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# New Insight on the Role of Transient Receptor Potential (TRP) Channels in Driven Gliomagenesis Pathways

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## 1. Role of TRP channels in glioma growth and progression

Gliomas are primary brain tumours believed to arise from glial cells or their progenitors. They account for 78% of malignant brain tumours (Shwartzbaum et al., 2006). The vast majority of gliomas is high-grade glioblastoma multiforme (GBM), and is characterized by almost unrestrained growth. Consequently, the median survival of patients with GBM was approximately 12 months (Huncharek & Muscat, 1998). While research has generated abundant information regarding the growth characteristics of these cancers, clinical care remains palliative and the prognosis dismal (Butowski et al., 2006). Gliomagenesis and progression are complex processes only partly understood. At molecular level, tumor progression and the associated heterogeneity is likely the result of multiple mutations in certain key signaling proteins (Furnari et al., 2007). Among these proteins, the Transient Receptor Potential (TRP) channel family has been identified to profoundly affect a variety of physiological and pathological processes (Kiselyov et al., 2007; Nilius et al., 2007). Members of TRP channels control cellular homeostasis by regulating calcium flux, cell proliferation, differentiation and apoptosis; moreover, in the last years an additional role for TRP ion channel family in malignant cancer growth and progression has been recognized (Xu et al., 2001; Wisnoskey et al., 2003; Xin et al., 2005; Bidaux et al., 2007; Prevarskaya et al., 2007; Gkika & Prevarskaya, 2009). Approximately thirty TRPs have been identified to date, and are classified in seven different families: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPML (Mucolipin), TRPP (Polycystin), and TRPA (Ankyrin transmembrane protein) and TRPN (NomPC-like) (Montell, 2003) (Fig.1).

The expression levels and activity of members of the TRPC, TRPM, and TRPV families have been correlated with malignant growth and progression (Duncan et al., 1998; Tsavaler et al., 2001; Wissenbach et al., 2001; Thebault et al., 2006; Amantini et al., 2007; Caprodossi et al., 2008; Nabissi et al., 2010). TRP channels may regulate glioma growth and progression at different levels by controlling cell proliferation, inhibiting apoptosis, stimulating angiogenesis and triggering the migration and the invasion during tumor progression (Table 1).

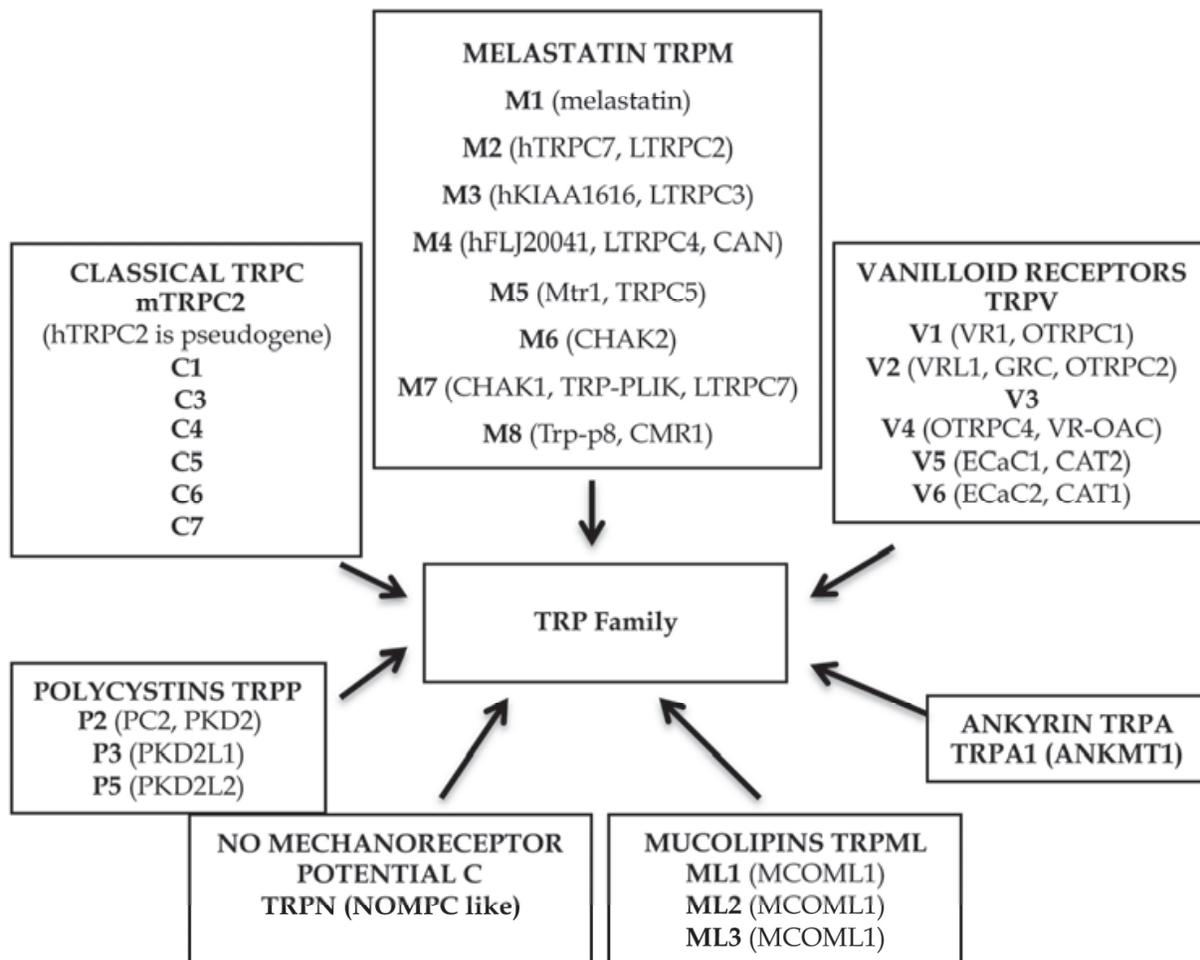


Fig. 1. TRP superfamily. TRP subgroups are represented in square, the members are indicated for each subfamily.

## 2. Role of TRPC and TRPV channels in cell cycle arrest and cytokinesis in malignant glioma

Growth control of cancer cell populations has been studied extensively over the past decades and research has identified a multitude of transmembrane TRP channels involved in this process (Schönherr, 2005; Santoni et al., 2011) (Fig.2). While our understanding of their exact role in the physiology of cell proliferation remains tentative, many TRP channel agonists or antagonists also stimulate or retard cell population growth, which support the notion that TRP channels are intrinsic component of the cell cycle. In particular, calcium  $Ca^{2+}$  signaling plays an important role in normal and aberrant cell proliferation, and some members of the  $Ca^{2+}$ -permeable TRPC family have demonstrated a role in the proliferation of many types of cancer cells (Malarkey et al., 2008). Using a combination of molecular, biochemical and biophysical approaches, it was demonstrated the expression of five TRPC channel proteins (TRPC1, TRPC3, TRPC4, TRPC5 and TRPC6) in patient biopsies and cell lines derived from glioma patients (Tables 1). Activation of TRPC channels typically occurs through the triggering of phospholipase C and this signaling cascade is the target of a number of G-protein-coupled receptors and receptor tyrosine kinases. An important form of

