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Glioma-Parvovirus Interactions: Molecular Insights and Therapeutic Potential

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1. Introduction

Brain tumours remain one of the most devastating diseases of modern medicine. Although they only represent approximately 1.9% of primary tumours in Europe, their mortality is around 70% and they are within the group of the 10 cancer types causing the highest yearly mortality rate. Gliomas are malignancies of neuroepithelial origin and represent 40-60% of brain tumours. In particular, glioblastoma multiforme (GBM, astrocytic tumours of type IV) is the most aggressive and frequent of primary brain tumours, representing 60% of gliomas. Despite clinical practice advances, the mean survival time of GBM patients has not improved significantly within the last few decades, and it remains around 12-15 months. Current standard of care includes maximal safe surgical resection, and a combination of radio- and chemotherapy with concomitant and adjuvant temozolomide or carmustine wafers (Wen and Kesari 2008). At the moment, the clinical improvement reached is modest, with a 5-year survival rate of less than 5% (Mangiola et al. 2010). The poor results obtained with conventional therapies may be explained by their relatively unspecific nature (Newton 2010), the inefficient delivery of many drugs to the tumoral tissue due to the blood-brain and blood-tumour barriers, as well as by the intrinsic radio- and chemo-resistance of GBM (Newton 2010).

In light of the limitations of conventional treatment strategies, the necessity of new approaches that would be more effective against GBM became evident. The current understanding of the molecular biology of GBM has set researchers on the path of more targeted and specific therapies exploiting the molecular properties of the tumour. Most targeted agents are tyrosine kinase inhibitors, or monoclonal antibodies directed against either cell surface growth factor receptors or intercellular signaling molecules (angiogenesis) (Van Meir et al. 2010). The overall experience of the monotherapy with targeted agents has shown limited efficacy, with response rates of less than 10-15% and no prolongation of survival (Clarke et al. 2010; Van Meir et al. 2010). Other promising therapies for GBM are also currently being investigated, including combined therapy with targeted agents, immunotherapy, gene therapy, or oncolytic virotherapy (Clarke et al. 2010; Van Meir et al. 2010).

Virus-mediated therapy, or virotherapy, is emerging as a promising biological approach to complement or potentiate physical and chemical anti-cancer conventional treatments (reviewed in Eager and Nemunaitis 2011). The increasing knowledge on molecular mechanisms underlying cancer development, and on the host-virus interphase regulating viral infections, is allowing the rational design of virotherapies against some human tumours. Ideally, the infection of a clinically competent oncolytic virus candidate should specifically target, replicate in, and destroy the tumour cells, but sparing surrounding non-transformed cells. Multiple restrictions and uncertainties operating at different levels, such as at cellular (specificity of tumour markers in non-transformed cells, tumour microenvironment), anatomical (accessibility, vascular barriers), or physiological (innate and specific immune responses) levels, constitute important challenges against effective virotherapy. In spite of them, intensive research efforts being conducted in many laboratories are developing or using RNA and DNA oncolytic viruses for glioma therapy (see other chapters of this book). Indeed, clinical trials were performed (Haseley et al. 2009; Kroeger et al. 2010) or are currently in progress against glioblastoma using different virotherapeutic approaches. For the first time H-1, a member of the *Parvoviridae*, is within the ongoing clinical trial protocols (<http://clinicaltrials.gov/>). Some general features of this virus family, as well as molecular bases of the anti-glioma activities of the parvoviruses, are reviewed below.

