Particulate Matters Affecting IncRNA Dysregulation and Glioblastoma Invasiveness: In Silico Applications and Current Insights

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Abstract
With a reported rise in global air pollution, more than 50% of the population remains exposed to toxic air pollutants in the form of particulate matters (PMs). PMs, from various sources and of varying sizes, have a significant impact on health as long-time exposure to them has seen a correlation with various health hazards and have also been determined to be carcinogenic. In addition to disrupting known cellular pathways, PMs have also been associated with IncRNA dysregulation—a factor that increases predisposition towards the onset or progression of cancer. IncRNA dysregulation is further seen to mediate glioblastoma multiforme (GBM) progression. The vast array of information regarding cancer types including GBM and its various precursors can easily be obtained via innovative in silico approaches in the form of databases such as GEO and TCGA; however, a need to obtain selective and specific information correlating anthropogenic factors and disease progression—in the case of GBM—can serve as a critical tool to filter down and target specific PMs and IncRNAs responsible for regulating key cancer hallmarks in glioblastoma. The current review article proposes an in silico approach in the form of a database that reviews current updates on correlation of PMs with IncRNA dysregulation leading to GBM progression.

Keywords Glioblastoma multiforme · Particulate matter · Long noncoding RNA · In silico studies

Introduction
All solid and liquid particles, suspended in air all together, are called particulate matter and they include hazardous as well as non-hazardous particles (Harrison and Yin 2000). It comprises organic and inorganic particles, e.g., pollen, soot, dust, liquid droplets, and smoke. These particles differ in size, composition, and origin. The sources of PM can be natural as well as manmade. Anthropogenic activities like combustion of fossil fuel in vehicles (Omidvarborna et al. 2015), dust on road, power plants, stubble burning, various industrial processes, and wet cooling towers generate a considerable number of particulates. On the other hand, natural sources of particulate matter are dust storms, forest fires, volcanic eruptions, grassland fire, and sea spray (Anderson et al. 2012; Kundu and Stone 2014). With an increase in industrialization and anthropogenic activities, exposure to these PMs was seen to increase alongside a notable increase in health hazards such as cognitive impairments, respiratory disorders, and even carcinomas (Harrison and Yin 2000; Harbo Poulsen et al. 2020; Santibáñez-Andrade et al. 2020; Shaddick et al. 2020).

Glioblastoma multiforme, based on its histopathological tumors (GBM), is a WHO categorized grade IV brain tumor. It primarily develops in the glial cells, i.e., the astrocytes, microglia, and oligodendrocytes, and is known for its infiltrative and aggressive nature (Urbańska et al. 2014; Hanif et al. 2017). GBM is a highly malignant and essentially incurable form of brain cancer with approximately 3 out of 100,000 cases annually that typically result in deaths in the first 13 to 15 months after diagnosis. GBM, often developing in then trans barrier space of the blood–brain barrier (BBB), displays a high level of heterogeneity and was earlier classified based on their genetic profiles into three molecular subtypes, i.e., proneural, which is commonly seen in younger patients and is less pathological, classical which has low mortality with aggressive chemotherapy and
mesenchymal which shows extensive necrosis and inflammation (Sidaway 2017; D’Alessio et al. 2019). Currently, GBM is classified into primary and secondary subtypes based on the presence of isocitrate dehydrogenase (IDH) gene wherein a wild type is observed in the more clinically found primary GBM while an IDH mutant corresponds to secondary GBM type (Louis et al. 2016; D’Alessio et al. 2019; Silantyev et al. 2019; P. Zhang et al. 2020a). The former may arise de novo, i.e., it begins as a grade IV tumor with no lower grade precursor whereas the latter one progresses from lower grade tumor and leads to grade IV malignant tumors (Zhang et al. 2020b). In addition to the mutational status of IDH, various other predictive markers such as the 6-O-methylguanine DNA methyltransferase (MGMT) enzyme or growth factor receptors such as EGFR and PDGFR can often indicate and correspond to GBM pathology (Brennan et al. 2013). The preferred line of diagnosis of glioblastomas is often imaging-based results via magnetic resonance imaging (MRI), or computed tomography (CT) followed by a standard line of treatment, i.e., surgical resection coupled with chemotherapy and radiation, however, due to its highly infiltrative nature along with technological limitations has left a gap for development of better diagnostic and treatment protocols making the optimal use of biomarkers, in this case specific to GBM (Stupp et al. 2005).

No singular reason can be attributed to the development of GBM in patients but there have been significant results highlighting the role of factors like high-dose exposure to ionizing radiation (Gupta and Burns 2018; Deshors et al. 2019; Todorova et al. 2019), carcinogens in air pollution like particulate matter (PM) (Huang et al. 2017a; Harbo Poulsen et al. 2020), and certain long non-coding RNA (lncRNA) dysregulation (Ma et al. 2020; Miguel et al. 2020) in GBM progression. Disruption of lncRNA is been involved in glioblastoma (Zhang et al. 2019a). They are involved in tumor cell proliferation, invasion, therapy resistance, and cancer stem cell differentiation (Zhang et al. 2019a). Various studies have uncovered consistent evidences supporting the upregulation and downregulation of certain lncRNA in GBMs wherein numerous roles of lncRNAs were seen as decoys, ceRNAs, and epigenetic regulators (Uddin et al. 2020); this points to the need for us to conceptualize and study the dynamics associated with lncRNA dysregulation to optimize disease pathology and therapeutics (Huarte 2015; Dong and Cui 2019; Stackhouse et al. 2020; Zhang et al.).

The application of in silico analysis substitutes exhaustive literature searches and data management. It optimizes and integrates information that is otherwise too vast for comprehension. Primarily, it refers to prediction using computational approaches by data mining, computational modelling, sequence alignments, similarity searches, mathematical modelling, and so on to develop user-friendly databases, making it an advantageous tool in studies employing vast data repositories and procuring results with quicker predictions in a high-throughput mode (Edelman et al. 2010; Iourov et al. 2014; Wilks et al. 2014; Yang et al. 2015; Vougas et al. 2019; Zhu et al. 2020). Use of various databases is now also being employed to primarily study disease models such as cancers—ONCOMINE, NSBI GEO, RNAz—and their regulatory factors such as lncRNAs, to be discussed ahead at length.

