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Chapter 11

Deregulation of Cell Polarity Proteins in Gliomagenesis

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1. Introduction

Gliomas are the most common central nervous system neoplasms that arise from the transformation of astrocytes or their precursor cells. Glial tumors develop as a result of stepwise accumulation of genetic alterations, which disrupt the cell cycle arrest pathways or activate various signal transduction pathways. Despite recent advances in treatment modalities such as surgical techniques, radiation therapy, chemotherapy and targeted gene therapy, their prognosis remains poor. Gliomas are graded from I to IV according to the 2007 World Health Organization (WHO) malignancy scale. Grade I lesions are benign and quite constrained with a slow propagation rate and they constitute the most common glioma of children, pilocytic astrocytoma. Grade II tumors, called diffuse astrocytoma have a slow growth rate and a high degree of cellular differentiation, with their ability to diffuse into normal brain parenchyma and progress toward more malignant form. Grade III tumors include anaplastic astrocytoma, which are characterized by a higher cellular density and the plentiful persistence of atypia and mitotic cells. Grade IV tumors are the most frequent malignant gliomas and they are characterized as glioblastoma with high recurrence rate. GBMs include two subtypes, primary GBMs arise `*de novo*' and secondary GBMs develop due to accumulation of mutations in lower grade gliomas. EGFR amplification, LoH 10q, $p16^{Ink4A}$ deletion and PTEN mutations are the common genetic alterations associated with primary GBMs whereas p53 mutations and PDGFR amplifications are frequent in secondary GBMs (Ohgaki and Kleihues., 2007; Holland., 2001). These genetic alterations disrupt the cell cycle arrest pathways or activate various signal transduction pathways. Mutation of the p53, retinoblastoma (RB) and PTEN, deletion of $p16^{Ink4A}$, activation of the Ras and Akt pathways, and amplification of CDK4 and EGFR contribute to the development of gliomas (Cavenee., 1992; Hayashi et al., 1997).

Cell polarity is an essential phenomenon in several biological processes that contribute to normal tissue integrity and maturity. Several studies in different genetic models has identified and revealed different roles of polarity complexes in maintenances of stem cell population and their asymmetric division (Knoblich., 2010), T-cell function like migration in response to chemokines and antigens (Krummel and Macara., 2006), neuronal cell axon and dendritic specification (Arimura and Kaibuchi., 2007) and cell polarity is crucial for epithelial cell and tissue polarization for maintenance of multicellular structures and perform normal physiological functions like secretion, absorption and distribution of cytoplasmic and membrane proteins in appropriate positions within the cell in order to conduct proper signals.

2. Cell polarity regulators and their deregulation in cancer

Proficient research work in organisms like *Caenorhabditis elegans* and *Drosophila melanogaster* has led to discovery of three different polarity complexes which are asymmetrically distributed within the cell. They are Partitioning defective (Par) complex consists of Par3, Par6 and an atypical protein kinase C, Crumbs complex consists of Crumbs, Pals1 (Protein associated with Lin seven 1) and Pals1-associated tight junction protein (PATJ) and Scribble complex consists of Scribble, Discs large (Dlg) and Lethal giant larvae (Lgl). Crumbs polarity complex and the Partitioning defective (Par) polarity complex are localized to the apical cortex, whereas members of the Scribble polarity complex are localized at the basolateral regions of the cell (Bilder and Perrimon., 2000; Humbert et al., 2006).