2. The Parvoviruses: General features and anti-cancer properties

2.1 Parvovirus capsid structure and genome organization

The *Parvoviridae* is a family of spherical, non-enveloped icosahedral viruses (Berns and Parrish 2007). The number of viruses being identified as members of this family is rapidly increasing in the recent years. Current classification from the International Committee of Taxonomy of Viruses (ICTV) for the *Parvoviridae* includes two subfamilies and nine genera (see Figure 1A). The parvoviral capsids are ~260 Å in diameter, and encapsidate a ssDNA genome of ~5000 nucleotides. The number of capsid protein species per virion varies among parvoviruses, but are generally composed by three polypeptides, VP1, VP2 and VP3 (molecular weights in the range of 60-84 kDa). Capsids contain 60 copies (in total) of VP protein subunits in a T=1 icosahedral capsid arrangement. The three-dimensional structure of the capsid, which has been determined to high resolution by X-ray crystallography for many members (Tsao et al. 1991; reviewed in Chapman and Agbandje-McKenna 2006), shows a conserved overall topology of eight-stranded antiparallel beta-barrel core motif that forms the contiguous capsid shell, and large loop insertions between the beta-strands. The surface features include small protrusions (spike-like) commonly at the icosahedral three-fold axes, and depressions that may be located at the icosahedral two-fold (dimple-like) and/or around the five-fold (canyon-like) axes.

Virus members of the autonomously replicating Parvovirus genus infect mammals and have a wide range of natural hosts, including humans, monkeys, dogs, livestock, felines and rodents. A main molecular model of this genus is the mouse parvovirus Minute Virus of Mice (MVM), which genome is organized as two overlapping transcription units (see Figure 1B) timely regulated (Clemens and Pintel 1988). The left-hand gene driven by the P4 promoter encodes the NS1 and NS2 nonstructural proteins, and the right-hand gene driven by the P38 promoter encodes the VP1 and VP2 structural proteins. In spite of its small size

(only 5 Kb), the use of alternate splicing, extensive postranslational modifications and proteolytic processings, maximize the coding capacity of the parvovirus genome. The two NS polypeptides play multiple roles in virus life cycle. The smaller NS2 protein (28 kDa) contains three isoforms arising from alternate splicings that can bind several cellular proteins and shuttle from the nucleus to the cytoplasm via the CRM1 export pathway. Functions assigned to NS2 include assisting capsid assembly, messenger translation, DNA replication, and virus production in a cell type specific manner. The larger NS1 (82 kDa), is a multifunctional nuclear phosphoprotein, highly toxic for most cells, and performing crucial activities in the MVM unique rolling-hairpin mode of DNA synthesis (see below).

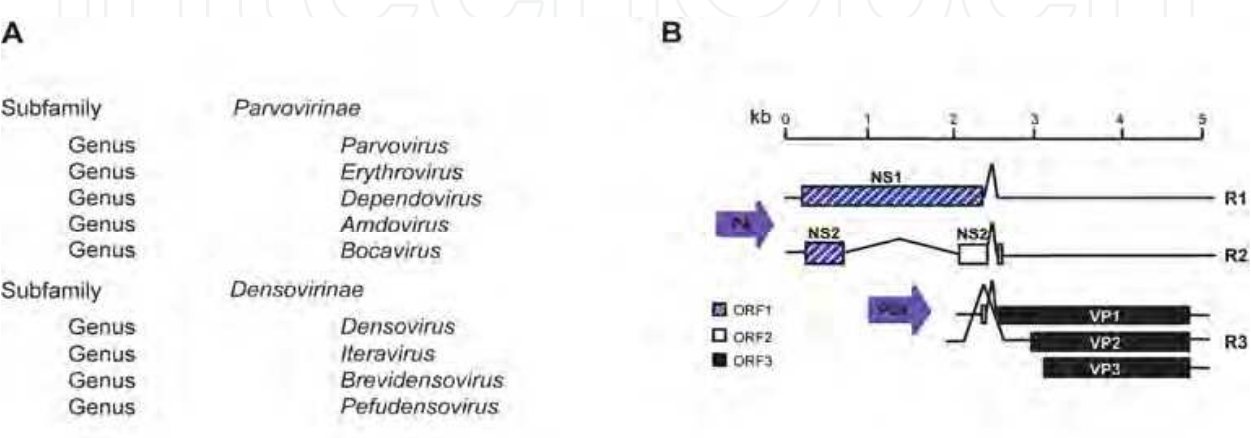


Fig. 1. Outline of the *Parvoviridae*. (A) Taxonomic structure of the *Parvoviridae* (from Tijssen et al. 2011, *in press*). (B) Organization of the MVM genome. The position of the two promoters (P4, P38) are designated by arrows. Splicing sites, and virus coded main non-structural (NS1, NS2), and structural (VP1, VP2) polypeptides are illustrated in their respective reading frame (based on Cotmore and Tattersall 1987).