Environmental Factors, PMs, and Health Hazards

In the aftermath of decades of industrialization and urbanization, a fold increase in air pollution, causing approximately 7 million deaths worldwide, was observed, declaring it a major environmental crisis. Activities like unsupervised and rampant burning of fossil fuel and unfiltered release of industrial exhausts into the atmosphere slowly noticed a categorical correlative increase in mortality in addition to various health hazards ranging primarily from respiratory disorders, impaired cognitive functions, stroke, loss of white matter, to a variety of carcinomas (Gauderman et al. 2015; Mudu et al. 2020; Santibáñez-Andrade et al. 2020). These particles differ in size categorized by the USEPA. They are divided into 3 categories: (1) coarse particles or PM10, these are the particles with aerodynamic diameter of 10–2.5 μm. These particles can easily penetrate to the lungs and get into the blood stream; (2) fine particles or PM2.5, these are the particles with aerodynamic diameter between 2.5 and 0.1 μm. These particles are capable of crossing the blood–brain barrier; (3) ultrafine particles or PM0.1, these particles have aerodynamic diameter of 0.1 μm or less than that. These particles are known to cause highest oxidative stress (Bhargava et al. 2018; Zhang et al. 2018; Santibáñez-Andrade et al. 2020). Various multietnic studies over the years indicated the presence of particulate matter (PM) to be the common denominator in this case, and thus, active research to identify the intricacies of these carcinogenic particulate matters with disease onset and pathology is being extensively studied.

Metastasis, a process mediated by epithelial mesenchymal transition in the cancer cells, is the key factor responsible for cancer proliferation and various PM particles have been observed to carry out the disease progression by modulation this hallmark of cancer (Sánchez-Pérez et al. 2009; Deng et al. 2013). PM2.5 is one such PM that has been correlated with high proliferative cancers displaying a fold increase in malignancy due to it affecting known EMT mediating pathways such as TGF-β/Wnt pathway, NOTCH signalling pathway, and SMAD signalling pathway. Additionally, PM2.5 has also been seen to play an integral role in cell death resistance by activating PI3K-AKT pathway in the cells in addition
to mediating generation of ROS radicals and induction of mitochondrial stress response (Chen et al. 2005; Sánchez-Pérez et al. 2009; Deng et al. 2013; Heßelbach et al. 2017).

Furthermore, evidences of PM$_{2.5}$ mediating angiogenesis by inducing pro-angiogenic factors and disrupting genomic stability by downregulating DNA repair enzymes and epigenetic alterations strengthen the hypothesized role of this PM as a key causative agent of various medical anomalies, primarily cancer (Huang et al. 2017b; Zhang et al. 2017b; Li et al. 2018a). Evidences from in vitro studies have suggested that exposure to PM2.5 can cause certain changes in the brain that induces tumorigenesis (Zhang et al. 2018; Araújo et al. 2019). Thus, we can infer that PM2.5 can reach the brain via the blood stream crossing the blood–brain barrier (Poulsen et al. 2020). PM2.5 is seen to have prominent role in diseases like Parkinson disease and Alzheimer disease. PM2.5 exposure is related to cell proliferation, anti-apoptotic effects, and activations of angiogenic factors (Santibáñez-Andrade et al. 2020). Epithelial-mesenchymal transition which is said to be the one of the major events that promote tumor metastasis is also seen to be affected by PM2.5 (Xu et al. 2019a), as the risk of cancer mortality increases by several folds when the patient is exposed to PM2.5 after cancer diagnosis (Ou et al. 2020).

**Particulate Matters and GBM**

The common occurrence of a high air pollution index often increases the possibility of exposure to carcinogenic PMs resulting in onset of disease pathology (Manisalidis et al. 2020; Wu et al. 2020a, b; Ou et al. 2020). Various evidences have highlighted the role of coarse particulate matter in brain inflammation piquing an interest to study the neurodegenerative and tumorigenic effects on exposure to concerning levels of air pollution (Merk et al. 2020; Lu et al. 2021). A prominent European observational study with a cohort sampling method identified positive association between absorbance of PMs as a result of traffic exposure and the occurrence of brain tumors wherein statistically significant associations between air pollutants (PMs) and malignant tumors were noted (Andersen et al. 2018; Zhang et al. 2018) creating a scope for further studying PMs in lieu of brain tumors or gliomas. Furthermore, correlation between exposure to PMs and their effect on neural biomarkers was found in a crossover study with a group of 50 healthy volunteers wherein further indication of disruptions of blood–brain barrier alongside high levels of stress was also noted (Liu et al. 2017).

India being a developing nation has seen a reported increase in various health hazards in the past few decades (Kandlikar 2000; Smith 2000; Manisalidis et al. 2020). Daily exposure to these PMs via their various sources has not only developed numerous pathologies such as asthma, premature pregnancies, and tuberculosis, but also numerous types of cancer such as lung carcinoma, melanomas, and even glioblastomas (Khilnani and Tiwari 2018; Jindal et al. 2020). With over 1.6 million new incidences of cancer detected nationwide, each year, regulation of air pollutants and limited exposure to PMs is imperative apropos of public health and welfare (Krishnatraya and Kataki 2020). Due to the fine size of these PMs, once breathed in and detained in the tissues by internal impaction, PMs can easily travel across the blood–brain barrier (BBB)—the cellular line of defense (Shih et al. 2018). Studies analyzing gene expression of genes associated with neuro-endocrine responses, inflammation, tumorigenesis, and proliferative responses recorded an upregulated response in their expression after prolonged exposure (1–3 months) to these PM. Simultaneous upregulation of genes encoding interleukin 13α1 and cytokine IL-6 further indicated and confirmed instances of inflammation in the brain post-PM exposure. Furthermore, the upregulation of the Ras-related botulinum toxin substrate 1 (RAC1) gene associated with various carcinomas additionally supported the role of these PMs in tumorigenesis.