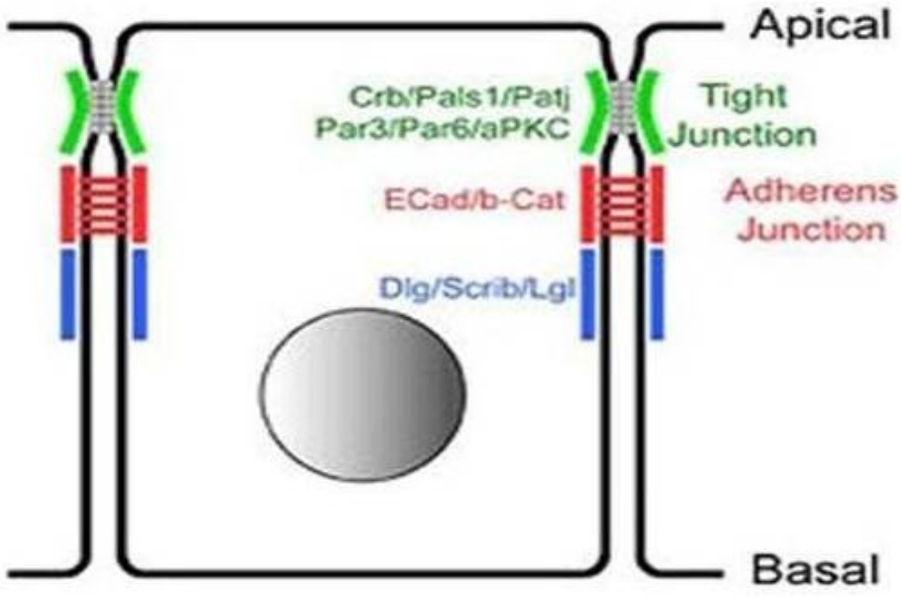

Figure 1. Localization of cell polarity complexes in epithelial cell. Par complex consisting of Par3, Par6, aPKC and Crumbs complex consisting of Crb, Palsl, PAT J are localized apically in the region of tight junctions (T Js). Scribble complex consisting of Scrib, Dlg and Lgl is localized basolaterally in the region of adherens Junction. (this illustrationis reproduced fiom l)Djiane laboratory)

2.1. PAR polarity complex

Par complex was initially identified in *C.elegans* and it consists of two scaffold proteins, PAR6 and PAR3 and an atypical protein kinase C, aPKC. In mammals Par6 protein is encoded by three different genes PAR6A/C, PAR6B and PAR6D/G, Par3 is encoded by *PAR3A* and *PAR3B* genes and two *aPKC* genes, *aPKCλ*/ι and *aPKCζ* encode two different proteins. Par3 and Par6 interact with each other via their PDZ domains and the interaction between Par 3 protein to aPKC/Par6 is dynamic and aPKC-dependent phosphorylation can expel Par3 from the aPKC/Par6 unit (Horikoshi et al., 2009). PAR complex is essential for defining the appropriate apicolateral axis and assembly of tight junction proteins at their respective position.

2.2. Crumb polarity complex

Crumbs polarity complex was identified in *Drosophila* and in mammals it consists of transmembrane protein CRB encoded by *CRB1*, *2*, and *3* genes along with two cytoplasmic scaffolding proteins PALS1 and PATJ. CRB1 connect to PDZ domains of Pals1 and PATJ through C-terminal ERLI motif. Pals1 is a member of the membrane-associated guanylate kinase (MAGUK) family, which has a PDZ domain, two L27 domains, a SH3 domain and a guanylate kinase domain. PATJ has 10 PDZ domains and one L27N domain (Tepass and Knust., 1993). CRB complex is involved in formation of tight junctions and differentiation of the apical membrane.

2.3. SCRIB polarity complex:

Scribble, Dlg and Lgl were identified in Drosophila as tumor suppressors, in mammals SCRIB is also called VARTUL. Scribble is a member of LAP family with leucine-rich repeats and PDZ domains, while Dlg in mammals exists in five isoforms and it is a member of the MAGUK family containing PDZ domains. Lgl which exists as Lgl1 and Lgl2 in mammals does not contain PDZ domains but has WD40 domains, which is thought to mediate interactions with phosphorylated serine and tyrosine (Dow et al. 2007).