2.2 Parvoviruses as oncolytic agents

Many of the members of the *Parvoviridae* were initially isolated from tumours or from transformed cell lines in culture, corresponding with the requirement of these viruses for multiple functions provided by proliferative cells. This unique biological feature, together with requirements for diverse factors that are linked to the neoplastic growth, account for the capacity of the parvoviruses to infect and lyse preferentially cells transformed by a high diversity of physico-chemical and biological agents (Mousset and Rommelaere 1982; Cornelis et al. 1988), and to interfere with tumour formation in animal models (Toolan and Ledinko 1965; Dupressoir et al. 1989; reviewed in Rommelaere et al. 2010). These studies validated, at least for some parvoviruses, many of the requirements that oncolytic viruses should fulfill to be used in the clinic, such as oncotropism, no genomic integration, low toxicity of structural components, or apathogenicity for humans.

This review is focused on the interactions of glioma cells with two parvoviruses which oncolytic properties have been best evaluated, the rat parvovirus H-1, and the p and i *wild-type* strains of the mouse parvovirus Minute Virus of Mice (MVM). Over the past decade, the characteristics of the infection of these viruses in rodent and human glioma cell lines, primary human glioblastoma cultures, and preclinical xenotransplanted animal models, have been extensively studied (see Table 1).

Infectious Parvovirus	Human GBM	Infection/Mechanism	Reference
MVMp	U373MG	Cytotoxic and productive infection/ Postencapsidation restriction	(Rubio et al. 2001)
MVMi	U87MG	Cytotoxic non-productive/ Viral DNA replication blockade	(Rubio et al. 2001)
H-1	U373MG and primary cultures	Productive cytotoxic infection/ Viral replication and maturation	(Herrero et al. 2004)
MVMp, MVMi	M059J, U87MG	Limited virus spread and cell death/ Not reported	(Wollmann et al. 2005)
H-1	U373MG, U138MG, NCH82, NCH89, NCH125 and NCH149	Death in cells resistant to TRAIL and cisplatin/ Cytosolic accumulation of lysosomal cathepsins B, L and reduction of the levels of cystatin B and C	(Di Piazza et al. 2007)
MVMp	U373MG	Productive and nuclear capsid assembly/ Raf-1 phosphorylation of capsid subunits	(Riolobos et al. 2010)
H-1	NCH82, NCH89, NCH125 and NCH149	Cytotoxic in radioresistant gliomas/ combination of ionizing radiation and H-1	(Geletneky et al. 2010a)
MVMp	U373MG	Productive gene expression/ PKR translational control	(Ventoso et al. 2010)
H-1	U87MG	Regression of glioma in immunodeficient rats/ Viral oncolysis in the tumor	(Geletneky et al. 2010b) (Kiprianova et al. 2011)

Table 1. Contributions on human Glioma-Parvovirus interactions.

The first report about cytotoxicity of a parvovirus against transformed neural cells was on the MVMp and MVMi infection of rat C6 glioma and several human glioblastoma and astrocytoma cells (Rubio et al. 2001). The MVM infections of human cells were cytotoxic but poorly productive, as found some years afterwards by an independent study (Wollmann et al. 2005). Although a parallel study with the MVM and H-1 viruses has not being carefully addressed, several subsequent reports suggested that H-1 is a more powerful oncolytic agent against human glioblastoma, regarding the levels of both cytotoxicity and virus yield in culture (Herrero et al. 2004; Di Piazza et al. 2007). Further recent preclinical studies have convincingly supported H-1 as anti-glioblastoma agent for clinical purposes, as its infection synergized with radiation (Geletneky et al. 2010a), and moreover it improved survival and remission of advanced intracranial U87MG human glioblastoma in rat models (Geletneky et al. 2010b; Kiprianova et al. 2011). However, as discussed below for MVM, there are particularly interesting aspects in the non-productive glioma-parvovirus interaction, as they may uncover molecular processes altered in glioma and helping to identify cellular targets for cancer treatments.