The onset of glioblastoma cannot be narrowed down to a particular cause, instead the presence of a singular or a myriad of physical, chemical, etiological, epidemiological, or lifestyle-based predispositions can be attributed to the progression of GBM (Ljubimova et al. 2018; Harbo Poulsen et al. 2020). Several studies have notably pointed towards PM playing a role in intracranial central nervous system tumor progression but there have also been inconsistencies and a paucity of conclusive results (Shih et al. 2018; Poulsen et al. 2020). However, epidemiological studies (Andersen et al. 2018; Harbo Poulsen et al. 2020; Turner et al. 2020) specifically investigating the role of PM in tumor malignancy, in the recent years, have categorically indicated the role of PMs (PM$_{2.5}$) as a risk factor in gliomas in addition to other tumor subtypes. Known evidences of PMs dysregulating cellular pathways such as cell cycle (Li and Nel 2006; Longhin et al. 2013; Santovito et al. 2020), angiogenesis (Kaur and Katnoria 2016; Chen et al. 2017), and EMT (Chi et al. 2018; Xu et al. 2019b) indicate towards cancer proliferation, even in the case of glioblastoma. Upregulation of pathways inducing epithelial-mesenchymal transition, angiogenesis, and even drug resistance resulting in various types of carcinomas has been attributed to exposure to PMs; however, studies indicating the involvement of PMs and IncRNA dysregulation highly buttress their role in GBM progression. Evidentiary studies have noted the interaction and upregulation of IncRNAs such as MEG3, HOTAIR, MALAT1, and NEAT1 which are known regulators of EMT by regulating their respective cellular pathways or by acting as ceRNAs and GBM and subsequently contribute to disease progression (Zhou et al. 2015; Li et al. 2018b; Miguel et al. 2020; H. Chen et al. 2019; Q. Chen et al. 2018; Gupta et al. 2010; L. Zhang et al. 2020).
Pathogenic Mechanisms of PMs in GBM Progression

Saturation of the air available to us for breathability with toxic contaminants such as various particulate matters may not have an immediate visible effect alongside clinical symptoms; however, a long-term exposure can undeniably lead to detrimental pathological repercussions such as asthma, chronic obstructive pulmonary disease (COPD), stroke, and carcinomas (Lee et al. 2020). Cancer, irrespective of the type, is a complex web of signalling cascades and their molecular modifiers wherein a small irregularity—in this case, long-term exposure to environmental factors such as PMs—can potentially initiate a ripple effect at a molecular level resulting in dysregulated cell signalling cascade and ultimately resulting in tumor progression. PMs are well studied and researched in lung carcinomas; however, their role at a molecular level has been seen to increase oxidative stress in various other cancer types making it a prominent risk factor initiating the onset of GBM and its progression (Vattanasit et al. 2014). PM-mediated ROS stress response often leads to activation of ROS-sensitive signalling cascades such as the mitogen-activated protein kinases (MAPKs) and its upstream regulatory pathway, phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), which in turn leads to overexpression of specific transcription factors potentiating GBM progression. Additionally, PMs have also been seen to induce DNA damages that can potentially activate more than one carcinogenic pathway (Lee et al. 2020; Li et al. 2021). Apart from the known carcinogenic effect of PMs, the extent of their toxicological effect is also directly proportional to their concentration wherein glutathione transferase was observed as one of the key effect modifiers correlating it with a ROS stress response in cells (Orach et al. 2021). GBM progression and etiology could further be attributed to lncRNAs present in the cells. They are often packed and shipped in membrane-bound vesicles, extracellular vesicles, that are compacted with an array of biomolecules and that on uptake by the recipient non-cancerous cell often result in activating and dysregulating known oncogenic pathways; one such crucial cargo content is a variety of ncRNAs (Wang et al. 2018a) (Fig. 3).

PM-Mediated Epigenetic Regulation and GBM Progression

There are various key genes responsible for the development and regulation of various cancers; however, apart from the specific genes, various regulatory elements play a key role as genetic modifiers. Non-coding RNA contributes as one of the key modifiers of any cancer landscape wherein different kinds of ncRNAs such as IncRNAs, miRNAs, circRNAs, and snoRNAs together dysregulate existing cellular pathways leading up to a cancer phenotype (Candido et al. 2019; Rynkeviciene et al. 2018; Zhang et al. 2020a, b, c, d). In glioblastoma, a variety of studies have indicated the role of miRNAs and IncRNAs aiding in cellular proliferation, anti-apoptotic pathways, angiogenesis, and chemoresistance. These non-coding RNAs seem to bind with gene regulatory elements, transcription start sites, and promoter sequences and alter gene expression. Some are even responsible for chromatic modification leading to expression of previously silenced genes. In the case of GBM, various chromatin regulatory elements result in aiding the aggressiveness of the glioma type. In glioblastoma, several types of ncRNA play a pivotal role in leading to GBM progression and also in suppressing it; miRNAs such as mir-21, mir-148a, and mir-5-5p are crucial regulators of GBM progression in addition to lncRNAs HOTAIR, MALAT1, CCAT2, H19, and HIF1α playing a similar regulatory role (Mukherjee and Pillai, 2021; Stella et al. 2021; Gao et al. 2019b; Bountali et al. 2019; Y, Zhang et al. 2020a; L. Chen et al. 2019).

