these studies evaluated the professional expositions rather than the neurocognitive functions involved in the profession.

4. The cellular and molecular hypotheses

It appears increasingly clear that glial tumors emerge from particular initiating cells (cells of origin) transformed by the activation of oncogenic signaling pathways resulting from acquired molecular alterations. The emergence of a tumor in a given area of the brain, which is itself shaped by loco-regional functional characteristics as previously reviewed, is a complex phenomenon in which the tumor cell of origin, the molecular sustaining phenomena and the cellular microenvironment (called stroma) are closely intertwined. Therefore, it is difficult to consider separately the cellular, molecular and functional hypotheses on the origin of gliomas.

Currently available data in the literature on these complex issues present common characteristics: (1) they result from studies conducted in transgenic mice with transgenes expression both restricted to particular development stages and cell lineages, (2) they relate mainly to high-grade gliomas. Understanding of the molecular and cellular events involved in the genesis of DLGG suffers for now from the lack of lifelike animal model.

4.1. Cellular hypothesis

The oligodendrocyte precursor cells (OPC) and neural stem cells (NSC) have been identified as possible cells of origin of gliomas. OPC represent the major cycle-related population of the adult normal brain, dispersed throughout the gray and white matter. Considering former publications (Lindberg et al., 2009; Persson et al., 2010; Sugart et al., 2011), OPC seemed particularly involved in the origin of low-grade gliomas. This finding is in good accordance with clinical observations reported by Vergani et al., with a systematic involvement of cortex in a series of 43 DLGG suggesting a centripetal tumor growth (Vergani et al., 2011). To go further, Galvao et al. showed that OPC might transform into malignant glial cells by a two-step process. An initial step of malignant transformation through inactivation of TP53 and NF1 genes is followed by a reactivation involving mTOR pathway (Galvao et al., 2014).

Other studies show that, in experimentally raised gliomas, there is interplay between the nature of the cell of origin and the triggered oncogenic signaling pathways. Each of these two elements involved in malignant transformation exerts its influence and the type of glioma thus obtained is the result of their combination.

To find out whether adult lineage-restricted progenitors of central nervous system cells are possible initiating cells of glioblas-
tumors, Alcantara Llaguno et al. induced inactivation of NFI, Pten and TP53 genes in neural progenitor cells (NPC) and OPC (Alcantara Llaguno et al., 2015). They obtained two different types of glioblastomas. These tumors were different with regard to their molecular profile, their location in the brain and survival duration of mice developing these tumors. Each type was related to a different cell of origin i.e. NPC or OPC. This work demonstrated that the same oncogenic sequence could give rise to a different tumor type depending on the cell type in which it exerts its action. However experimental tumors thus obtained were histologically classified as glioblastomas, in both cases. On the other hand, in a recent study, Lindberg et al. showed that, depending on the oncogenic pathways activated in the OPCs, a tumor of oligodendrogial or astrocytic type would arise (Lindberg et al., 2014). Overexpression of PDGF-B produced tumors similar to human grade II and grade III oligodendrogliomas while activation of the K-RAS/akt pathway lead to grade III and IV astrocytic tumors. The main finding provided by this work is that the importance of the cells of origin seems inferior to genetic aberrations in determining tumor histopathology.

An additional degree of complexity is added by the high specialization of the different brain areas at the cellular level. This underlies intrinsic variations, within a given cell type, related to the location, with repercussions on molecular patterns. One again in mice, Ko et al. reported distinct gene spatial expression patterns in neurons, astrocytes and oligodendrocytes when analyzed from different brain areas (Ko et al., 2013). Gene expression patterns showed strong mirror symmetry between the left and the right hemispheres. Astrocyte and oligodendrocyte-specific transcripts displayed spatially clustered expression patterns less numerous and with less precise boundaries than for neurons.

The regional molecular variability exhibited by these different cell types can also be seen in their biological behavior. In an animal model of glioblastoma, the oncogenic induction gives tumors whose growth rate is different depending on the subtype of astrocytes in which oncogenic stimulation was performed. Astrocytes expressing the glutamate aspartate transporter (GLAST) gave rise to more slowly growing tumors than astrocytes expressing glial fibrillary acidic protein (GFAP) (Irvin et al., 2016).