Interaction among these three complexes dictates them to localize in their respective positions, for example Lgl1 and 2 can compete with Par3 for binding to a module of Par6 and aPKC and aPKC phosphorylate Lgl releasing it from the Par6/aPKC dimer, ensuing its localization to the basolateral region of cells (Betschinger et al. 2003). These complexes induce their function by regulating cytoskeleton architecture and there is a substantial data showing direct link with small GTPases of the Rho family and Cdc42, Rac1 and RhoA, control the cytoskeletal changes in cells by switching between an active GTP-bound state and an inactive GDP-bound state. For example Par3 can bind the Rac-activator Tiam1 during tight junction formation and Par6/Par3 regulates Cdc42-mediated Rac1 activation through Tiam1 in neuronal cells (Nishimura et al. 2005). These multifaceted interactions between polarity proteins and with small GTPases is essential for maintenance of polarity and carrying out normal physiological functions of the cell and any aberrant regulation in any of these proteins is related to tumor genesis.

Cell polarity proteins regulate cancer cell properties like proliferation, apoptosis, and epithelial-mesenchymal transition. Studies have shown that Par6 induces growth factor independent proliferation of human mammary epithelial cells by activating MAPK signaling through aPKC and Cdc42/Rac (Muthuswamy et al. 2008). aPKC can regulate cell proliferation through ERK and SRC-3 dependent manner (Castoria et al. 2004 and Yi et al. 2008) and knock down of aPKC in MCF-7 breast cancer cell line inhibited cell proliferation. Down regulation of Scribble induces JNK-dependent cell death (Brumby and Richardson. 2003) and in similar manner inhibition of aPKC increases apoptosis of MDCK cell by activating GSK3β (Kim et al., 2007). Acquisition of mesenchymal property by cancer cells during metastasis is due to change in the cell architecture which is regulated by cell polarity proteins. Research in genetic model *Drosophila* led to discovery that Scribble, DLg, Lgl, Par and Cdc42 cooperate with Rasv12 during invasion (Pagliarini and Xu. 2003). TGFβ signaling has been shown to phosphorylate Par6 protein which leads to RhoA degradation through Smurf1 (Wang et al., 2003). ZEB1 which is a transcriptional regulator of EMT represses the expression of polarity proteins like Crumbs, Lgl2 and PATJ ultimately leading to mesenchymal transition (Aigner et al., 2007).

Cancer is a multistep process whereby cells first acquire benign over proliferation due to genetic assaults, followed by inhibition of apoptosis and increased cell proliferation. The conversion of benign to malignant form is accompanied by loss in cell-cell to contact and apical-basal polarity which ultimately leads to EMT associated with invasion into different parts from the site of cancer. During cancer progression steps these different polarity complexes are either aberrantly expressed or mislocalised from their respective locations. Genetic studies in model organisms and *in vitro* cell culture has shown that these polarity complexes append to take apart in diverse hierarchy of human cancer. aPKC is over expressed in various human cancers like non-small cell lung cancer, ovarian cancer and its expression level correlates with over expression of Cyclin E and with their poor prognosis (Regala et al., 2005 and Eder et al., 2005). In human esophageal squamous cell carcinoma Par3 gene is homozygously lost with reduced protein expression (Zen et al., 2009). Par6 is regarded as a tumor promoter as it is over expressed in human breast cancer and its interaction with TGFβ receptor implicates its role in EMT (Ozdamar et al., 2005).

However contribution of Crumb complex for tumor progression is not completely elucidated. Few studies have shown that Crb-3 expression negatively correlates with metastatic behavior of cells as its decreased expression is associated with increased expression of vimentin and reduced expression of E-cadherin (Bhat et al., 1999). Assembly of Crumb complex leads to phosphorylation of transcription effector molecule of Hippo signaling pathway TAZ/YAP which in turn leads to inhibition of TGF-β-SMAD signaling essential for vimentin expression (Varels et al., 2010). ZEB1 and SNAIL represses the Crumb complex activity. PATJ and Pals1 are required for tight junction (TJ) assembly. PATJ is targeted for degradation by human papiloma virus (HPV) oncoprotein during development of cervical cancer (Javier. 2008). Till date there is no evidence for role of Pals1 in cancer, however few studies in mice model have shown that Pals1 is essential for survival since its loss results in embryonic lethality.