3. Parvovirus genome replication may be restricted in human glioblastoma

The two best characterized strains (p and i) of the MVM, exhibiting distinct tropism in spite of their sequence and capsid structure similarity (reviewed in Cotmore and Tattersall 2007), conform a valuable system to explore molecular aspects of virus-host interactions in human gliomas (Rubio et al. 2001). MVMp infection of U373MG was cytotoxic and productive,

whereas U87MG and SW1088 astrocytoma cells were resistant to this virus. The MVMi infections were more interesting, as they uncovered novel insights on parvovirus-tumour cells interactions. Although this virus did not complete its life cycle, it efficiently killed the U373MG, U87MG, and SW1088 astrocytic tumour cells. The abortive infection was not restricted at the transcription or gene expression steps, as the viral messenger RNAs, as well as both non-structural (NS1) and structural (VP1, VP2) proteins, accumulated to normal levels. However, in the U87MG glioblastoma, MVMi failed to amplify its DNA genome. All these analyses consistently showed that only the non-availability of multimeric replicative DNA forms to be encapsidated hampered MVMi virions maturation in the U87MG cells.

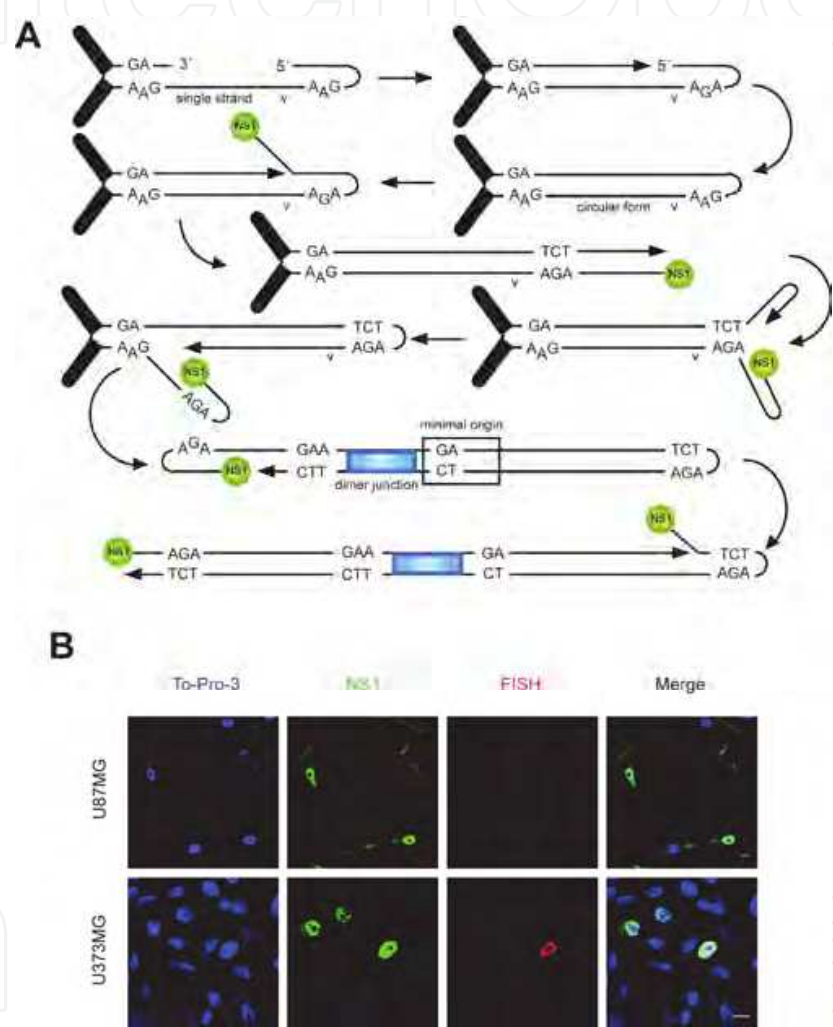


Fig. 2. Distinct genome replication capacity of parvovirus MVM in human glioblastomas. (A) Model of MVM genome replication (based on Cotmore and Tattersall 1995). The ssDNA virus genome is illustrated showing the particular structure of the 3' left and 5' right termini and their base mispairing. Only the initial steps of the model leading to the configuration of the dsDNA monomeric (mRF) and dimeric (dRF) intermediates, are outlined. (B) DNA replication of MVMi in human U87MG and U373MG cells. The glioblastomas were infected by MVMi, fixed and proceeded for immunofluorescence at 48hpi. Staining was with an anti-NS1 antibody and FISH using MVM specific TxR-oligonucleotides. NS1 protein accumulated into the nucleus in both glioblastoma cells, but MVM replication occurring only in U373MG, are shown (scale bar, 10 μ m).

The molecular mechanisms underlying the failed DNA amplification of MVMi in U87MG glioblastoma remain unclear, although some clues can be drawn. As shown in Figure 2B, the U87MG, as the fully permissive U373MG cells, expressed high amounts of NS1 protein (the major viral replicative factor) that translocated normally into the nucleus, although viral DNA was not synthesized to detectable levels (Gil-Ranedo et al., in preparation). When the viral DNA replicative intermediates accumulated in U87MG were resolved in agarose gels (Rubio et al. 2001), a conversion of the incoming viral genome (ssDNA) to the monomeric replicative form (mRF) occurred. However, the subsequent synthesis of the dimeric form (dRF) was not observed. These findings are next interpreted under a current MVM replication model (Figure 2A). The conversion reaction (ssDNA to mRF) is exclusively accomplished by