The tumor cellular environment other than glial cells also plays a role in tumor development, particularly in the case of DLGG experiencing slow growth with a prolonged cohabitation with normal cells. Immune cells represent one of the major components of the tumor microenvironment. Indeed, the immune system is involved in immune tolerance allowing the tumor to settle and then to progress. The immune cells present within the tumor are microglia, resident macrophages of the central nervous system, but also macrophages from peripheral blood that infiltrate secondarily the tumor (tumor associated macrophages TAM). All together, microglia and blood macrophages represent 30–50% of the infiltrating cells in gliomas. Accumulating evidence indicates that microglia and TAM promote glioma growth and invasion (Hambardzumyan et al., 2016). At this level too, the diversity encountered between different brain areas is manifested: it has been known for a long time that the distribution and morphology of microglial cells varies from region to region of the brain (Lawson et al., 1990).

Similarly to glial cells whose behavior is modulated by the function within a specific brain region (see the “functional theory”), immune cells in the tumor microenvironment are impacted by the functional activity of the brain region invaded. Garafolo et al. used the xenograft of glioblastoma cell lines to show that an enriched environment influences tumor development in mice (Garafalo et al., 2015). Indeed, the enriched environment induced the increase of two factors in the tumor microenvironment. The first of them is IL15 that caused accumulation of natural killer (NK) cells in the tumor. NK cells have a direct anti-tumor activity. The second is the important mediator Brain-derived neurotrophic factor (BDNF) that reduced macrophage infiltration and induced a reduction in tumor size.

4.2. Molecular hypothesis

Once the onset of the tumor is achieved, other molecular events are going to take over and allow tumor development. As a logical consequence of the influence of the nature and the location of the original cell, and of the activated oncogenic pathway, molecular profiles determined on resected tumors vary from one region to another.

During the past fifteen years, a number of anatomo-molecular studies showed significant correlations between the location of DLGG and the tumor molecular patterns. First, the IDH mutation, considered as an early key event in the genesis of DLGG, is found with a frequency that varies according to the tumor location. DLGG with IDH mutation are more frequently found in the anterior part of the brain, especially in the frontal lobe in several studies in limited series often mixing DLGG and high-grade gliomas (Stockhammer et al., 2012; Ren et al., 2012; Leeper et al., 2015; Brat et al., 2015). In a recent work from our team (Darlix et al., unpublished data) in a homogeneous and consecutive series of 198 DLGG patients, we confirmed that frontal tumors are more frequently IDH mutant compared to temporo-insular tumors (87.1% vs 57.5%, p<0.001) (Fig. 3).

Second, 1p19q loss, another molecular hallmark of DLGG, has also a different distribution depending on the location. Similarly co-deleted 1p19q gliomas were found more significantly in the anterior part of the brain, especially in the frontal lobe (Laglade-Donadey et al., 2004; Zlatescu et al., 2001; Mueller et al., 2002; Huang et al., 2008; Ren et al., 2012; Leeper et al., 2015). This result has also been confirmed in our recent work, with the presence of a 1p19q codeletion in 45.2% of frontal DLGG compared to
17.0% of tempo-insula DLAGG (p = 0.003) (Fig. 3). However, the anatomo-molecular studies published so far have some limitations. Most importantly, their methodology for determining groups of tumors according to their locations often relied on a subjective assessment of lobar anatomy, while it is needed to use different approaches to deal with the question of multi-lobar tumors. In addition, the majority of these studies were conducted on series including gliomas of different grades (Lagle-Donadey et al., 2004; Stockhammer et al., 2012) or a small number of homogeneous tumors (Gozé et al., 2009; Metellus et al., 2010; Stockhammer et al., 2012).

The molecular regional differences yet observed in DLAGG would have consequences on the outcome of these tumors because prognosis value has been assigned to some of them, especially IDH mutation and 1p/19q loss. Therefore, the tumor location could be in itself a prognostic factor.

