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REVIEW ARTICLE

The Unexpected Roles of Aurora A Kinase in Gliobastoma Recurrences

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Abstract The main obstacle for the cure of glioblastoma (GBM) is systematic tumor recurrence after treatment. More than 90 % of GBM tumors are indeed recurrent within 5 years after diagnosis and treatment. We urgently need new therapies to specifically address these deadly relapses. A major advance in the understanding of GBM recurrence is the identification of GBM-Initiating Cells (GIC), characterized by their abilities for self-renewal, multilineage differentiation, and proliferation. It appears that these features of GIC could be modulated by the mitotic kinase Aurora A (AurA). Indeed, besides its role in mitosis, AurA has recently been identified to regulate alternative functions like cell polarity, asymmetric cell division, and epithelial to mesenchymal transition. All these properties may help explain GBM therapeutic resistance and recurrence. In this review, we make the hypothesis that AurA could significantly contribute to GBM recurrences and we focus on the possible roles of AurA in GIC.

Key Points

The therapeutic targeting of glioblastoma (GMB)-initiating cells (GIC) may help to reduce GBM tumor recurrences

Aurora A kinase, AurA, plays key roles in cell polarity, asymmetric cell division and epithelial to mesenchymal transition, which may be crucial for GIC therapeutic resistance and GBM relapses

AurA targeting represent a promising tool to prevent GBM recurrence

1 The Therapeutic Challenge of GBM

1.1 Current Treatments

Although the incidence rate of central nervous system (CNS) primary tumors is moderate (27.86 per 100,000 people in the United States), almost the half of the malignant CNS tumors are glioblastomas (GBM), which are usually fatal within the year [1, 2]. Standard treatment of GBM starts with maximal safe surgical resection of the tumor. Despite great improvements in neuroimaging techniques, the invasive pattern of GBM sets limitations for surgery. Most of the time, complete tumor resection is impossible without damaging healthy brain tissues [3]. Cancer cells left behind after surgery are likely to initiate tumor recurrence, which is why surgery is systematically followed by radiotherapy and chemotherapy.

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Radiotherapy enhances survival from 3–4 months to 7–12 months compared to surgery alone. An additional chemotherapeutic treatment with the alkylating agent temozolomide (TMZ) increases the median survival rate to 15–21 months in 45 % of the patients [4–7].

1.2 GIC-Targeted Therapies

GBM tumors are composed of heterogeneous cell populations which exhibit distinct tumorigenic potentials. A few GBM cells have stood out for their high potential for self-renewal, multilineage differentiation (multipotency), and proliferation [8]. These cells were identified as GBM-initiating cells (GIC) given their abilities for initiate and maintain tumor growth; just like normal stem cells in healthy tissues. The identity and the roles of GIC have been recently reviewed [9]. Briefly, GIC may be a mechanism of GBM relapses given that they are the only cells able to establish whole tumors in mice that mimic the histocytology of human GBM. Cerebral injection of 100 primary GIC induces GBM tumors whereas engraftment of 10^5 non-GIC cells fails to form tumors [10, 11]. In vitro, GIC divide continuously to form undifferentiated and multipotent spheres in suspension cultures. GIC neurospheres reflect the behavior of stem cells (quiescent cells) or of progenitor cells (characterized by a faster division rate) [12, 13]. Moreover, it is now clear that distinct GIC populations coexist within one tumor and display different tumorigenicity and independent genomic evolution [14], a situation that explains the absence of a bona fide GIC marker. These observations led to the development of new therapies specifically targeting GIC in order to reduce GBM recurrences (reviewed in [15]). Clinical trials are currently testing inhibitors designed to disrupt the self-renewal, differentiation, and proliferation of GIC, such as inhibitors of the Hedgehog (HH), Notch, Wnt, TGF-β, BMP, VEGF, BMP, and PARP signaling [16–23].

1.3 GIC and Therapeutic Resistance

The GIC-targeted therapies seem to improve the therapeutic response of GBM tumors, but only to some extent, and until now no therapeutic target stood out. This failure may be a consequence of the therapeutic resistance of GIC. Indeed, GIC modulate pathways of DNA repair responses (Chk1/2, PARP1, MGMT), drug efflux (BCRP1), and anti-apoptotic mechanisms in order to resist radiotherapy and chemotherapy [24–27]. GIC can also escape surgery by migrating in perivascular niches through their high migratory abilities [28]. We and others have demonstrated that GIC can specifically invade the sub-ventricular zones (SVZ) in response to the production of the CXCL12 chemokine [29–31]. SVZ, located along the ependymal layer on lateral ventricle wall, are stem cells niches, crucial for the regulation of adult neurogenesis. Interestingly, the SVZ are particularly propitious for gliomagenesis since they are abundant in growth factors and permissive to proliferation [32]. GBM tumors in contact with the SVZ are associated with a lower survival, a low response to radiotherapy and higher risks of multifocal or distant progression [33, 34]. The hypothesis is that stem cells niches provide a suitable cellular and molecular environment for stem cells, including GIC, helping them to survive and to resist standard treatments [15].