TRP channel	Function/s	References
TRPC1	Chemotaxis in response to EGF stimulation Calcium signaling during cytokinesis (Multinucleated-giant cells), stimulates proliferation Up-regulates hypoxia-induced VEGF expression Histamine-induced Ca(2+) entry	Sontheimer, 2010  Bomben & Sontheimer, 2018 Bomben & Sontheimer, 2010  Wang et al., 2009  Barajas et al., 2008
TRPC3	Ca(2+) influx, PAR-1-mediated astrocytic activation [Ca(2+)] <sub>i</sub> signaling	Nakao et al., 2008  Grimaldi et al., 2003
TRPC4	Histamine-induced Ca(2+) entry	Barajas et al., 2008
TRPC6	Increase intracellular Ca(2+) induced by PDGF, stimulates G2/M phase transition and clonogenic ability; increases tumor volume in a subcutaneous mouse model of xenografted human tumors and decreases mean survival in mice in an intracranial model Increases [Ca(2+)] <sub>i</sub> elevation coupled to NFAT activation; stimulates hypoxia-induced Notch1-driven growth, invasion and angiogenesis	Ding et al., 2010       Chigurupati et al., 2010
TRPV1	Ca(2+) influx, p38MAPK-dependent apoptosis	Amantini et al., 2007
TRPV2	Inhibition of cell survival and proliferation, increase sensitivity to Fas-induced apoptosis in an ERK-dependent manner	Nabissi et al., 2010
TRPM2	ROS-induced cell death	Ishii et al., 2007
TRPM8	Increases intracellular Ca(2+), BK channel activity, cell migration	Wundergem et al., 2008 Wundergem & Bartley, 2009

Table 1. Expression and function of TRP channels in human gliomas

TRPC activation has been shown downstream of the epidermal growth factor receptor (EGFR) (Odell et al., 2005) that is the major growth factor receptor activated in malignant gliomas. Indeed, mutated or amplified EGFR is often observed in malignant gliomas and has been associated with the increased cell proliferation seen in them (Bryant et al., 2004). In Cos-7 cells, EGFR activation causes phosphorylation of TRPC4 and results in channel insertion into the plasma membrane (Odell et al., 2005). Additionally, knockdown of TRPC4 in human corneal epithelial cells suppresses epidermal growth factor (EGF)-induced cell proliferation, again linking proliferation to TRPC channels (Yang et al., 2005). Among TRPC channels, TRPC6 and TRPC1 seem to play a major role in the control of cell cycle and glioma

cell proliferation. Functional TRPC6 channels were overexpressed in human U251, U87, and T98G glioma cell lines. Moreover, increased TRPC6 expression was found in GBM biopsies compared with normal brain tissue, suggesting a role for TRPC6 in malignant growth of gliomas *in vitro* and *in vivo* (Ding et al., 2010). TRPC6 channels have been implicated in cell proliferation and hypertrophic gene expression through the activation of the calcineurin-nuclear factor of activated T-cell (NFAT) pathway in normal (K. Kuwahara et al., 2006; Onohara et al., 2006) and malignant cells (Bomben & Sontheimer, 2008). Because glioma cells lack the expression of voltage-gated calcium channels (Kunzelmann, 2005) and Ca(2+) signaling promotes G<sub>1</sub>/S phase transition and cell cycle progression in a variety of cell types (Lipskaia & Lopré, 2004; M. Kuwahara et al., 2006), the TRPC6-mediated sustained elevation of [Ca(2+)]<sub>i</sub> and calcineurin-NFAT pathway activation is vital for the proliferation and malignant growth of gliomas under hypoxia. Consistently, inhibition of hypoxia-induced TRPC6 expression causes a dramatic decrease in NFAT activation (Buchholz & Ellenrieder, 2007). In glioma cells, inhibition of TRPC6 activity or expression by using a dominant-negative mutant TRPC6 (DNC6) or RNA interference, respectively, attenuated the increase in intracellular Ca(2+) induced by platelet-derived growth factor (PDGF), suppressed cell growth and clonogenic ability, induced cell cycle arrest at the G<sub>2</sub>/M phase, and enhanced the antiproliferative effect of ionizing radiation. Cyclin-dependent kinase 1 (Cdk1) activation and cell division cycle 25 homolog C (Cdc25) expression regulated the DNC6-induced cell cycle arrest. Inhibition of TRPC6 activity also significantly reduced tumor volume in a subcutaneous mouse model of xenografted human tumors and increased mean survival in mice in an intracranial model (Ding et al., 2010). In addition to TRPC6 a role for TRPC3 in glioma cell proliferation has been suggested. The TRPC3 channel has been found to cause intracytoplasmic calcium oscillations in rat glial cells (Grimaldi et al., 2003). In rat cortical astrocytes, thrombin via Ca(2+) signal, induces TRPC3 upregulation and enhanced proliferation, and these effects were inhibited by TRPC3 blockers and siTRPC3 RNA (Shirakawa et al., 2010). Ca(2+) mobilization mediated by TRPC3 is associated with thrombin-induced morphological changes in human astrocytoma cells (Nakao et al., 2008). Glioblastoma multiforme proliferates extensively and cells often undergo incomplete cell divisions, resulting in multinucleated cells. Cytokinesis, which begins at the onset of anaphase, is the division of remaining cytoplasmic substances in the cell, aside from the nuclear events of mitosis (Glotzer, 2005; Eggert et al., 2006). Recent evidence (Bomben & Sontheimer, 2010) indicated that the functional loss of TRPC1 channels involved in agonist-induced calcium entry and reloading of intracellular Ca(2+) stores disrupts glioma cytokinesis leading to bizarre and greatly enlarged multinucleated glioma cells (GMGCs) showing slow growth (Palma et al., 1989). Pharmacological inhibition of TRPC1 expression using the continuous administration for up to 4 days of the chronic inhibitor of TRPC channels, SKF96365, or TRPC1 suppression using a doxycycline inducible shRNA knockdown approach, causes loss of functional channels and store-operated calcium entry in glioma cells, and a significant decrease of tumor size, respectively. This effect is associated with reduced cell proliferation and, frequently, with incomplete cell division due to arrest at the G<sub>2</sub>/M phase of the cell cycle (Stark & Taylor, 2006). Cytokinesis is typically described with two key components being the central spindle and the contractile ring. RhoA guanosine triphosphatase GTPase is one key player in contractile ring formation, which is important for actin nucleation and myosin activation (Bement et al., 2006). Recently reports

have indicated an association between TRPC1 and RhoA (Mehta et al., 2003) and independently of TRPC6 and RhoA in certain cell types (Singh et al., 2007). Finally, receptors belonging to the TRPV channel family have been found to inhibit *in vitro* glioma cell proliferation. In this regard, we have recently reported that TRPV2 mRNA was expressed in benign astrocyte tissues, and its expression progressively declined in high-grade glioma tissues as histological grade increased. TRPV2 negatively controls glioblastoma survival and proliferation. In U87 glioma cells, silencing of TRPV2 by RNA interference (siRNA) affects several genes controlling cell cycle and proliferation (Nabissi et al., 2010). Down-regulation of CD95/Fas and parallel up-regulation of CCNE1, CDK2, E2F1, Raf-1 gene expression was observed in siTRPV2-U87 glioma cells as respect to controls. Moreover, TRPV2 knock-out increased glioblastoma proliferation and survival in an ERK-dependent manner. Inhibition of ERK activation by treatment of siRNA-TRPV2 U87 glioma cells with the specific MEK-1 inhibitor PD98059, promoted Fas expression and restored Akt/PKB pathway activation leading to reduced cell survival and proliferation (Nabissi et al., 2010). Conversely, TRPV2 transfection of primary MZC glioblastoma cells also reduced glioma viability and proliferation (Nabissi et al., 2010).