The lncRNA repository is responsible for carrying out a myriad of cellular roles and has a similar effect in brain tissues as well. IncRNAs play a key role in modulating the epigenetic landscape during glioblastoma development (Uddin et al. 2020). The molecular interplay of IncRNA, acting as ceRNAs (competing endogenous RNAs), is intertwined with various miRNAs wherein without undergoing gene modification a variance in phenotypic characteristic is observed (Liz and Esteller 2016; Dashti et al. 2020). IncRNAs, once transcribed, can carry out modifications in gene expression either by causing chromatin rearrangement or by binding to promoters, miRNArsc, or specific proteins such as enhancer of zeste homolog 2 (Ezh2), polycomb-repressive complex (PCR2), DNA methyltransferases (DNMTs), and many more (Wilusz et al. 2009). The interaction of IncRNAs with proteins acts as a key causative agent in cancer progression by aiding in proliferation (Dashti et al. 2020; Jin et al. 2020a, b, c; Luo et al. 2020), invasion (Chen et al. 2018; Zhang et al. 2020a; R. Su et al. 2020), migration (Zhou et al. 2020), apoptosis (Hui et al. 2019), and chemoresistance (Chen et al. 2019d). In gliomas, IncRNAs such as PLAC2 are known to bind to signal transducer and activator of transcription 1 (STAT1) followed by which this complex downregulates the CDK2 causing an arrested cell cycle and inhibition of proliferation (Hu et al. 2018). Interaction of IncRNA NEAT with RNA binding proteins (RBPs) such as Ezh2 which causes promoter silencing of GSK3b, Axin2, and ICAT, in addition to promoting WNT/β catenin signalling as a result of glioma invasiveness (Chen et al. 2018). Interactions with DNA methyltransferases with IncRNAs as seen in the case of LINC00467 have seen to play a role in glioma invasiveness by interacting with the p53 promoter resulting in a change in gene expression (Zhang et al. 2020a).
The molecular interplay of lncRNAs lies in close association with other non-coding RNAs (ncRNAs) such as microRNAs (miRNAs) that are usually 22 nucleotides long and circular RNAs (Y. Zhang et al. 2020a). Commonly found upregulated lncRNAs in the GBM TME such as H19, HOTAIR, SNHG5, Xist, MALAT1, NEAT1, and CRNDE and downregulated lncRNAs such as MEG3 and TUG1 have been observed to aid in angiogenesis, proliferation, apoptosis, and even migration—known hallmarks of cancer progression. CRNDE is a known lncRNA that acts via the mTOR pathway (Wang et al. 2015) involving myc, cyclinD1, p53, and PTEN genes—all known targets of mir384 which in turn is a known regulator of the protein PIWIL4, a key player in STST3 phosphorylation (Zheng et al. 2016). Apoptosis-stimulating protein of p5 (iASPP) gene is a key regulator in the apoptotic pathway, the expression of which is inhibited by the activation of the gene inhibitor activated in turn by the lncRNA UCA1 which also further inhibits the expression of miR-182 (He et al. 2017)—an miR responsible for the cell proliferative pathway (Li et al. 2019). Additionally, an upregulation in then levels of UCA1 downregulates miR-122, which originally is associated with the function of tumor progression and proliferation. HOTAIR is a known lncRNA and a target for miR-326 (Ke et al. 2015) and miR-148b-3p (Wang et al. 2016); combined effects of these lncRNA-miRNA complexes act as good inhibitors for tumor proliferative, migrative, and invasive processes as observed in U251 and U87 (glioblastoma cell lines). Additionally, fibroblast growth factor (FGF) (Lungu et al. 2008), a known target of this lncRNA-miRNA complex, is further seen to activate oncogenic pathways of PI3K/AKT signalling. Furthermore, suppressed expression of HOTAIR results in regulation of apoptosis as correlated with cellular levels of bromodomain and extra-terminal family protein (BRD4) (Pastori et al. 2015). Levels of NEAT1 have been seen to inversely correlate with the patient survival rates (He et al. 2016). It suppresses apoptosis by interacting with miR-449b-5p—an activator of MET oncogene. Furthermore, the miR let-7e is a known direct target of NEAT1 that aids in cell proliferation via the PI3K/AKT pathway (Zhen et al. 2016). MALAT1 remains as the most debatable lncRNA in terms of molecular interplay in cancers. In GBM, MALAT1 has been found to be both downregulated and upregulated wherein higher levels correlate with better survival of patients with glioma. MALAT1 also is known to downregulate the levels of miR-155 which is a known target for FBXW7, a tumor suppressive gene (Cao et al. 2016a). In the context of GBM, the role of FBXW7, the circRNA responsible for coding the FBXW7 185aa, a protein with a key role in modulation of hypoxia as a result of regulating the Warburg effect, has also found its place in modulating the glioblastoma epigenetic landscape (Yang et al. 2018; Yang et al. 2020). A common occurrence in GBM with respect to lncRNA is seen with their role in sponging miRNAs as can be seen in the case of oncogenic lncRNA Sox2ot that sponges mir200 resulting in EMT facilitation; lncRNA PART1 plays a tumor suppressive role by sponging mir190a-3p that consecutively downregulates the PTEN/Akt signalling, H19 acting as ceRNA and regulating EMT by sponging mir130a-3p—a fairly common way of lncRNA-mediated tumorigenesis (Heßelbach et al. 2017; Huang et al. 2017c; Li et al. 2018b; Wang et al. 2018a, b, c; Chen et al. 2019a, c, d; Wang et al. 2019a, b; H. Chen et al. 2020a; W. Chen et al. 2020b; Stackhouse et al. 2020; Feng et al. 2021; Chen et al. 2019a; Jin et al. 2020a, b, c).