Scribble complex, regarded as fly tumor suppressor genes and basolateral polarity complex are regulated at different levels in human cancers. Dlg and Lgl proteins are down regulated

and mislocalised in tumors of breast, prostate, lung, ovary, cervical and liver.scribble and Dlg are targeted for degradation by viral oncoproteins from HPV(Thomas et al., 2005), Human T-cell leukemia (HTLV) (Okajima et al., 2008) and their expression levels are correlated with loss of tissue architecture. Scribble is miss localized in cervical, colon, endometrial and prostate cancer (Nakagawa et al., 2004, Gardiol et al., 2006, Ouyang et al., 2010 and Pearson et al., 2011). In *Drosophila* genetic study, it has been exposed that loss of Scribble function alone is not sufficient to induce tumor, instead Scrib mutant cells expressing oncogenic Raf, Ras or Notch results in loss of apical-basal polarity, neoplastic overgrowth and metastasis.

3. Cell polarity in glial cell

Glial cells include myelinating oligodendrocytes, Schwann cells and astrocytes and they execute diverse functions that are vital for the development, functioning and regeneration of neurons. Unlike epithelial cells which require cell polarity for polarization of cellular components and neurons for axon and dendrite specification, glial cells require cell polarity for migration and myelination.

Oligodendrocytes and Schwann cells are responsible for myelination of neurons, it requires proper sorting of proteins and lipids and polarized membrane trafficking to organize myelin domains and maintain this highly polarized phenotype (DeBruin and Harauz. 2007). Astrocytes are the cells which carry out major functions in brain including interactions with neurons and blood vessels (Schipke and Kettenmann., 2004), migration towards inflammation called astrogliosis (Ridet et al. 1997) which requires polarization of astrocytes into front-rear axis. Astrocytes polarize and migrate by interacting with extra cellular matrix components. Upon interaction of ECM with integrin receptors on astorcytes, activates intracellular signaling through small G proteins like Rac and Cdc42 for controlled polarization and orientation (Heasman and Ridley. 2008). Guanine exchange factors are in charge for the GDP–GTP exchange and therefore are the major regulators of small G proteins activity. It has been shown that cell polarity protein Scrib plays a crucial role in astrocyte migration by binding with Rac and Cdc42-specific exchange factor βPIX and controlling the localization of Cdc42 at leading edge of migratory processes (Osmani et al. 2006). Besides Scrib other evolutionary conserved polarity proteins like Par protein complex is implicated in astrocyte migration. Par6-aPKC complex controls and regulates the microtubule organization during astrocyte migration. The GTP-bound form of Cdc4 binds to Par6 and activates aPKC kinase at leading edge of astrocyte (Etienne-Manneville et al., 2005).

4. Loss of cell polarity during gliomagenesis

Previously loss of cell polarity was regarded as post effect of cancer, but recent research work led to discovery that cell polarity is lost and responsible for tumorigenesis and its progression. Loss of cell polarity in brain tumors is not well documented and very few works like Klezovitch

et al. have show that loss of cell polarity causes severe brain dysplasia using Lgl1 knockout mice. We analyzed total of 50 astrocytic tumor samples from Krishna Institute of Medical Sciences (Hyderabad, India), they were classified histopathologically according to the WHO classification: 16 pilocytic astrocytoma (PILO; grade I), 8 diffuse astrocytomas (DA; grade II), 7 anaplastic astrocytomas (AA; grade III), and 19 glioblastoma multiforme (GBM; grade IV) and one normal brain sample was obtained during autopsy for the expression of Scribble polarity complex in astocytic tumors. All samples were obtained from patients after taking the informed consent form patients or their guardians. Using western blotting and immuno histochemical examination we found that protein levels of Scrib was negatively associated with increase in the tumor grade and in few GBM samples Scrib was completely absent. Immuno fluorescence staining as shown in Fig. 2, 3, 4 revealed that in control brain astrocytes, Scrib was localized at the end of astrocyte processes and it was mislocalised in low grade tumors with complete absence in GBM (Khamushavalli et al., unpublished data).