Another factor to be considered in the GIC therapeutic resistance is their “cellular plasticity”. Indeed, non-GIC can be reprogrammed into a GIC phenotype, which is why the targeting of both GIC and non-GIC may be required to eradicate GBM recurrences [35]. Finally, most of the standard treatments target rapidly dividing cells, whereas GIC are spared since they can enter into a quiescent state. Chen *et al.* showed that TMZ transiently stops tumor growth in mice, but does not prevent the ensuing tumor recurrence. In the same study, quiescent GIC-like cells maintain tumor growth through the production of transient populations of highly proliferative cells [36]. This finding shows the importance of GBM tumor dormancy that depends on cancer stem cells (CSC) division. CSC can divide through asymmetric cell divisions (ACD), like normal stem cells. ACD allow maintaining a constant number of stem cell while generating distinct progenitor cells, unable to self-renew, but able to divide rapidly. ACD is often dysregulated in CSC and accompanied by changes in proliferation, self-renewal, cell cycle, cell polarity, and genomic instability [37].

As the mitotic kinase Aurora A (AurA) is involved in ACD, but also in some features suspected to play a role in GBM relapses, we propose to discuss in this review the possible importance of AurA in GBM recurrences. As several recent papers described the regulation of AurA in physiological conditions, we will not review this point [38–40].

2 Roles of AurA in Normal and Cancer Cells

In mammals, cell division takes place every 24–30 h in highly renewing tissues. Each time a cell divides, there is a risk of chromosome instability (CIN) which could lead to malignant transformation. This explains why approximately 90 % of human solid tumors are aneuploid. Thus, cell division has to be a rigorously orchestrated process, which requires efficient, timely, and specific regulations to allow the proper chromosomal segregation to daughter cells [38]. Among the members of this regulatory network, the AurA centrosomal kinase is known to be crucial for the entry of the cell into mitosis both at the molecular and at the structural level: AurA (i) unlocks the G2/M restriction point by activating CDK1/CyclinB, a complex that brings the M phase onset and (ii) prepares the

cell to divide by promoting centrosomes maturation and mitotic spindle formation [39].

Considering its central role in mitosis, the dysregulation of AurA in highly proliferative cancer cells is consistent. The chromosomal region of the *AURKA* human gene (20q13.2) is a hotspot for cancer amplification [41]. AurA overexpression is known to promote centrosome amplification, CIN and aneuploidy that, in turn, could induce the malignant transformation of the cell [42]. AurA can also promotes tumorigenesis through deregulated modulation of alternative pathways such as p53, BRCA1, Myc, NFkB, Wnt/β-catenin, mTOR, and cyclin [43–49]. In gliomas, the expression of AurA increases with the tumor grade (I to IV) while being associated with the Ki-67 proliferation index and with low survival [50, 51]. AurA overexpression in GBM promotes mitotic failure and supernumerary centrosomes [52, 53]. Moreover, AurA inhibition potentiates the cyto-suppressive effect of both ionizing radiation and TMZ on GBM cells and xenograft mice models [50, 54, 55]. These findings emphasize the role of AurA in GBM therapeutic resistance.

Besides these oncogenic activities, recent studies revealed unexpected roles of AurA that may be even more significant for GBM tumor recurrence. AurA has notably been identified as a key regulator of cell polarity, ACD, and epithelial to mesenchymal transition (EMT), potentially crucial for GBM relapse and GIC tumorigenicity.

3 The Unexpected Roles of AurA in GBM

3.1 Principles of Asymmetric Cell Division

Asymmetrical cell division (ACD) is a specific property of normal stem cells. During an asymmetrical stem cell division, the cellular constituents are asymmetrically segregated by establishing an unbalanced spindle orientation. This stereotyped spindle orientation depends on the centrosome positioning during interphase. Distribution of the cellular constituents specifies then the fate of daughter cells toward a self-renewing stem cell or a rapidly dividing progenitor cell. By balancing self-renewal with differentiation, ACD maintains a constant number of stem cell while producing distinct differentiated cells appearing after a progenitor clonal expansion [56].