5. The environmental theory

Beyond their preferential locations within the brain, DLAGG also seem to present with a heterogeneous distribution at the geographical level (Darlix et al., 2014). Indeed, a few studies have previously suggested such an heterogeneity in the geographical distribution of gliomas, at the worldwide or European level, with a trend towards higher incidence rates in highly-developed countries (http://globocan.iarc.fr/) (Dolecek et al., 2012; Crocketti et al., 2012). However these studies have major limits. First, they included gliomas of all grades and even primary central nervous system tumors (PCNST) other than gliomas. Second, they compared the incidence rates at an international or even intercontinental level, resulting in an obvious bias due to differences among continents and countries in terms of case registrations and access to healthcare. In a study from our team based on data from the French Brain Tumor DataBase (Rigau et al., 2011), we analysed the geographical distribution of a homogeneous series of 4790 newly-diagnosed and histologically confirmed diffuse WHO grade II and III gliomas in metropolitan France, over a four-year period (2006–2009) (Darlix et al., 2014). The overall crude rate was 19.4/106. We found that the geographical distribution by region was heterogeneous, in any case, with higher incidence rates in Northeast and central parts of France (Figs. 4 and 5). Since France has a unique healthcare system, access to healthcare is likely to be similar in all regions, with a roughly homogeneous distribution of neurosurgical centers. Therefore, the demonstrated uneven geographical distribution of DLAGG raises the question of the role of environmental risk(s) factor(s) (environmental theory).

To date, there is no identified environmental risk factor of DLAGGs. Interestingly, in France, a geographical heterogeneity in the incidence rates was highlighted for all cancers, with a higher incidence in the North and Northeast regions (data from the National Cancer Institute: http://www.e-cancer.fr/publications/69-epidemiologie/574-la-situation-du-cancer-en-france-en-2011). Especially, the distribution of colorectal cancer was comparable to that of WHO grade II and III gliomas in our study, with similar higher incidence rates in the Northeast part of France. A working hypothesis could be that these two diseases may share some risk factors. For example, some diets were validated as risk factors in colorectal cancer with red and processed meat, alcohol, obesity or abdominal fat being strongly associated with a higher risk of colorectal cancer, while the “Mediterranean diet” prevents its occurrence (Chan et al., 2011; Aleksandrova et al., 2013). Also, it is to note that the consumption of red and processed meat is higher in the Northeast regions of France (CREDOC, research center for the study and the observation of living conditions, http://www.credoc.fr/pdf/4p/101.pdf). A working hypothesis could thus be that diet factors may have an impact on the risk of developing WHO grade II and III gliomas. N-nitroso compounds, mostly found in processed meat, are considered as carcinogenic (National Research Council, 1981). They induced an increased occurrence of glioma in rats after intravenous injections of N-nitroso compounds (Maekawa and Mitsumori, 1990). However, this hypothesis is to be considered with caution. Indeed, processed meat has been inconsistently associated with glioma risk in epidemiological studies, with a modest increase of the glioma risk associated with consumption of processed meat in case-control studies but not in cohort studies in two recent meta-analyses (Saneei et al., 2015; Wei et al., 2015). Other diet factors have been studied, but none has been associated with DLAGG or glioma risk yet. Another interesting observation is the relative similarity between the geographical distribution of WHO grade II and III gliomas (Darlix et al., 2014) and that of multiple sclerosis (Fromont et al., 2010). In the same vein, these two diseases may share some risk factors. Indeed, there is strong evidence that environmental factors influence the distribution of multiple sclerosis (Ebers, 2008). In particular, sunlight exposure is significantly associated with multiple sclerosis prevalence, sunny areas being associated with low prevalence. This association probably involves vitamin D, as a low prevalence of multiple sclerosis has been reported in countries with a poor amount of sunlight but a high consumption of vitamin D (oily fish) (Ebers, 2008). We could thus hypothesize that sunlight and vitamin D intake influence the risk of WHO grade II and III gliomas. Based on the map of the sunlight provided by the Joint Research Center of the European Commission (available at: http://re.jrc.ec.europa.eu/pvygis/cmaps/eu_cmsa_opt/G_opt_FR.png), it seems that regions with low sunlight correlate with those with higher incidence rates of WHO grade II and III gliomas in our study, supporting the hypothesis of an association between sunlight and WHO grade II and III gliomas risk. This hypothesis is supported by only one study that found an inverse association between UVB irradiance and brain tumor risk (Mohr et al., 2010), but needs to be further investigated in independent studies.