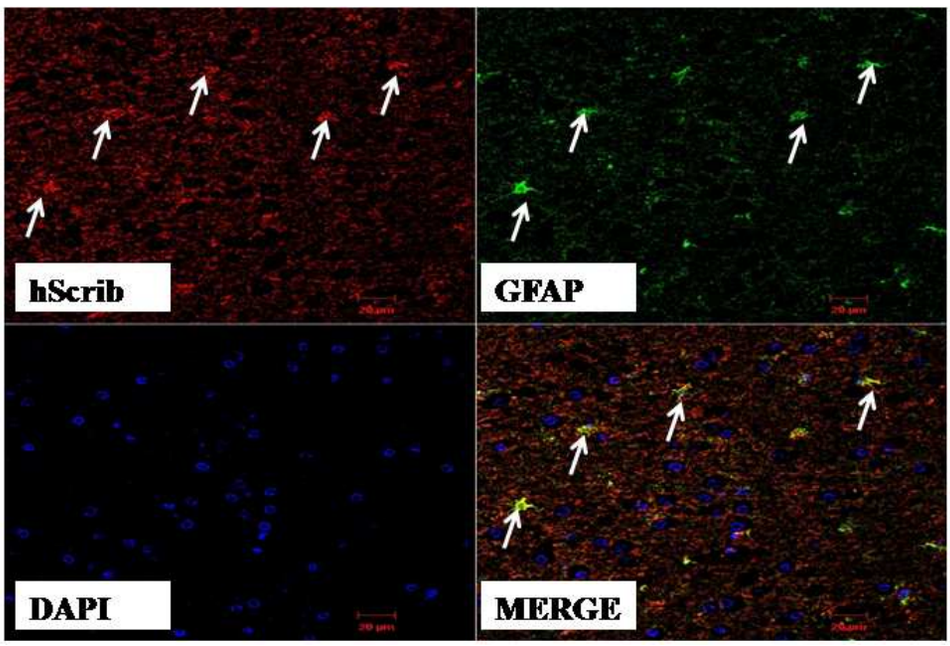

Figure 2. Localization of hSrib in control astrocytes: Paraffin-embedded control brain section was prepared from autopsy brain specimen. Secations were incubated with anti-rabbit-hScrib and anti-mouse-GFAP specific primary antibodies (1:100 dilution) overnight at 4°C and anti-rabbit-TRITC and anti-mouse-FITC secondary antibodies were used for 1 h at room temperature. DAPI was used for the detection of nuclei and fluorescence was captured under Leica confocal microscope. Representative figure showed the localization of hScrib in GFAP positive astrocyte processes.

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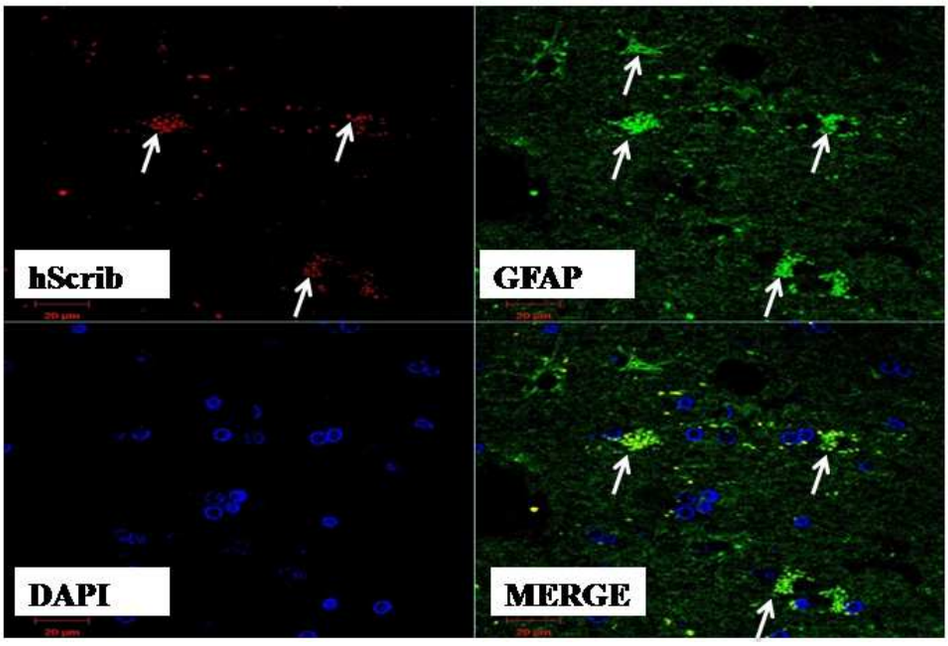