Studies on Drosophila neuroblasts (NB) have revealed basic principles of polarity, spindle orientation and cell-fate determination during ACD (reviewed in [57]). NB divide unequally in order to generate a large apical NB and a small basal cell that will differentiate into neurons or glia. AurA has been identified as a key regulator of asymmetric NB divisions in Drosophila. During metaphase, AurA activates aPKC (atypical Protein Kinase C), which recruits the apical complex required for the establishment of NB polarity [58]. Before chromosomal separation, AurA phosphorylates $Pins^{LINKER}$ (Partner of Inscuteable) to allow a proper spindle orientation [59]. At interphase, AurA controls cell fate decision via the reactivation of aPKC to promote the basal distribution of Numb. Numb is a cell-fate determinant, which blocks self-renewal through Notch inhibition [60, 61]. AurA loss leads to ACD failure, which forces NB to divide symmetrically and to proliferate continuously. AurA is therefore regarded as a tumor suppressor that reduces NB self-renewal and promotes their differentiation [62]. Paradoxically, AurA overexpression in Drosophila NB induces tumor overgrowth due to centrosome dysfunction [63].

3.2 Asymmetric Cell Division in Cancer

Altered ACD is highlighted in several cancers including leukemia, breast, and brain tumors [64–66]. Like normal stem cells, CSC generally divide both symmetrically and asymmetrically in order to maintain cancer growth [67]. In leukemia, the balance between symmetric and asymmetric divisions of hematopoietic precursor cells can be regulated by microenvironments and genetic alterations [64]. In breast cancer, the higher rate of breast CSC (BCSC) symmetric division is progressively counterbalanced in favor of ACD during mammospheres growth [65]. In brain tumors, cellular heterogeneity is mainly engendered through symmetric divisions, but GIC also divide asymmetrically to maintain their CSC pool. Indeed, GIC asymmetrically segregate the CD133 stem cell surface marker during their dividing cycles [68]. ACD disruption in GBM cells causes anarchic self-renewal, uncontrolled proliferation and impaired differentiation [69]. In view of these findings, it would be interesting to test the role of AurA in the asymmetric GIC division and its impact on GIC tumorigenecity.

4 Epithelial to Mesenchymal Transition

4.1 EMT in Cancer

Epithelial and mesenchymal cellular transitions result from reorganization of cell structure, shape and junctions. An epithelial cell tightly packed into the epithelial tissue can become a free and motile mesenchymal cell, or vice versa [70]. During early embryonic development, EMT allows the development of the embryonic mesoderm, which evolves into various tissues. In late stages of development, MET (Mesenchymal to Epithelial Transition) enables mesoderm cells to generate epithelial tissues [71].

EMT is also exploited by tumor cells as a prerequisite for tissue invasion. Several EMT transcription factors (e.g. Twist, FOXC2, Smad5, Snail, Slug) enhance the mesenchymal phenotype of cancer cells, which improve their invasiveness and

therapeutic resistance [72–77]. In addition to tumor invasion, EMT can favor the acquisition of a CSC phenotype. An induced EMT in mammary epithelial cancer cells provides them a stem cell phenotype characterized by the ability to form mammospheres and to initiate tumor in mice [78, 79]. This observation suggests that some invasive cancer cells, considered as low proliferative cells, may be self-renewing CSC. This type of cancer cell may be particularly tumorigenic given that they can invade surrounding tissues and initiate recurrent tumors.

4.2 EMT in GBM Tumors

Several factors involved in EMT are able to enhance GBM cell migration and tumor invasion. N-cadherin expression level modulates centrosome positioning, integrin-mediated polarity, speed, and direction of glial cell migration [80]. NCAM (Neural Cell Adhesion Molecule) expression is an indicator for the invasion zone and for poor prognosis [81, 82]. The EMT proteins ZEB1 [83], Twist [84], E-cadherin [85], and Snail [86] also promote GBM cells migration. It is debatable whether molecular GBM subtypes (i.e. neural, proneural, classical, and mesenchymal) may predict the patient clinical outcome. Nevertheless, the mesenchymal subtype tends to be associated with poorer survival due to low therapeutic response [87, 88]. Moreover, tumor recurrence after treatment is often accompanied by shift into a more pronounced mesenchymal phenotype [89]. All these findings demonstrated that EMT can influence the invasiveness and the therapeutic response of GBM tumors.

Additional data suggest that EMT may be a specific property of GIC. Primary GBM, but not secondary tumors (GBM stemming from a lower grade glioma), express both mesenchymal and stem cells markers. Primary GBM cells can be forced to differentiate into multiple mesenchymal cell lineages [90]. The EMT transcription factor ZEB1 is overexpressed in invasive gliomas and induces migration of human neural stem cells [91]. We have shown that CXCL12, the chemokine responsible for GIC-directed migration to the SVZ, is also able to promote EMT in GIC [29]. Moreover, the mesenchymal activation of GIC promotes resistance to radiotherapy [92, 93]. In addition, circulating GIC, characterized by a strong mesenchymal phenotype, are the only cells potentially metastasizing outside the brain (reviewed in [94]). In summary, these findings reveal that EMT seems to be closely linked to GBM aggressiveness and to cancer cells immaturity leading to tumor recurrences.