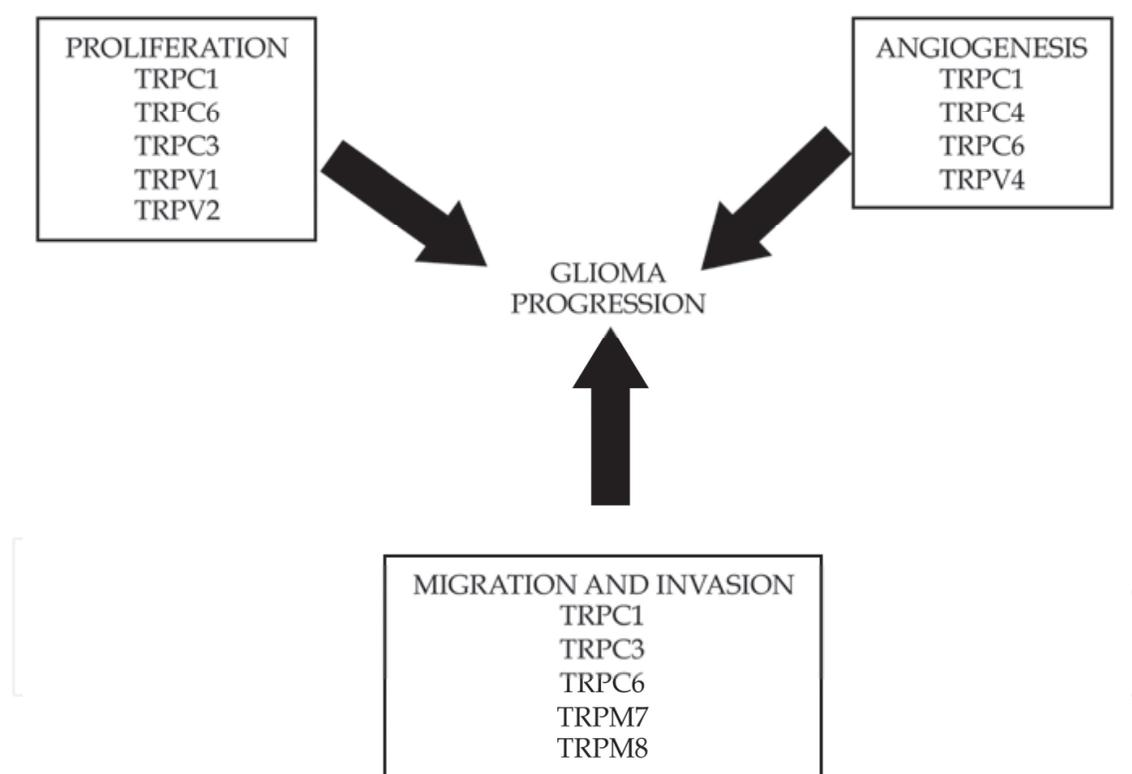


Fig. 2. TRP and glioma progression. In each square are represented the members of the TRP family, that are involved in the main processes driving glioma progression.

### 3. Role of TRPC and TRPV channels in hypoxia-induced angiogenesis of human gliomas: Role for VEGF and angiopoietin-1

Tumor microvessels are highly tortuous with sluggish flow and diminished gradient for oxygen delivery and increased susceptibility to thrombosis and microhemorrhages. The

GBM microvasculature provides little support in oxygen/nutrient delivery, paradoxically contributing to exacerbate a metabolic mismatch between supply and demand leading to progressive hypoxia and eventually necrosis. In addition with the poor vascular architecture, endothelial cells associated with tumor vasculature fail to form tight junctions and have few associated pericytes or astrocytic foot processes leaving the integrity of the brain blood barrier compromised. This process requires that endothelial cells respond to a variety of extracellular signals that activate receptors responsible for growth and differentiation. VEGF (Vascular Endothelial Growth Factor), and Angiopoietin are key molecules in the promotion of angiogenesis via activation of the VEGFR (VEGF Receptor), and Tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (TIE) expressed on vascular endothelial cells (Lutsenko et al., 2003). The  $\text{Ca}^{2+}$  is another important second messenger and its entry through plasma membrane affects the angiogenesis. VEGF causes an increase in intracellular  $\text{Ca}^{2+}$  concentration in cultured endothelial cells (Criscuolo et al., 1989) through both intracellular  $\text{Ca}^{2+}$  release and extracellular  $\text{Ca}^{2+}$  entry (Brock et al., 1991; Faehling et al., 2001; Wu et al., 1999; Cheng et al., 2006) and up-regulates vascular permeability (Criscuolo et al., 1988). Many of its physiological functions are dependent on  $\text{Ca}^{2+}$  influx (Kawasaki et al., 2000; Faehling et al., 2002) through a store-independent mechanism (Pocock et al., 2000). Vascular permeability has been shown to be dependent on calcium influx, possibly through a TRPC-mediated channels. In particular, recent data indicate that TRPC6 represent an obligatory component of cation channels required for the VEGF-mediated increase in cytosolic calcium and subsequent downstream signaling that leads to processes associated with angiogenesis. The TRPC6 channel can be activated by VEGF. Overexpression of a dominant negative TRPC6 construct in human microvascular endothelial cells (HMVECs) inhibited the VEGF-mediated increase in cytosolic calcium, migration, sprouting, and proliferation. In contrast, overexpression of a wild-type TRPC6 construct increased the proliferation and migration of HMVECs (Hamdollah Zadeh et al., 2008). Inhibition of TRPC6 in HUVECs by pharmacological or genetic approaches arrested HUVECs at G2/M phase and suppressed VEGF-induced HUVEC proliferation and tube formation. Furthermore, inhibition of TRPC6 abolished VEGF-, but not FGF-induced angiogenesis in the chick embryo chorioallantoic membrane (Ge et al., 2009). Reduced oxygen availability (hypoxia) in the surrounding brain tissue is a major driving force behind GBM angiogenesis, and the low oxygen environment in the brain is positively related to GBM aggressiveness and poor prognosis (Hockel & Vaupel, 2001). The role of Hif-1 $\alpha$  in tumor growth and invasion is well established (Semenza, 2003). Hif-1 $\alpha$  protein was undetectable or low in glioma cells under normoxic conditions but increased markedly under hypoxia. Similarly, Notch1 activity was low in glioma cells but was elevated after the hypoxic switch. In addition to Notch1, other components of the Notch pathway were increased in glioma cells after the hypoxic switch. Specifically, the levels of Jagged-1 protein were increased under hypoxia. The molecular signals that link tissue hypoxia, Hif-1 $\alpha$  activation to tumor angiogenesis are poorly understood. In glioma cells, the expression of TRPC6 is low or undetectable. Hypoxia by inducing Notch1 activation, increases TRPC6 expression in primary GBM and cell lines derived from GBM. Knockdown of TRPC6 expression inhibits glioma angiogenesis. Moreover, pharmacologic inhibition of Notch blocked the hypoxia-induced upregulation of TRPC6. The induction of TRPC6 expression in gliomas was TRPC subtype specific because other members of TRPC subfamily were unaffected. Although