Figure 3. Localization of hScrib in grade II astrocytoma: Paraffin-embedded grade II astrocytoma section was prepared and incubated with anti-rabbit-hScrib and anti-mouseGFAP specific primary antibodies (1:100 delution) overnight at 4°C and anti-rabbit-TRITC and anti-mouse-FITC secondary antibodies were used for 1 h at room temperature. DAPI was used for the detection of nuclei and fluorescence was captured under Leica confocal microscope. Representative figure showed the diffuse localization and low level expression of hScrib in GFAP positive astrocytes.

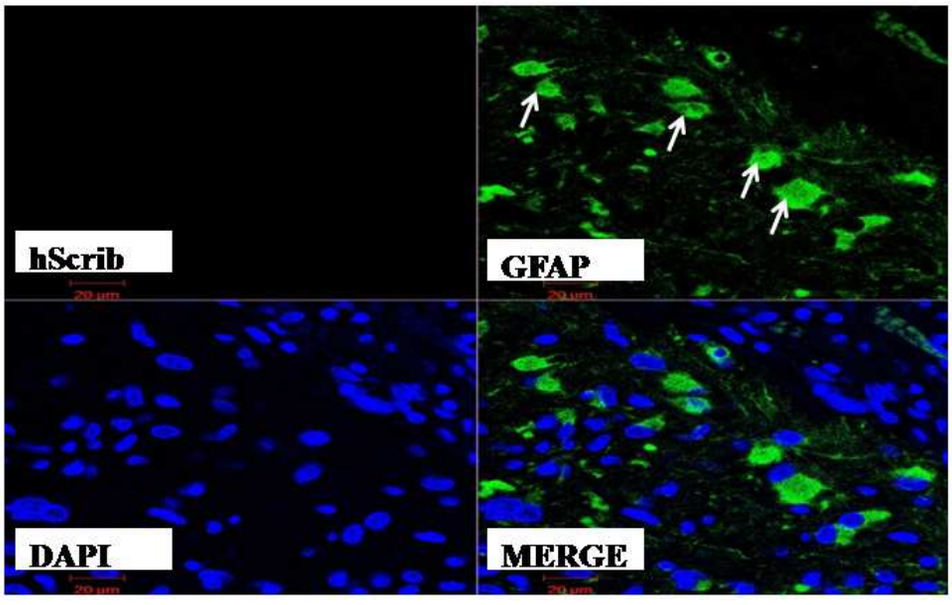

Figure 4. Localization of hScrib in grade IV astrocytoma: Paraffin-embedded grade II astrocytoma section was prepared and incubated with anti-rabbit-hScrib and anti-mouseGFAP specific primary antibodies (1:100 delution) overnight at 4°C and anti-rabbit-TRITC and anti-mouse-FITC secondary antibodies were used for 1 h at room temperature. DAPI was used for the detection of nuclei and fluorescence was captured under Leica confocal microscope. Representative figure showed the loss of hScrib in GFAP positive astrocytes

5. Conclusion

Loss of cell architecture and cell-cell contacts is the hall mark of metastasis, and these process are regulated by cell polarity proteins. Recent work in different cancers has revealed the expressional loss and mislocalisation of cell polarity proteins and their potential role as tumor suppressors. Till date there is no report explaining the role of these polarity proteins in glioma and the above results indicate that cell polarity proteins do have role in glioamgenesis and further research is necessary to elucidate how these proteins are deregulated during glioma prosression.

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