4.3 Role of AurA in EMT

AurA ensures microtubules (MT) dynamics that control cell polarity during ACD, mitosis, and migration. AurA inhibition impairs MT shrinkage, growth rate, frequency rescue and nucleation during interphase of mitotic HeLa cells [95]. In post-mitotic neurons, aPKC activates the AurA-NDEL1 (nudE neurodevelopment protein 1 like 1) pathway to promote MT-based neurite extension of migrating neurons [96]. The apical junction complex (AJC), which forms the epithelial cell junctions, can only be preserved if cells are polarized [97]. Polarity loss, frequently observed in cancer, lead to EMT, involving cancer cells migration (reviewed in [37, 98]).

In GBM, nothing is known about the role of AurA in EMT. Nevertheless, AurA has been identified as a regulator of cell polarity, EMT and migration in various epithelial tumor cells, including in BCSC. AurA inhibition improves the epithelial phenotype of BCSC and prevents the development of distant metastases in mice [99]. Another study supports these first observations, showing that AurA overexpression induces breast cancer metastasis by reorganizing the actin cytoskeleton through the cofilin-PI3K pathway [100]. In nasopharyngeal carcinomas, cell migration decreases in response to epithelial markers expression induced after AurA inhibition [101]. AurA overexpression in CSC from head and neck tumors provokes their mesenchymal activation via stabilization of Snail, which in turn represses E-cadherin [102, 103]. In esophageal squamous cell carcinoma, AurA promotes cell migration through the activation of the MAPK and Akt pathways leading to the secretion of MMP-2 (matrix metalloproteinase-2), which allows the degradation of extracellular matrix components [104]. AurA is also overexpressed in colorectal CSC (CR-CSC) and promotes CR-CSC migration [105].

5 AurA As a Therapeutic Tool to Target CSC

AurA overexpression in GBM also affects GIC behaviors and therapeutic responses. Evidences suggest AurA activity is more crucial for the survival and proliferation of GBM neurospheres (a feature linked to a GIC phenotype) than differentiated GBM cells monolayers [54]. Indeed, GBM neurospheres treated with AurA inhibitors exhibit more spindle defects, polyploidization, increased senescence, differentiation, and apoptosis compared to adherent GBM cells [106, 107]. AurA also seems to mediate therapeutic resistance of GIC: AurA inhibition improves the response of GBM neurospheres to TMZ and radiotherapy [54, 107]. De Bacco *et al.* showed that the c-MET receptor, a potential functional marker of GIC, activates the Akt-AurA pathway to promote DNA repair mechanisms and radioresistance [108–110]. Altogether, these data highlight the role of AurA in GIC self-renewal and therapeutic response. In view of all these promising anti-tumor effects, the selective P-AurA inhibitor alisertib is currently in a phase I clinical trial in patients with recurrent GBM developed after radiation therapy [16].

6 AurA Inhibitors in Clinical Trials for Solid Tumors

Alisertib is the leader of the AurA inhibitors [111]. AurA inhibitors show promising anti-tumor activities in clinical trials, but with adverse effect such as neutropenia, stomatitis, and somnolence (reviewed in [112]). Among them, non-selective AurA inhibitors (ENMD2076, AT9283, Danusertib, MK-0457, MSC1992371A, and PR-0381473S) show promising results but involve stronger adverse effects such as febrile neutropenia, fatigue, diarrhea, and hypertension [16, 113, 114]. A specific AurA inhibitor, MLN8054 (Millennium Phamaceuticals, Cambridge, MA, USA), tested in clinical trials, showed a limited efficacy due to strong benzodiazipeine-like adverse effects. A structural adaptation of MLN8054 give rise to a new specific AurA inhibitor, MLN8237 (Millennium Pharmaceuticals), also called alisertib. Alisertib treatment induces less adverse effects and strong anti-tumor activity in patients with leukemia, myeloma, neuroblastoma, lymphoma, ovarian, breast, and other advanced solid tumors [16, 115].

7 Conclusion

The biggest issue of GBM is the recurrence of the tumor after treatment. GIC may play a role in tumor recurrences, given that those cells may resist standard treatments and initiate secondary tumors in experimental approaches. In search for GIC-targeted therapies, AurA turned out to be an effective tool to counteract GIC features linked to “stemness”. Besides mitosis-related oncogenic activities, recent evidence highlighted the significance of AurA in GIC tumorigenecity. AurA controls cell polarity during ACD and EMT, two key factors for cancer invasion, therapeutic resistance and tumor relapses. In this way, AurA may contribute to GBM recurrence by regulating GIC polarity. Taken together, these data highlight the possible involvement of AurA in GBM recurrences, making AurA a new promising target in GBM therapy.

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Compliance with Ethical Standards

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Conflict of Interest Estelle Willems, Arnaud Lombard, Matthias Dedobbeleer, Nicolas Goffart and Bernard Rogister declare no conflicts of interest.

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