Notch signaling is critical for TRPC6 upregulation, it remains to be determined whether the Notch pathway directly or indirectly, through cross-talk with other transcription factors (Gustafsson et al., 2005; Song et al., 2008), regulates TRPC6 transcription. TRPC6 activity is increased with EGFR activation (Odell et al., 2005), suggesting a link between growth factor response to tumor growth, and angiogenesis. Functionally, TRPC6 causes a sustained elevation of intracellular calcium that is coupled to the activation of the calcineurin-nuclear factor of activated T-cell (NFAT) pathway. Pharmacologic inhibition of the calcineurin-NFAT pathway substantially reduces hypoxia-induced glioma progression (Mosieniak et al., 1998; Chigurupati et al., 2010). The activation of TRPC6 by Galphaq induces RhoA activation and increased  $[Ca^{2+}]_i$  that stimulate thrombin-induced increase of actinomyosin-mediated endothelial cell contraction, cell shape change and consequently increased endothelial permeability. Inhibitor of Galphaq or phospholipase C and the  $Ca^{2+}$  chelator, BAPTA-AM, abrogated thrombin-induced RhoA activation. By contrast, activation of TRPC6 by oleoyl-2-acetyl-sn-glycerol (OAG), the membrane permeable analogue of the Galphaq-phospholipase C product, diacylglycerol, induced RhoA activity. Receptor-operated  $Ca^{2+}$  activation was mediated by TRPC6. Thus, TRPC6 knockdown significantly reduced  $Ca^{2+}$  entry and prevented RhoA activation, myosin light chain phosphorylation, and actin stress fiber formation as well as inter-endothelial junctional gap formation in response to either OAG or thrombin (Singh et al., 2007). Lysophosphatidylcholine (lysoPC) has been also found to induce a rapid translocation of TRPC6 in endothelial cells, that triggeres calcium influx resulting in externalization of TRPC5. Activation of this novel TRPC6-TRPC5 channel cascade by lysoPC, inhibits endothelial cell migration. TRPC5 siRNA down-regulates the lysoPC-induced rise in  $[Ca^{2+}]_i$  and reverts the inhibition of EC migration (Chaudhuri et al., 2008), suggesting a negative role played by this channel in the regulation of EC migration. Finally, the phosphatase and tensin homologue (PTEN), has been found to serves as a scaffold for TRPC6 channel by enabling cell surface expression of the channel.  $Ca^{2+}$  entry through TRPC6 induces an increase in endothelial permeability and directly promotes angiogenesis (Kini et al., 2010) (Fig 3). PTEN is a dual lipid-protein phosphatase that catalyzes the conversion of phosphoinositol 3,4,5-triphosphate to phosphoinositol 4,5-bisphosphate and thereby inhibits PI3K-Akt-dependent cell proliferation, migration, and tumor vascularization. Recently, a PTEN phosphatase-independent mechanism in regulating  $Ca^{2+}$  entry through TRPC6 has been reported. PTEN tail-domain residues 394-403 permit PTEN to associate with TRPC6, and thrombin promotes this association. Deletion of PTEN residues 394-403 prevents TRPC6 cell surface expression and  $Ca^{2+}$  entry (Kini et al., 2010). Other TRPC channels have been found to be involved in glioma angiogenesis. Studies in zebrafish, have demonstrated that the involvement of TRPCs channels in angiogenesis represents a reminiscent of the role of TRPC channels in axon guidance (Yu et al., 2010). Activation of TRPC1 seems to be essential for the angiogenesis *in vivo*. Knockdown of TRPC1 by antisense oligonucleotides severely disrupted angiogenic sprouting of intersegmental vessels (ISVs). *In vivo* time-lapse imaging revealed that the angiogenic defect was attributable to impairment of filopodia extension, migration, and proliferation of ISV tip cells. TRPC1 acts synergistically with VEGFA in controlling ISV growth, and appeared to be downstream to VEGFA in controlling angiogenesis (Yu et al., 2010). Recently a role for TRPC1 in hypoxia-induced VEGF expression in U87 glioma cells has been reported. TRPC1 siRNA markedly inhibits hypoxia-induced up-regulation of

VEGF mRNA and protein levels (Wang et al., 2009). TRPC1-dependent  $\text{Ca}^{2+}$  influx induced by VEGF also increases endothelial permeability. Angiopoietin-1 (Ang1) that exerts a vascular endothelial barrier protective effect by blocking the action of permeability-increasing mediators such as VEGF, inhibited the VEGF-induced  $\text{Ca}^{2+}$  influx and increased the endothelial permeability in a concentration-dependent manner. Ang1 interfered with downstream IP3-dependent plasmalemmal  $\text{Ca}^{2+}$  entry. Anti-TRPC1 antibody (Ab) inhibited the VEGF-induced  $\text{Ca}^{2+}$  entry and the increased endothelial permeability. TRPC1 overexpression in endothelial cells augmented the VEGF-induced  $\text{Ca}^{2+}$  entry, and application of Ang1 opposed this effect. Consistent with the coupling hypothesis of  $\text{Ca}^{2+}$  entry, Ang1 by inhibiting the association of IP3 receptor (IP3R) and TRPC1, abrogates the increase in endothelial permeability (Jho et al., 2005). Although the previously reported study has been focused on Ang1 regulation of TRPC1 activation, we cannot rule out the involvement of other relevant TRPC channels. TRPC4 acts as a functional homologue in mouse endothelia to TRPC1 in humans (Nilius et al., 2003; Tiruppathi et al., 2002). For agonist-induced  $\text{Ca}^{2+}$  entry in mouse aortic endothelial cells, TRPC4 was essential as either a channel-forming subunit or a constituent required for channel activation (Freichel et al., 2001). Because TRPC1 and TRPC4 can oligomerize (Hofmann et al., 2002), it is possible that both may be needed for the VEGF-induced  $\text{Ca}^{2+}$  entry. The importance of TRPC4 in regulation of endothelial permeability in mice has been reinforced by the observations that the effects of Ang1 on VEGF-induced  $\text{Ca}^{2+}$  entry and permeability were mimicked by deletion of the TRPC4 gene in mice (Tiruppathi et al., 2002). Finally, VEGF-induced activation of  $\text{Ca}^{2+}$  entry can also occur via TRPC6 which is activated by PLC-generated DAG (Pocock et al., 2001, 2004). TRPC4 has been also found to control thrombospondin-1 (TSP-1) secretion and angiogenesis in renal cell carcinoma (RCC) (Veliceasa et al., 2007). TRPC4 loss has been lead to impaired  $\text{Ca}^{2+}$  intake, misfolding, retrograde transport and diminished secretion of antiangiogenic TSP-1, thus enabling angiogenic switch during RCC progression. TRPC4 has been recently reported to be expressed in glioma cells (Wang et al., 2009), however at present no data on the role of this channel in the inhibition of glioma angiogenesis has been provided so far. Membrane-stretch activated TRPV calcium channels have been known to mediate the orientation of endothelial cells lining blood vessels thus influencing the angiogenesis. So, TRPV4 channels expressed in the plasma membrane of capillary endothelial cells is required for mechanical-induced changes in focal adhesion assembly, cell orientation and directional migration. Recent reports indicate that activation of the mechanosensitive TRPV4 in capillary endothelial cells, stimulates phosphatidylinositol 3-kinase-dependent activation and binding of additional  $\beta 1$  integrin receptors, which promotes cytoskeletal remodeling and cell reorientation. Inhibition of integrin activation using blocking Abs and knock-down of TRPV4 using siRNA, suppress capillary cell reorientation. Activation of TRPV4 channels by force transfer from integrins and CD98 may enable compartmentalization of calcium signaling within focal adhesions. This early-immediate calcium signaling response required the distal region of the  $\beta 1$  integrin cytoplasmic tail that contains a binding site for the integrin-associated transmembrane CD98 protein, and application of external force to CD98 within focal adhesions activated the same ultra-rapid calcium signaling response (Matthews et al., 2010). Thus, mechanical forces that physically deform extracellular matrix (ECM) guide capillary cell reorientation through an "integrin-to-integrin" signaling mechanism mediated by activation of mechanically gated TRPV4 channels on the cell surface (Thodeti et al., 2009). We have recently reported the expression of TRPV4 channels in glioma cell lines (Santoni et al., 2011), however the potential role of TRPV4 in the migration of endothelial cells during glioma angiogenesis is at present unknown.