A large number of studies exist that correlate the lncRNA dysregulation with GBM progression (Table 1); however, an earlier date of consistent data, joining one of the dots between lncRNA dysregulation and GBM, can now be attributed to PMs. Thus, the detrimental interaction of PMs with known lncRNA species has been correlated with GBM progression. A study with lung epithelial cells elucidates the dysregulated IncRNA landscapes on exposure to PMs indicating a notable abnormal expression of ncRNAs. A substantially high level of MALAT1 expression was triggered by exposure to resulting in EMT (Huang et al. 2017b). Additionally, the involvement of the AHR-CYP1A1 pathway which plays a necessary role in managing the toxicity and physiological impacts of toxic metabolites is seen to interact with various types of lncRNAs making them a notable target to study the interactions of these PMs at a molecular level. lncRNAs have also resulted in cells acquiring cancer cell-like phenotype (CSC) (Huang et al. 2017c; Li et al. 2018b) and have seen to increase the permeability of vascular endothelial cells which plays a crucial role in cancer cell intravasation and extravasation. It does so by inhibiting lncRNA HCG18 (Huang et al. 2017c; Wang et al.). PM2.5-exposed cell gets transformed into cancer cell by being angiogenic with the help of a lncRNA which upregulates VEGF (Yang et al. 2020; Santibáñez-Andrade et al. 2019). Various studies have reported results that categorically suggest the induction of lncRNA MALAT1 in vitro, which initiates a cascade by impacting known EMT regulator Zeb1 consecutively resulting in metastasis and disease progression by downregulating mir-204. MEG3 which is associated with bcl-2- and caspase-induced apoptosis undergoes dysregulation by PM interaction. Increase in HOTAI was also observed by PM obtained from cigarette smoke, and lastly, changes in H19 levels were also noted on exposure to PM, all results notably highlighting the role and involvement of PM in lncRNA interactions (Heßelbach et al. 2017; Li et al. 2018c; Wang et al. 2019a, b). Thus, dysregulated levels of lncRNAs in gliomas and dysregulation of lncRNAs
| S. No | IncRNAs (associated with glioblastoma) | Expression level | Role in GBM progression | Interaction with PMs | References |
|-------|---------------------------------------|------------------|-------------------------|----------------------|------------|
| 1     | TUG1                                  | Downregulation   | Proliferation and inhibition of apoptosis | PM2.5               | Stackhouse et al. (2020), Liao et al. (2019) |
| 2     | GATA6-AS                               | Downregulation   | Proliferation and inhibition of apoptosis | -                   | Stackhouse et al. (2020), Liao et al. (2019) |
| 3     | DGCR5                                 | Downregulation   | Anti-apoptotic, proliferation, EMT, invasion | -                   | Wu et al. (2020a, b) |
| 4     | MALAT1                                 | Upregulation     | Metastasis and tumorigenesis, invasion, drug resistance | PM2.5               | Steinfeld et al. (2015), Stackhouse et al. (2020) |
| 5     | CASC7                                 | Downregulation   | Tumor progression        | PM2.5               | Stackhouse et al. (2020), Chen et al. (2019a) |
| 6     | CASC9                                 | Upregulation     | Tumorigenesis            | PM2.5               | Liu et al. (2018) |
| 7     | LINCO1426                              | Upregulation     | Proliferation, invasion and survival | -                   | Wang et al. (2020a, b) |
| 8     | NEAT1                                 | Upregulation     | Proliferation and invasion | PM2.5               | Zhou et al. (2018a, b), Chen et al. (2018a) |
| 9     | PART1                                 | Downregulation   | Tumor progression and cell growth | -                   | Jin et al. (2020a, b, c) |
| 10    | HOTAIRM1                              | Upregulation     | Proliferation, invasion and tumor progression | -                   | Li et al. (2018a, b, c, d, e), Shi et al. (2020) |
| 11    | H19                                   | Upregulation     | Proliferation, invasion and angiogenesis | PM2.5               | Liu et al. (2020) |
| 12    | HOTAIR                                | Upregulation     | Proliferation, invasion, therapy resistance, chromatin remodelling | PM2.5               | Stackhouse et al. (2020) |
| 13    | CRNDE                                 | Upregulation     | Cell growth, invasion, anti-apoptotic | PM2.5               | Zhang et al. (2020) |
| 14    | MEG3                                  | Downregulation   | EMT, invasion, cell proliferation | PM2.5               | Buccarelli et al. (2020) |
| 15    | AGAP2-AS1                             | Upregulation     | Proliferation             | -                   | Xu et al. (2021) |
| 16    | PCAT1                                 | Upregulation     | Anti-apoptotic, radiation resistance | -                   | Zhang et al. (2019a) |
| 17    | AHIF                                  | Upregulation     | Invasion, anti-apoptotic, radiation resistance | -                   | Dai et al. (2019, a) |
| 18    | LINC01494                             | Upregulation     | Proliferation, migration, invasion | -                   | Li et al. (2019a, b) |
| 19    | GAS5                                  | Downregulation   | Proliferation, invasion and migration | PM2.5               | Li et al. (2019) |
| 20    | ATB                                   | Upregulation     | Invasion                  | -                   | Bian et al. (2019) |
| 21    | TALNEC2                               | Upregulation     | Tumorigenesis, radiation resistance | -                   | Brodie et al. (2017) |
| 22    | LINCO0467                             | Upregulation     | Proliferation and invasion | -                   | Zhang et al. (2019b) |
| 23    | SNHG12                                | Upregulation     | Drug resistance           | PM2.5               | Lu et al. (2020) |
| 24    | MATN1-AS1                             | Downregulation   | Proliferation, invasion | -                   | Han et al. (2019) |
| 25    | NR-002791                             | Downregulation   | Tumorigenesis             | -                   | Wang et al. (2018a, b, c, d) |
| 26    | SBF2-AS1                              | Upregulation     | Drug resistance           | -                   | Zhang et al. (2019b) |
| 27    | BDNF-AS                               | Downregulation   | Proliferation, invasion, tumor progression | PM2.5               | Su et al. (2020) |
| 28    | PSED1B-AS1                            | Upregulation     | Tumorigenesis             | -                   | Yao et al. (2020) |
| 29    | HOXC-AS3                              | Upregulation     | Proliferation, invasion migration | -                   | Wang et al. (2019a, b) |
| 30    | PXN-AS1                               | Upregulation     | Tumorigenesis             | -                   | Chen et al. (2020a) |
| 31    | HIF1A-AS2                             | Upregulation     | Maintain mesenchymal GSC  | -                   | Mineo et al. (2016) |