The uneven geographical distribution of DLAGGs in France also raises the question of the role of genetic risks factors that could be different depending on the geographical region considered (genetic susceptibility, the “genetic predisposition theory”).

6. The genetic predisposition theory

Genetic susceptibility variants could also impact on the risk of DLAGG development and have been widely studied in the past years to better understand the origins of this entity. Interestingly, about 5% of glioma patients have a familial glioma history (Malmer et al., 2007). While these aggregations could be in relation with the environment (subjects in a family share environmental exposures), they suggest the existence of a genetic susceptibility. Among susceptibility factors, monogenic genetic traits account for 1% of familial cases of glioma (Rice et al., 2016). Beyond these monogenic syndromes, some non-syndromic genetic factors of susceptibility seem to influence the risk of glioma as well (Scheuer et al., 2010).

A familial history of brain tumor is a risk factor of glioma (including DLAGG (Rice et al., 2016; Scheuer et al., 2010) and oligodendrogial tumors (McCarthy et al., 2011)) in non-syndromic families. In the study published by McCarthy et al., the risk of developing a diffuse WHO grade II and III oligodendroglioma was increased in patients with a familial history of PCNST (odds-ratio = 1.8 CI 95% 1.1–3.1) (McCarthy et al., 2011). In a Swedish study, the standardized incidence was 3.65/105 (CI 95% 2.31–5.47) for first-degree relatives of DLAGG patients, and 7.00/105 (CI 95% 3.35–12.87) for siblings, which is significantly higher than the reported incidence in the general population (Malmer et al., 2002).
Various studies have tried to characterize these familial gliomas on a genetic point of view. First, comparative genomic hybridization techniques were used and have suggested relatively close chromosomal profiles in familial gliomas and in sporadic gliomas, with only few inconsistently-reported specific alterations (Idbaih et al., 2007). Other studies used linkage analyses to identify candidate genes/genetic variants in familial gliomas. The GLIOGENE project (« Genetic Epidemiology of Glioma International Consortium ») was set up in 2006 and includes glioma families treated in 14 institutions and five countries (Malmer et al., 2007). It allowed the identification of a region of interest located on chromosome 17q (Shete et al., 2011). Sequencing analyses of this specific region pointed out several candidate genes (Myo19, KIF18B, SPAG9 in particular) (Jalali et al., 2015). However, none of these genes was incriminated in all the described glioma families. Another region of interest located on chromosome 15q23 was reported in several studies (Paunu et al., 2002). These linkage studies, however, face major difficulties, due to the poor survival of many glioma patients: only few families comprise more than two cases alive simultaneously.