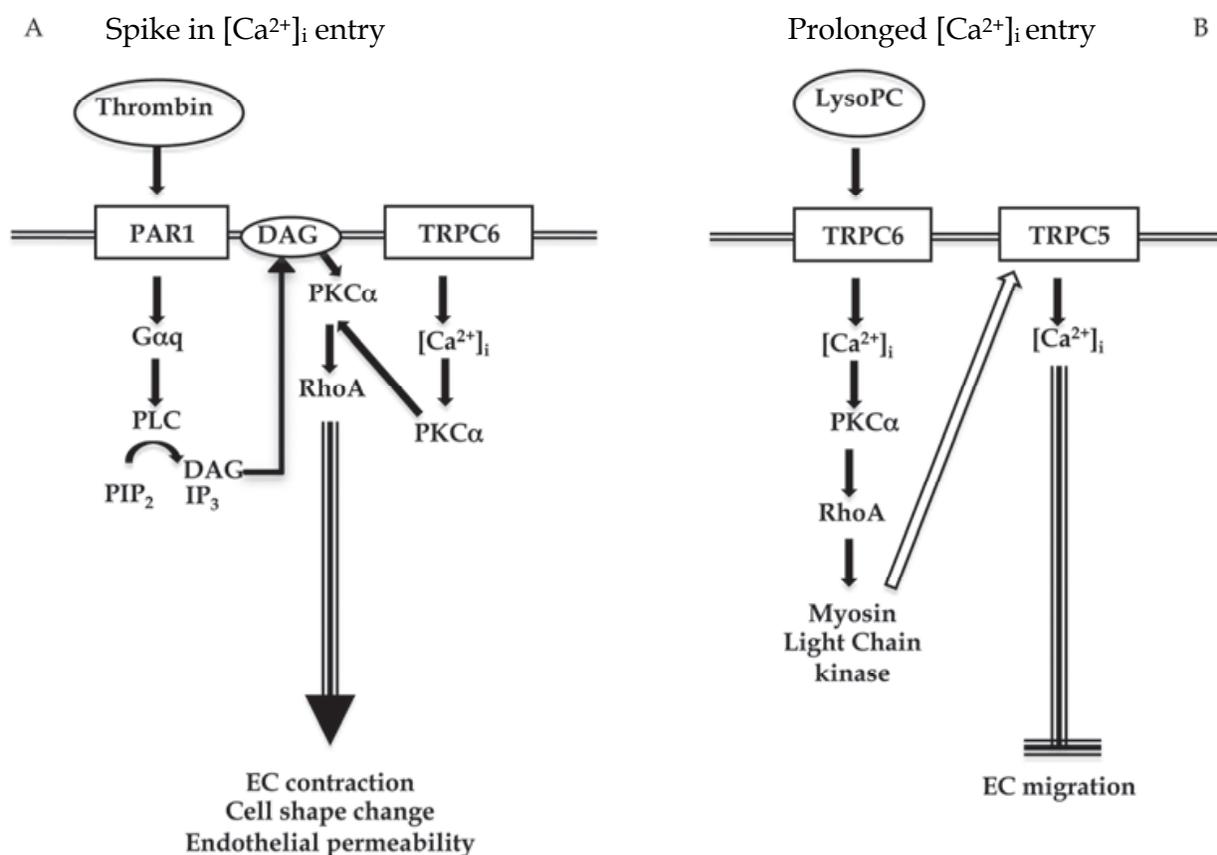


Fig. 3. Different modes of TRPC6 activation and cellular response, in glioma cells A) Spike in  $[Ca^{2+}]_i$  entry induces endothelial cell (EC) contraction, cell shape and permeability; B) while prolonged  $[Ca^{2+}]_i$  entry by LysoPC-induced TRPC6 activation inhibits EC migration.

#### 4. TRPC and TRPM channels stimulate glioma cell migration and invasion

Glioblastoma multiforme is extremely invasive and consequently the clinical prognosis for patients is dismal. Invasion by glioma cells into regions of normal brain is driven by a multifactorial process involving cell interactions with ECM and with adjacent cells, as well as accompanying biochemical processes supportive of proteolytic degradation of ECM, and active cell movements (Bomben et al., 2010). These processes bear a striking resemblance to the robust inherent migration potential of glial cells during embryogenesis. Invasion and migration of glial tumors differ from other tumors where local spread is very limited and dissemination occurs hematogenously or via the lymphatic system. As they spread and form metastasis, glioma cells migrate through the narrow extracellular brain spaces often following the path of nerve fiber or blood vessels. Invading glioma cells commonly assume an elongated spindle-shaped morphology, suggesting that the cells have shrunk to fit into the narrow space into the brain (Sontheimer, 2008). Several studies have focused on the understanding of different molecular mechanisms expressed by invading tumor cells. Gliomas utilize a number of proteins and pathways to infiltrate the brain parenchyma including ion channels and calcium signaling pathways. Ion channels have recently involved in glioma invasion as a means to control cell volume or regulating  $Ca^{2+}$  signaling pathways in invasive cells. Calcium signaling has been shown to play important roles in glioma cell invasion (Komuro & Kumada, 2005). Cell shrinkage by adaptation of cell size

and volume to fit into narrow spaces is a prerequisite for cell movement and migration. Most immature cells that can migrate are well equipped to accumulate and release intracellular ions to shrink. How cell movement and invasion are coupled to the controlled activation of  $\text{Ca}(2+)$  channels is only partially understood (Mcferrin & Sontheimer, 2006). In glioma cells, invasion appears to involve a coordinated reduction in cell volume, which is mediated by the efflux of  $\text{Cl}^-$  and  $\text{K}^+$  through ion channels. The  $\text{Cl}^-$  efflux is accompanied by the movement of  $\text{K}^+$  ions. The principal pathway for  $\text{K}^+$  efflux from glioma cells appears to be via  $\text{Ca}(2+)$ -activated bradykinin (BK) channels, which have the unique ability to couple changes in intracellular  $\text{Ca}(2+)$  to changes in membrane  $\text{K}^+$  conductance and are expressed highly in glioma cells (Ransom & Sontheimer, 2001). In glioma cells, migration is accompanied by oscillatory changes in intracellular  $\text{Ca}(2+)$  in response to different stimuli (Grimaldi et al., 2003), which activate BK  $\text{K}^+$  channels, and the velocity of cell migration of glioma cells correlates with oscillatory changes in intracellular  $\text{Ca}(2+)$  concentration (Bordey et al., 2000). Among ion channels contributing to  $\text{Ca}(2+)$  signaling, cytoskeleton changes, movement and migration, the TRPM and TRPC channel families seem to play an important role. Thus, triggering of TRPM8 by the specific agonist, menthol (Wondergem & Bartley, 2009), as TRPC3 and TRPC6 (Kim et al., 2009) increases glioma cell  $[\text{Ca}(2+)]_i$  that in turn activates BK channels. Thus, TRP-mediated activation of  $\text{Ca}(2+)$  influx appears to be the prerequisite for cell migration and this  $\text{Ca}(2+)$  signal is instructive with regards to cell volume changes that occur down-stream. Cell shape, adhesion and migration have been regulated by actomyosin contractility. TRPM7-like transcripts current has been identified in rat microglia (Jiang et al., 2003). TRPM7 plays a role in linking receptor-mediated signals to actomyosin remodelling and cell adhesion. Activation of TRPM7 by BK, leads to a  $\text{Ca}(2+)$  and kinase-dependent interaction with the actomyosin cytoskeleton. Overexpression of TRPM7, by increasing the intracellular  $\text{Ca}(2+)$  levels resulted in cell spreading, adhesion and formation of focal adhesions (Clark et al., 2006). The effects of TRPM7 on cell morphology is directly dependent on integrin activation or is associated to increase in cytosolic  $\text{Ca}(2+)$  concentrations that affect the actomyosin cytoskeleton. The integrin activation can lead to the remodeling of the actomyosin cytoskeleton that promotes cell spreading via outside-in signaling pathways. Alternatively,  $\text{Ca}(2+)$  is an important second messenger in actin remodeling including polymerization, severing of filaments and F-actin-membrane interactions. The TRPC channels play a role in store-operated calcium entry (SOCE), and in particular TRPC1 is involved in SOCE in glioma cells (Bomben & Sontheimer, 2010). TRPC1-dependent migration and chemotaxis have been reported in different cell types such as myoblasts (Louis et al., 2008), renal epithelial (Fabian et al., 2008) and nervous cells (Wang & Poo, 2005) (Fig.2). Recently, (Bomben & Sontheimer, 2010) showed that TRPC1 channel association with lipid rafts is essential for glioma chemotaxis in response to stimuli, such as EGF, but not chemokinesis. EGF stimulation affects both TRPC trafficking (Bezzarides et al., 2004) and activation (Beech, 2005; Liu et al., 2009), and TRPC1 channel localization to the leading edge of migrating glioma cells. TRPC1 channels co-localize with the lipid raft proteins, caveolin-1. Chemotaxis toward EGF was lost when TRPC channels were pharmacologically inhibited or by shRNA knock-down of TRPC1 channels, yet without affecting unstimulated cell motility. Lipid raft integrity was required for gliomas chemotaxis; thus disruption of lipid rafts not only impaired chemotaxis but also impaired TRPC currents and decreased store-operated calcium entry. TRPC6 is markedly up-regulated under hypoxia in a manner dependent on Notch activation. The Notch-regulated transcriptional targets that are responsible for the development of the aggressive and