| 32    | HOXB-AS1                              | Upregulation     | Proliferation, invasion, migration | -                   | Chen et al. (2019) |
| 33    | LINCO0470                             | Upregulation     | Tumorigenesis, anti-apoptotic | -                   | Liu et al. (2018) |
| 34    | SOX20T                                | Upregulation     | Proliferation, invasion, tumor progression | -                   | Su et al. (2017) |
| 35    | DLEU1                                 | Upregulation     | Proliferation, anti-apoptotic | -                   | Liu et al. (2019) |
| 36    | XIST                                  | Upregulation     | Proliferation, invasion, migration | PM2.5               | Yao et al. (2014) |
| 37    | SNHG7                                 | Upregulation     | Tumor progression and cell growth | -                   | Xue et al. (2018) |
| 38    | HAS2-AS1                              | Upregulation     | Tumor progression         | -                   | Zhang et al. (2020a) |
| 39    | SNHG6                                 | Upregulation     | Proliferation             | -                   | Chen et al. (2018b) |
| S. No | IncRNAs (associated with glioblastoma) | Expression level | Role in GBM progression | Interaction with PMs | References |
|-------|--------------------------------------|------------------|--------------------------|----------------------|------------|
| 40    | SNHG15                               | Upregulation     | Drug resistance          | PM2.5                | Li et al. (2019) |
| 41    | TRG-AS1                              | Upregulation     | Proliferation            | -                    | Xie et al. (2019) |
| 42    | SNHG5                                | Upregulation     | Proliferation            | -                    | Chen et al. (2019) |
| 43    | LEF1-AS1                             | Upregulation     | Proliferation, invasion migration | - | Wang et al. (2017) |
| 44    | DANCN                                | Upregulation     | Tumor progression        | -                    | Li et al. (2018d) |
| 45    | SAMMSON                              | Upregulation     | Proliferation, invasion migration | - | Ni et al. (2021) |
| 46    | MIAT                                 | Upregulation     | Tumor progression        | PM2.5                | Bountali et al. (2019) |
| 47    | LOXL1-AS1                            | Upregulation     | Proliferation, invasion migration | - | Wang et al. (2018b) |
| 48    | TP73-AS1                             | Upregulation     | Drug resistance, invasion migration | PM2.5 | Mazor et al. (2019) |
| 49    | HOXA-AS3                             | Upregulation     | Proliferation, invasion migration | - | Chen et al. (2020a) |
| 50    | ADAMTS9-AS2                          | Upregulation     | Drug resistance          | -                    | Yan et al. (2019) |
| 51    | SNHG20                               | Upregulation     | Maintain GSC, tumorigenesis | - | Gao et al. (2019a) |
| 52    | PCAT6                                | Upregulation     | Tumor progression        | -                    | Liu et al. (2020) |
| 53    | GAPLINC                              | Upregulation     | Tumor progression, cell growth, migration invasion | - | Chen et al. (2019) |
| 54    | MNX1-AS1                             | Upregulation     | Proliferation, invasion migration | - | Zhang W et al. (2019a) |
| 55    | PABPC1                               | Upregulation     | Proliferation, invasion migration, anti-apoptotic | - | Su et al. (2020) |
| 56    | NBAT1                                | Downregulation   | Proliferation            | -                    | Liu et al. (2018b) |
| 57    | SCHLAP1                              | Upregulation     | Tumor progression, cell growth, proliferation | - | Ji et al. (2019) |
| 58    | MIR4435-2HG                          | Upregulation     | Proliferation, invasion | -                    | Xu et al. (2020) |
| 59    | CASP5                                | Upregulation     | Migration, invasion      | -                    | Zhou et al. (2015) |
| 60    | RPSAP52                              | Upregulation     | Maintain GSC             | -                    | Wang et al. (2020a, b, c) |
| 61    | UCA1                                 | Upregulation     | Anti-apoptotic, migration invasion | PM2.5 | Xin et al. (2019) |
| 62    | LINC00152                            | Upregulation     | Tumor progression, invasion | - | Chen et al. (2018b) |
| 63    | HOXA-AS2                             | Upregulation     | Tumorigenesis            | -                    | Shou et al. (2021) |
| 64    | MANITIS                              | Upregulation     | Angiogenesis             | -                    | Leisegang et al. (2017) |
| 65    | DCST1-AS1                            | Upregulation     | Proliferation            | -                    | Hu et al. (2004) |
| 66    | SNHG4                                | Upregulation     | Proliferation            | -                    | Wang et al. (2020c) |
| 67    | LINC00998                            | Downregulation   | Proliferation, tumor progression | - | Cai et al. (2020) |
| 68    | TPT1-AS1                             | Upregulation     | Proliferation            | -                    | Gao et al. (2020 Aug 12) |
| 69    | LINC01446                            | Upregulation     | Proliferation, tumorigenesis | - | Zhang et al. (2020b) |
| 70    | AC016405.3                           | Downregulation   | Proliferation, invasion migration | - | Ren et al. (2019) |
| 71    | HOXB13-AS1                           | Upregulation     | Proliferation, tumor progression | - | Xiong et al. (2018) |
| 72    | Lnc-TALC                             | Upregulation     | Drug resistance          | -                    | Wu et al. (2019) |
| 73    | NCK1-AS1                             | Upregulation     | Drug resistance          | -                    | Chen et al. (2020) |
| 74    | HMMR-AS1                             | Upregulation     | Tumorigenesis, proliferation, invasion, radiation resistance | - | Li et al. (2018d) |
| 75    | LINC00657                            | Downregulation   | Anti-apoptotic, proliferation | - | Chu et al. (2019) |
| 76    | AC030392.1                           | Downregulation   | Drug resistance          | -                    | Xu et al. (2018) |
| 77    | RNCR3                                | Downregulation   | Proliferation, anti-apoptotic | - | Zhang et al. (2020b) |
| 78    | TUSC7                                | Downregulation   | Drug resistance          | -                    | Shang et al. (2018) |
| 79    | RAMP2-AS1′                           | Downregulation   | Tumor progression, proliferation | - | Liu et al. (2016a, b) |
| 80    | RP11-838N2.4                         | Downregulation   | Tumor progression        | -                    | Liu et al. (2016b) |
by exposure to PMs as elucidated in different carcinomas hypothesize the correlated involvement of PMs in gliomagenesis via epigenetic regulations.