More recently, other genetic risk factors for glioma were studied, in particular genetic polymorphisms (Liu et al., 2010). These studies found associations between a number of single nucleotide polymorphisms (SNPs) and the risk of the glioma (Melin and Jenkins, 2013). To date, eight SNPs located in seven genes have been associated with an increased risk of glioma in genome-wide association studies (GWAS) (Melin and Jenkins, 2013): rare genetic variant in the TP53 gene (glioblastomas and other gliomas) (Stacey et al., 2011); genetic variants in the EGFR gene (gliomas) (Sanson et al., 2011); in the RTEL1 gene (« regulator of telomere elongation helicase ») (gliomas) (Shete et al., 2009); in the TERT gene (« telomerase reverse transcriptase ») (oligodendrogliomas and astrocytomas,
whatever the grade or the IDH status) (Shete et al., 2009); in the 8q24 locus/CCD26 gene (gliomas, in particular oligodendrogliomas and IDH-mutated tumors, and including DLGG) (Jenkins et al., 2012; Di Stefano et al., 2013); in the PHLD1 gene (IDH-mutated gliomas, whatever the tumor grade and histological subtype) (Di Stefano et al., 2013); and in the CDKN2B gene (Shete et al., 2009; Walsh et al., 2013). These SNPs identified by GWAS studies have been further confirmed in a large case-control study (Walsh et al., 2013), as well as in a meta-analysis (Rajaraman et al., 2012). Genetic variants of TERT, RTEL1, EGFR and TP53 were found associated with an increased risk of glioma, whatever the tumor grade or histological subtype. On the contrary, genetic variants of PHLD1 and CCD26 (+/− CDKN2B); conflicting results (Di Stefano et al., 2013) were shown to be associated with an increased risk limited to specific grades and/or histological subtypes of gliomas. Candidate-gene studies have also identified a number of candidate genes involved in several biological pathways: folate metabolism (Bethke et al., 2008a), DNA-repair pathways (XRCC ou « X-ray repair cross complementing group ») (Felini et al., 2007), apoptosis signaling pathway (i.e., CASP8 (Bethke et al., 2008b). However, none of these SNPs has been confirmed in the large case-control study published in 2013 (Walsh et al., 2013).

7. The clinical implications

Such spatiotemporal, functional, and biological considerations may have important implications with regard to the therapeutic strategy and management of DLGG patients. First, the dynamic interactions between DLGG and the brain may vary depending on the eloquence of the areas involved by the tumor. Indeed, slow-growing DLGG might induce cerebral plasticity, explaining why most patients showed no or only mild neurological deficit despite voluminous gliomas, even in the so-called “critical” regions (Desmurget et al., 2007; Duffau, 2005). Nonetheless, a recent
atlas of DLGG resectability demonstrated that some cerebral areas had low compensatory capabilities (Duffau, 2009b), constituting a “minimal common brain” among patients (Lus et al., 2011). As a consequence, the extent of surgical resection (and thus the median survival [Jakola et al., 2012]) is correlated with the location of the tumor (with regard to the cortex as well as the white matter pathways, therefore the distance from the subventricular zone), that is, with a better tumor removal in “non-eloquent” than in “eloquent” areas and in “compensable” rather than “non-compensable” structures (Chang et al., 2011; Duffau, 2009c; Duffau, 2012a; Yordanova et al., 2011). In addition, a different genetic pattern in tempo-insular DLGG, with a less frequent IDH mutation and 1p19q codeletion compared with frontal DLGG, could also account for the poorer prognosis of these tumors. Indeed, DLGG prognosis was shown to vary according to the tumor location, frontal DLGG being associated with a better intrinsic prognosis compared with temporal or insular tumors whatever the extent of resection (Capelle et al., 2013).

As a consequence, it might be pertinent to modulate the treatment strategies according to these two subgroups of patients, and discuss a more aggressive strategy for tempo-insular DLGG with, for example, earlier chemotherapy regimens after surgical resection.

The functional, cellular, molecular and environmental parameters discussed in this review illustrate very well the close relationships between the pathophysiology of gliomagenesis, the anatomo-functional organization of the brain, and the personalized management of DLGG patients. They will allow a better screening of the population in order to perform an early detection of DLGG – and thus to propose a more precocious and more efficient treatment (Duffau, 2012b; Mandonnet et al., 2014; Mandonnet et al., 2016) – as well as to improve our knowledge concerning the origin of DLGG.

8. Conclusions

The origins of DLGG are still unclear, but it seems plausible that an association of genetic susceptibility and biological, functional and environmental factors influence the risk of developing DLGG. Future studies will be needed to investigate these candidate etiologic factors taken together, since interactions between the environment, brain functions and tumor genes are likely. This will allow a better understanding of the origins of DLGG and of the clinical heterogeneity of this entity.

Authors’ contribution

All authors have made substantial contribution to this work: AD, CG and HD conceived and designed the paper, wrote the first draft of the manuscript, integrated the co-authors suggestions and approved the final version. VR, LB and LT helped conceiving the paper, revised the first draft of the manuscript, made substantial corrections and approved the final version.

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