malignant phenotypes in GBM remain poorly characterized. Notch signaling mediates hypoxia-induced tumor migration and invasion under hypoxic environment (Sahlgren et al., 2008). TRPC6 has been found to markedly inhibited glioma cell migration and invasion in response to hypoxia by regulating actin cytoskeleton assembling and disassembling which control cell shape, allowing the cell to move along the surface. The last step of invasion requires cytoskeletal rearrangements and formation of lamellipodia and filopodia for which the family of Rho GTPases plays an important role. Most Rho proteins, cycle between GTP-bound active and GDP-bound inactive state. From the family members, Rho stimulates formation of stress fibres and focal adhesion, Rac is required for the formation of lamellipodia and Cdc42 regulates cell polarity and filopodia formation (Teodorczyk & Martin-Villalba, 2009). A role for TRPC6 in Rho activation and actin cytoskeleton rearrangements has been suggested (Albert & Large, 2003). The TRPC6-mediated  $\text{Ca}^{2+}$  entry may contribute to invasion by promoting actin-myosin interactions and the formation and disassembly of cell-substratum adhesions that are important for glioma migration (Kim & Saffen, 2005). Moreover, a role for TRPC3 activation has been also proposed. Thus,  $\text{Ca}^{2+}$  entry in type I astrocytes and rat C6 glioma cells induced by OAG was  $\text{InsP}_3$ -independent and inhibited by a TRPC3 antisense (Grimaldi et al., 2003). In addition, TRPC3 is functionally involved in  $\text{Ca}^{2+}$  entry and thrombin stimulated morphological changes (cell rounding) induced by PAR-1 activation in 1321N1 human astrocytoma cells (Nakao et al., 2008). Finally, GBM cells express TRPM8 mRNA and protein, and its involvement in menthol and hepatocyte growth factor/scatter factor (HGF/SF) increase of  $[\text{Ca}^{2+}]_i$  and glioma cell migration has been reported (Wondergem et al., 2008). Menthol a TRPM8 agonist, stimulated influx of  $\text{Ca}^{2+}$ , membrane current, and migration of human glioblastoma DBTRG cells. The effects on  $\text{Ca}^{2+}$  and migration were enhanced by pre-treatment with HGF/SF. The effects on  $\text{Ca}^{2+}$  also were greater in migrating cells compared with non-migrating cells. 2-Aminoethoxydiphenyl borate inhibited all menthol stimulations. In addition, menthol, by increasing  $[\text{Ca}^{2+}]_i$  in human glioblastoma cells, resulted in activation of the large-conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  membrane ion channels (BK channels). Kinetic analysis showed that menthol increased channel open probability and mean open frequency after 5 min, and this increase was abolished either by added paxilline, tetraethylammonium ion or by  $\text{Ca}^{2+}$ -free external solution. In addition, inhibition of BK channels by paxillin reverses menthol-stimulated increase of  $[\text{Ca}^{2+}]_i$  and cell migration. Finally, menthol stimulated the rate of DBTRG cell migration into scratch wounds made in confluent cells, and this also was inhibited by paxilline or tetraethylammonium ion (Wondergem & Bartley, 2009). Invasion and metastasis are biologic hallmarks of malignant tumour. The invasion of ECM requires active degradation of ECM components. Tumour cells themselves secrete proteolytic enzymes (metalloproteinases, MMPs) or induce host cells to elaborate proteases (Pluda, 1997; Price et al., 1997; Liotta & Kohn, 1997). Glioma cells secrete MMPs to degradate the ECM surrounding invading cells (Levicar et al., 2003). In this regard, cannabidiol (CBD) has been found to impair the migration of U87 glioma cells in a cannabinoid receptor-independent manner (Vaccani et al., 2005), by increasing the tissue inhibitor of MMP1, (TIMP-1) (Ramer et al., 2010) and down-regulating the MMP-2 expression (Blazquez et al., 2008). Since CBD represents a specific ligand for TRPV2 (Qin et al., 2008), and being TRPV2 downregulated in the more invasive malignant gliomas (Nabissi et al., 2010), activation of this channel may represent an important target in anti-invasive chemotherapeutic strategy in GBM patients.