**In Silico Approaches: PMs, IncRNA, and GBM Progression Correlation**

With the addition of new results around the clock, modern research faces many hurdles when it comes to processing, compartmentalizing, and analyzing the available data. In order to establish favorable and specific connecting links (Fig. 1) from within the consortium of available data, employing the use of analytical or mathematical tools serves as the need of the hour. Bioinformatics paves the way to cinch such scientific occlusions with a diverse range of in silico approaches that not only serve as a crucial data repository but also help research take the much-needed go-ahead in analyzing and building our case to study various medical anomalies such as cancer which exists with various cellular, biological, physical, and etiological connecting links and a high number of casualties. To research, understand, and diagnose any pathology, the cellular transcriptome plays an indispensable role; however, a vast majority of the transcriptome remains unavailable for translation and thus plays a purpose in epigenetically regulating and altering the cellular landscape by sponging, employing decoy moieties, and chelators of various moieties altering the proteome and the cellular landscape with it. With thousands of gene coding for a vast number of transcripts, decoding the specific interactions of one particular transcript at a time becomes a herculean task and thus requires efficient compression and compilation of existing data while maintaining comprehensibility and providing user accessibility. The miniaturization of available vast datasets has been successfully achieved via computational approaches making use of bioinformatics. The ease of shortlisting a target molecule with specific molecular interactions plays a key role in unearthing pathology-specific epigenetic changes wherein the interaction of various non-coding RNAs such as IncRNA, miRNA, and ceRNAs has been mapped to understand the web of interaction (Falzone et al. 2019; Candido et al. 2019; Zhang et al. 2017a; Long and Li 2019; Cao et al. 2016a, b). The repository of available computational databases has made it possible to access and interpret profiling data, RNA seq data, IncRNA-miRNA interactions, (Y. Zhang, et al. 2017b) and many more such parameters which remained elusive to various pathologies resulting from dysregulated pathways such as cancers. The presence of multi-factorial dysregulation is a common occurrence in various cancer types; therefore, to filter out the key molecules amidst a stack of cellular transcripts with significant correlation remains a priority while developing any axes to study cancer types. Computational databases with inbuilt analysis tools have significantly contributed to easing the otherwise cumbersome research methodology.

An important establishment while dealing with a globally occurring disease with high rate of incidence such as glioblastoma is the variety of available databases. These databases, compacted with patient data stored over the years, serve as a key tool in not only understanding the epidemiological impact of the disease but also aiding us build a baseline with respect to the patient variables such as age, gender, ethnicity, and comorbidities. Databases such as The Cancer Genome Atlas Glioblastoma Multiforme (TCGA-GBM) (https://www.cancer.gov/tcga) are a research community aiming at correlating phenotype and genotypes in addition to relevant tumor imaging stored in The Cancer Imaging Archive (TCIA). GliomaDB, another interactive and comprehensive database, serves with the purpose of studying gliomagenesis by integrating and optimizing available information on various higher grade and lower grade gliomas from pre-existing databases such as TCGA, Gene Expression Omnibus (GEO) ([CSEL STYLE ERROR: reference with no printed form.]), US Food and Drug Administration (FDA), and many such notable organizations. ONCOMINE (Rhodes et al. 2004), on the other hand, serves as an efficient web-based data mining platform encompassing various cancer microarray databases and remains a robust provider of information of cancer transcriptome (C. Zhao et al. 2020) and proteome (Silantyev et al. 2019). These databases harness the input information and present it in an easily consumable format by employing statistical and mathematical algorithms or data mining via literature survey followed by compilation and compaction of the database. Efficient models that predict the interplay of various biomarkers for glioblastoma making use of in silico approaches wherein expression profiles of
lncRNAs and miRNAs were noted alongside the miRNA- lncRNA interactions which were then further mapped using computational software Cytoscape to elucidate the lncRNA-miRNA interaction network wherein the lncRNAs specifically denoted their role as ceRNAs (Cao et al. 2016b; Zhang et al. 2017a). A similar study with respect to breast cancer elucidated the web of lncRNA-miRNA interactions by identifying specific dysregulated ncRNA that were summarized from existing databases, namely NCBI, and then analyzed with respect to their associations with target genes and their mRNAs alongside gene ontology and the clinical and pathological features of the specific cancer type (Zhang et al. 2017b). Use of microarray analysis alongside gene ontology and Kyoto Encyclopedia of Genes and Genome (KEGG) analysis has also been carried out to study the gene targets of dysregulated lncRNAs and their interactions with specific mRNAs in the case of lung carcinomas caused as a result of PM exposure (Li et al. 2018a).

Just like cancer databases, a vast amount of information with respect lncRNA—one of the parameters of our article—remains available and open for interpretation and hence, in order to screen and strategically obtain the desired information pertaining to gene regulation, epigenetic modulation, or disease model about specific lncRNA or any other transcriptome, web-based interfaces are easily available for public access. Databases such as LNCipedia (Volders et al. 2019) comprehensively summarize lncRNA annotations and sequences which encompass approximately 56,000 genes and 127,802 transcripts wherein it makes use of RNA sequencing data and chromatin state maps in its databases. NRED (Dinger et al. 2009) exists as a database specifically catering annotated expression data of lncRNAs from diverse sources and helps in identifying specific lncRNA with the use of filter searches apropos of genomic context, target specifications such as deletions, overlaps, and so on. NONCODE (Zhao et al. 2016) is another key example of a comprehensive knowledge consortium dedicated to non-coding RNAs (ncRNAs) across various species wherein they are classified based on sample type, demography, gender, and disease type and further provides results based on simple searches for sequence, location, orthologs, function, or expression.