## 5. TRPV and TRPM channels trigger cell death in human glioma cells

Members of the TRPV and TRPM channels have been found to regulate apoptotic and necrotic cell death processes, respectively, as well as resistance to apoptotic stimuli in glioblastoma cells. In this regard, a role for TRPV1 in the apoptosis of glioma cells has been reported (Amantini et al., 2007). Thus, TRPV1 mRNA and protein expression was evidenced in normal astrocytes and glioma cells and tissues (Contassot et al., 2004; Amantini et al., 2007). TRPV1 expression inversely correlated with glioma grading, with a marked loss of TRPV1 expression in the majority of grade IV glioblastoma tissues. In addition, TRPV1 activation by the synthetic ligand, capsaicin (CPS) induced apoptosis of U373 glioma cells, and involved rise of  $\text{Ca}^{2+}$  influx, p38MAPK activation, mitochondrial permeability transmembrane pore opening and transmembrane potential dissipation and caspase-3 activation (Amantini et al., 2007). Similarly, an other TRPV1 agonist, arachidonylethanolamide (AEA) induces apoptosis of human glioma cells in a TRPV1-dependent-manner (Contassot et al., 2004). Resistance of cancer cells to chemotherapeutic-induced cytotoxicity during tumor progression partially depends by a decrease sensitivity to CD95/Fas-induced apoptosis (Amantini et al., 2009). Induction of cell death by some cytotoxic drugs seems to depend to an intact Fas/FasL system. Tumour progression by exerting selective pressure alters Fas status and subsequently affects the sensitivity of cancer cells to chemotherapy (Sindhwani et al., 2001). Glioblastoma cells are resistant to Fas-induced cell death. We have recently reported that TRPV2 negatively controls glioblastoma survival as well as resistance to Fas/CD95-induced apoptosis in an ERK-dependent manner. Silencing of TRPV2 by RNA interference (siRNA) in U87 glioma cells down-regulated Fas/CD95 and procaspase-8 expression, and up-regulated Bcl-X<sub>L</sub> mRNA expression. Moreover, TRPV2 siRNA increased glioblastoma survival to Fas/CD95-induced apoptosis in an ERK-dependent manner (Nabissi et al., 2010). Inhibition of ERK activation by treatment of the siRNA-TRPV2 U87 glioma cells with the specific MEK-1 inhibitor PD98059, reduced Bcl-X<sub>L</sub> protein levels, promoted Fas/CD95 expression and restored Akt/PKB pathway activation leading to reduced cell survival and increased sensitivity to Fas/CD95-induced apoptosis (Nabissi et al., 2010). These events are consistent with previous evidence showing that PI3K pharmacological inhibitors inhibited calcium overload and cell death in TRPV2-transfected mouse cells (Penna et al., 2006). Consistently, TRPV2 transfection of the primary MZC glioblastoma cells also reduced glioma viability and increased spontaneous and Fas/CD95-induced apoptosis, by inducing Fas/CD95 expression (Nabissi et al., 2010). Among TRPM channels, a role for the  $\text{Ca}^{2+}$  permeable TRPM2 channel in glioma cell death has been reported. Thus, insertion of TRPM2 in human A172 glioma cells enhanced cell death induced by  $\text{H}_2\text{O}_2$  (Ishi et al., 2007).

## 6. TRP channels as cross-road of deregulated transcriptional activity in glioma stem like-cells

Evidence that malignant gliomas may arise from and contain a minority tumour cells with stem cell-like (GSCs) properties has been increased by the demonstration that GSCs maintain the potential for self-renewal and multi-lineage differentiation that recap the phenotype of the original glioma (Galli et al., 2004; Singh et al., 2003; Yuan et al., 2004). Since GSCs has been suggested to play an important role in glioma initiation, growth, and recurrence, it is extremely important to understand the signal pathways that contribute to their formation and maintenance, with the future aims to eliminate GSCs from the bulk

tumor mass as a therapeutic strategy (Reya et al., 2001). Recent evidences adscript an emergent role of TRP channels in regulating neurogenesis (Tai et al., 2009) as well as neural differentiation (Shin et al., 2010), suggesting that deregulation of specific TRP target genes may be involved in gliomagenesis (Van Meir et al., 2010; Liu et al., 2010). In this regard, the expression of TRPV2 in normal neural stem/progenitor cells (NS/PC) from olfactory bulb and GSC lines derived from GBM patients, and a role of this TRP channel in the regulation of cellular proliferation and differentiation, have been observed (Nabissi et al., personal communication). Stem cells proliferation is maintained by a balance between proliferative and antiproliferative signals and any genetic or biochemical modifications that lead stem cells to become independent of growth signals, could induce an uncontrolled proliferation and possible tumorogenesis (Li & Neaves, 2006). GSCs divide core regulatory pathways with normal neural stem cells (NPSs), sharing developmental programs that lead NSCs to differentiate into astrocytes, oligodendrocytes and neurons (Galli et al., 2004; Singh et al., 2003), but induce in GSCs an aberrant differentiation (Cheng et al., 2010). GSCs are reported to express CD133 and nestin and to differentiate into cells expressing neuronal or glial cell markers upon growth factor depletion (Gunther et al., 2008). In addition to these NSC characteristics, glioma-derived neurospheres or CD133+ cells are tumorigenic and when transplanted into SCID mice formed secondary tumors with phenotypic and cytogenetic similarities to the patient tumor from which they were originally derived (Singh et al., 2003; Lee et al., 2006). Recent findings in GSCs demonstrated that the upregulation of classical pathways associated with neural development, as Notch, WNT, Hedgehog and TGF $\beta$ /BMT pathways (Clark et al., 2007; Silver & Steindler, 2009), induce in GSC-derived GBMs an invasive, angiogenetic, proliferative and chemoresistant phenotype (Sanai et al., 2005). So, modulation of these pathways may represent novel therapeutic approach for GBM. Notch is a family of hetero-dimeric transmembrane receptors composed of an extracellular domain responsible for ligand recognition, a transmembrane domain, and an intracellular domain involved in transcriptional regulation (Stockhausen et al., 2010). Notch proteins (and ligands) contain extracellular EGF-like repeats, which interact with the DSL domain of ligands. Activation of Notch upon ligand binding is accompanied by proteolytic processing that releases an intracellular domain of Notch (NICD) from the membrane tether. The NICD contains the RAM23 domain (RAM), which enhances interaction with the CSL protein, NLS (Nuclear Localization Signals), a CDC10/Ankyrin repeat domain ANK, which mediates interactions with CSL and other proteins, and a PEST domain rich in proline, glutamate, serine and threonine residues (Kopan, 2002). When Notch receptor is triggered by the ligands on the neighboring cells, the intracellular domain of the Notch receptor (NICD) is released from the membrane, after successive proteolytic cleavages by the  $\gamma$ -secretase complex. NICD then translocates into the nucleus and associates with the transcription factor RBP-J. This complex by secruiting other co-activators, stimulates the expression of downstream genes as Cyclin-D1, EGFR, and MAPK (Mitogen-Activated Protein Kinase) inducing cell proliferation, angiogenesis and chemoresistance, in GSCs (Stockhausen et al., 2010). Regarding the role of Notch signaling in GBM, gene microarray analysis have demonstrated that its expression in brain tumors correlated with good versus poor prognosis (Phillips et al., 2006). Moreover, in GBM tissue samples, high expression of Notch signal has been associated with high nestin levels, suggesting a correlation between GSCs and Notch expression (Purow et al., 2005; Lino et al., 2010; Boulay et al., 2007; Shih & Holland, 2006). Infact, Notch signaling plays a pivotal role in the maintenance of NSCs and leads to GSC-driven brain tumor development ( Lino et al., 2010; Louvi & Artavanis-

Tsakonas, 2006). Recently, has been demonstrated that Notch activation is increased during hypoxia and hypoxia direct GBM to the development of an aggressive phenotype and resistance to radiation and chemotherapy (Flynn et al., 2008). Regarding the relationship between Notch signaling and TRP channels, a direct correlation has been demonstrated in human glioma cell lines where TRPC6 transcripts have been found to be increased under hypoxic condition and the involvement of Notch in hypoxia-induced TRPC6 expression in glioma has been demonstrated. Silencing of Notch1 gene inhibits TRPC6 expression suggesting that Notch1 is required for hypoxia-induced TRPC6 over-expression (Chigurupati et al., 2010). In response to hypoxia, the hypoxia inducing factors (HIF1- $\alpha$  and HIF-2 $\alpha$ ) are stabilized and as a consequence VEGF and TGF $\alpha$  are up-regulated (Birlık et al., 2006). Moreover, hypoxia-induced endothelial cell proliferation is associated with an increase of AP-1 expression, elevated store-operated calcium entry, and enhanced TRPC4 expression (Fantozzi et al., 2003), suggesting that additional TRP channels may regulate angiogenic signals (Fig.4). The interplay between GSCs and the endothelial compartment seems to be critical in gliomagenesis. Thus, GSCs closely interacting with the endothelial cells in vascular niche, promote angiogenesis through VEGF release (Bao et al., 2006a; Folkins et al., 2009). GSCs are reported to express CD133

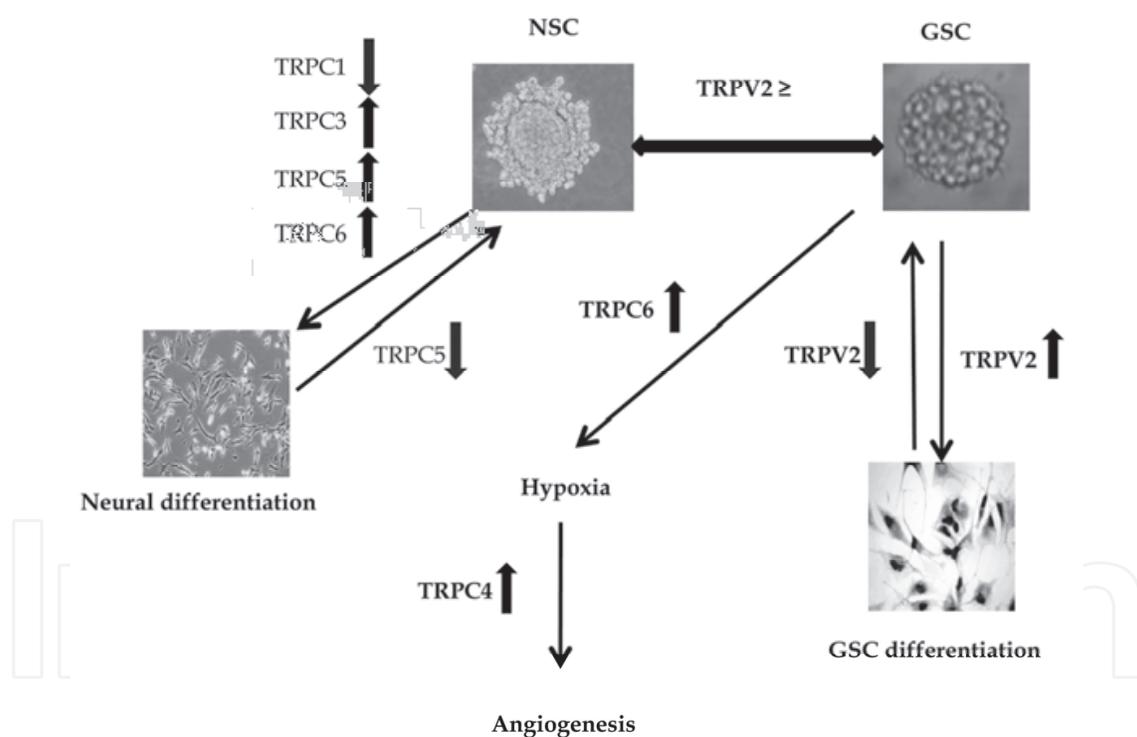


Fig. 4. The putative role of TRP channels in neural and glioma stem cell-like differentiation and angiogenesis. A schematic representation of different TRP members involved in the regulation of neuro- and glioma-genesis

and nestin (Yuan et al., 2004; Gunther et al., 2008) and have been demonstrated to have multipotent differentiative potential (Galli et al., 2004; Singh et al., 2003). Several authors have hypothesized that CD133<sup>+</sup> tumor stem cells are the source of the recurrent tumors after treatment (Chua et al., 2008; Bleau et al., 2009) and the CD133<sup>+</sup> cell population was enriched after radiation or chemotherapy and exhibited an increase in DNA repair capacity (Bao et

al., 2006b). A series of pathways, including the Sonic hedgehog (Shh) and Notch, have been shown to be implicated in glioma's resistance to alkylating agents and/or the maintenance of brain tumor stem cells (Ulasov et al., 2011; Clement et al., 2007). Moreover, overexpression of *Dkk-1*, a gene encoding for a Wnt antagonist protein, has been shown to sensitize the U87 glioma cells to the cytotoxic effects of bis-chloronitrosourea (BCNU) and cisplatin (Shou et al., 2002). In this regard, an inverse correlation between TRPV2 and SHH and Notch pathways (Phillips et al., 2006; Nabissi et al., 2010) in regulating chemoresistance to the alkylating agent bis-chloronitrosourea (BCNU), can be supposed. TRPV2 expression progressively declined in high-grade glioma tissues as histological grade increased, while Notch and SHH signaling was activated in GBM. Knockdown of TRPV2 gene in gliomas increased the resistance to BCNU cytotoxicity which was associated with Ras/MEK/Erk and Akt overexpression in chemosensitive glioma cells, while TRPV2 overexpression augmented the chemosensitivity of resistant glioma cells to BCNU. In addition, down-regulation of TRPV2 reduced Fas expression and Fas-mediated apoptosis (Nabissi et al., 2010). Parallely, upregulation of Notch 1, increased the resistance of glioma cell to apoptosis (Purow et al., 2005). Finally, forced Notch 1 overexpression in glioma cells increased the proliferation and the formation of nestin-positive, neurosphere-forming stem cells (Zhang et al., 2008). Overall, these data suggest that in gliomas, TRPV2 could be a downstream gene target of Notch signaling rescuing glioma cells to apoptosis and promoting cell proliferation.

## 7. Conclusions and prospectives

In this chapter, we have summarized current basic and translational changes and highlight the striking scientific advances regarding the expression and the function of the TRP channel family in glioma growth and progression, that promise to improve the clinical course of this lethal disease. These include a more comprehensive view of the interplay between changes in TRP channel expression and functions (e.g., TRPC, TRPM and TRPV family) and alterations in transcriptional and growth factor pathways (e.g., Notch, PTEN, HIF- $\alpha$ , EGFR) driving the uncontrolled cellular proliferation, aberrant angiogenesis, intense migration and invasion, increased resistance to apoptosis. Clearly, the identification of cluster of TRP ion channels altered during glioma progression presents an opportunity for improving the understanding of this cancer. The progress and depth of understanding of the role of ion channels, including the TRP family in glioma, together with truly manipulable experimental models, now offer a real opportunities for the development of effective target therapy (Santoni & Farfariello, 2011). Despite significant gaps in our understanding, a wealth of information now exists about clinical and biological behaviour of these tumours, the genetic pathways involved in gliomagenesis and the nature and the role of their alterations. The challenge is now to integrate all of this knowledge in an interdisciplinary way to full understand this disease and how its heterogeneity contributes to the relatively poor therapeutic responses of GBM patients. In regard to stem cell issue, the fact that the glioma-like stem cells (GSCs) that play an important role in the development and recurrence of malignant glioma, not only express TRP channels, but also show functional alterations in their expression and transcriptional regulation, combined with the evidence that they displayed nearly identical Ca(2+) transients and pharmacological sensitivities to TRP channel antagonists (Nabissi et al., personal communication; Weick et al., 2009), may

offer a new target for regulating GSC proliferation and developing novel therapeutic strategies. We are only at the begin of a new story; further studies on the expression and function of TRP channels in gliomas and GSCs must to be required to understand their contribute to malignant transformation and tumour progression, to delivery a specific target therapy in this devastating disease.

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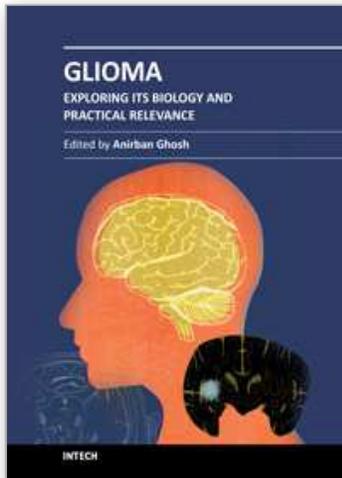
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