Although there exist databases devoted to singular broad topics such as cancer or lncRNAs, studies with a deep focus on specific disease models, in this case glioblastoma, often require easy navigation to correlate and identify various intricacies such as related gene expression, epigenetic modulation, involved cellular pathways, and angiogenesis (Iser et al. 2017; Sun et al. 2017). Thus, with a growing focus on understanding disease pathology of complex diseases such as GBM, with more than one factor responsible for onset or progression, our lab proposes the need for data accumulation and dataset generation that can correlate known contributing factors such as lncRNA as either biomarkers (Cao et al. 2016a) or molecular agents mediating dysregulation mediated by particulate matter exposure to study GBM progression (Fig. 2). Though, a niche topic, such databases if constructed can aid in quick searches and precise understanding of specific underlying factors such as lncRNA or PMs responsible for specific disease progression.
Remedial and Therapeutic Approaches

GBM is known for its variety of incitants which are responsible for its onset and progression. Other than exposure to any chemical, physical, etiological, or biological carcinogenic causal agent, particulate matter has also significantly contributed to the disease pathology (Urbańska et al. 2014). Due to a high rate of malignancy and poor diagnosis of glioblastoma, treatment strategies have been limited to surgical resection, radiation therapy, and chemotherapeutic drugs such as temozolomide or bevacizumab. However, with the use of nanoparticles, pharmacokinetics, and bio-engineering, new therapeutic strategies with combinational therapy are being actively researched to investigate and curb GBM progression. However, despite the advancements in therapeutics, remedial strategies to curb one’s exposure to PMs can play a decisive and crucial role in avoiding carcinomas.

Decades of epidemiological research have correlated the role of particulate matter with an array of physiological dysregulations and diseases. Once across the BBB, these PMs aid in transcriptome dysregulation by disrupting various cellular pathways that ultimately result in GBM progression via increased invasiveness, angiogenesis, and metastasis. Additionally, PMs such as PM$_{2.5}$ have also been seen to play a role in chemoresistance as seen in the case of doxorubicin, a chemotherapeutic drug associated with inhibiting apoptosis and upregulating levels of glutathione (GSH) (Dai et al. 2019a; Merk et al. 2020).

Particulate matters such as PM$_{2.5}$, PM$_{10}$, ultrafine particles, polycyclic aromatic carbons, benzo[a]pyrene, and various heavy metal exhausts on exposure over time have invariably pointed at a predisposition towards carcinomas. Therefore, a need to develop remedial strategies to eliminate these PMs as causal agents is of pivotal importance. Employing the use of various types of filters to sieve out particulate matter is an important stepping stone in eliminating the inhalation and intake of PMs. Filters with varying pore sizes and types such as porous type, fibrous type, and activated carbon nanotube type efficiently absorb the particulate matter from air sources (Sai Charan et al. 2021). Air purifiers and anti-bacterial nanofiber filters such as HEPA are now commonly being used. Furthermore, actively limiting exposure to known carcinogens such as cigarette smoke or industrial emission by inculcating positive lifestyle changes can have a considerable effect on one’s physiological well-being.

![Graphical illustration representing PM-mediated carcinogenic changes in glial cells potentiating glioblastoma onset and progression](image_url)
Conclusion

The past centuries have undoubtedly observed an increase in air pollution which has been regarded as a top priority in the global agenda. An estimate of 4.2 million deaths on an annual basis can be attributed to air pollution. With 55.3% of the world exposed to particulate matter especially noxious and toxic PMs such as PM$_{2.5}$, a significant impact on health can be seen by an increase in a wide array of diseases such as cognitive abnormalities, respiratory disorders, metal poisoning, and various types of carcinomas. Prolonged exposure to these PMs has significantly seen a detrimental effect on cellular pathways such as lncRNA dysregulation as discussed earlier (Krzyzanowski and Cohen 2008). Several known lncRNAs such as MALAT1, MEG3, HOTAIR, and H19 that are known to regulate various hallmarks of cancer such as epithelial-mesenchymal transition, angiogenesis, metastasis, and resistance to cell death are significantly affected by presence of PMs such as PM$_{2.5}$ and ultrafine particles. Dysregulation of these lncRNAs further leads to activation of various oncogenic cellular pathways resulting in onset or progression of various carcinomas, including glioblastomas (Fig. 3).

Glioblastoma multiforme exists as a fatal morbidity with many precursors and causative agents. Extensive in silico approaches over the years have substantiated the array of gene expressions, mutations, and cellular pathways responsible for the progression of this disease in online repositories and databases. These databases such as TCGA, ONCOMINE, GEO, and many others act as efficient search engines and online archives where one can procure filtered search results to study various aspects of specific diseases (Fig. 4). In the case of GBM, data ranging from patient cases such as gender, ethnicity, patient survival rate, GBM subtype, transcriptomic analysis, gene mutations, known precursors, or even comorbidities are available. This displayed array of data increases the ease of screening and obtaining precise information for extensive research and future studies. However, in the case of diseases with multiple precursors such as GBM, individual databases focus primarily on the one cancer type with searches based on key factors such as cellular (lncRNA) or environmental (PMs). This proposed database is a significant way forward in correlating air pollution with disease pathology. In terms of research, it not only narrows down the search for the desired cellular candidate, in this case a particular lncRNA, responsible for a specific function in GBM progression but also correlates and presents the proposed reason of the dysregulation, i.e., specific particulate matters. The current approach of preparing a database can notably be used for niche research studies, specifically focusing on air pollutants and their effect on the cancer transcriptome.
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Author Contribution  SM and UK did the literature search and contributed to the preparation of the main draft of the review manuscript under the supervision of PP; DD assisted in the in silico strategies of the study and helped in conceptualizing the work along with PP.

Availability of Data and Materials  Data was obtained after intense literature review from known database repositories.

Declarations

Ethics Approval  For this review, ethical approval was not required/applicable.

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Competing Interests  The authors declare no competing interests.

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