cellular factors S-phase dependent, involving elongation by the δ and other cellular polymerases (Bashir et al. 2000), which are apparently functional in U87MG cells. For several of the following steps of the replication model, the NS1 endonuclease and helicase activities are essential to provide 3'OH ends for the replication fork to proceed (Nuesch et al. 1995). It seems therefore likely that these NS1 activities, or the interaction with cellular factor recruited to the MVM origin of replication to assist NS1 activities (Christensen et al. 1997; Christensen et al. 2001), are not functional in infected U87MG cells.

It is worth mentioning that the infection of human glioblastomas by other parvoviruses may be not restricted at the DNA replication level. The also autonomous H-1 rat parvovirus, closely related to MVM, productively infected the U373MG human glioblastoma cell line, as well as human short-term cultures derived from histologically and immunologically confirmed glioblastomas (NCH82, NCH89, NCH125, NCH149) and gliosarcoma (NCH37). Cell killing, viral DNA amplification, protein expressions and infectious virus particles production was demonstrated in all of these cultures (Herrero et al. 2004). The broader host range of H-1 than MVM toward human glioblastomas may suggest that subtle genetic changes between parvovirus genomes may result in drastically different infection outcomes.

4. Translational control of parvovirus gene expression in glioblastoma

The degree of permissiveness of many host cells to a particular virus infection is regulated, to a great extent, at the level of the accessibility of the translational machinery to the viral messenger RNAs. The complexity of virus-host interaction at this level is exemplified by the multiple mechanisms evolved by viruses (e.g. affinity of viral messengers for the ribosome, or dependence on initiation factors) to overcome the also evolving cellular barriers (Bushell and Sarnow 2002; Schneider and Mohr 2003). A major role at this interface is played by the Protein Kinase R (PKR), which is activated by the dsRNA species generated by the replication of RNA and some DNA viruses (Balachandran and Barber 2000; Elde et al. 2009). Upon activation, PKR phosphorylates the Ser51 residue of the alpha subunit of the initiation factor 2 (eIF2 α), preventing eIF2 from forming the ternary complex with GTP and the initiator Met-tRNA (Dever 2002; Dey et al. 2005), leading to the inhibition of translation initiation and thus aborting virus multiplication. The multiple strategies evolved by viruses to inhibit or bypass PKR activation include for example binding to PKR (Kitajewski et al. 1986; Gale et al. 1998), sequestering the dsRNA (Lu et al. 1995), or recruiting a host phosphatase that dephosphorylates eIF2 α (He et al. 1997).

Cell transformation is often associated to reduction or complete suppression of the antiviral defense mechanisms, including PKR responsiveness. For example, some leukemia-derived

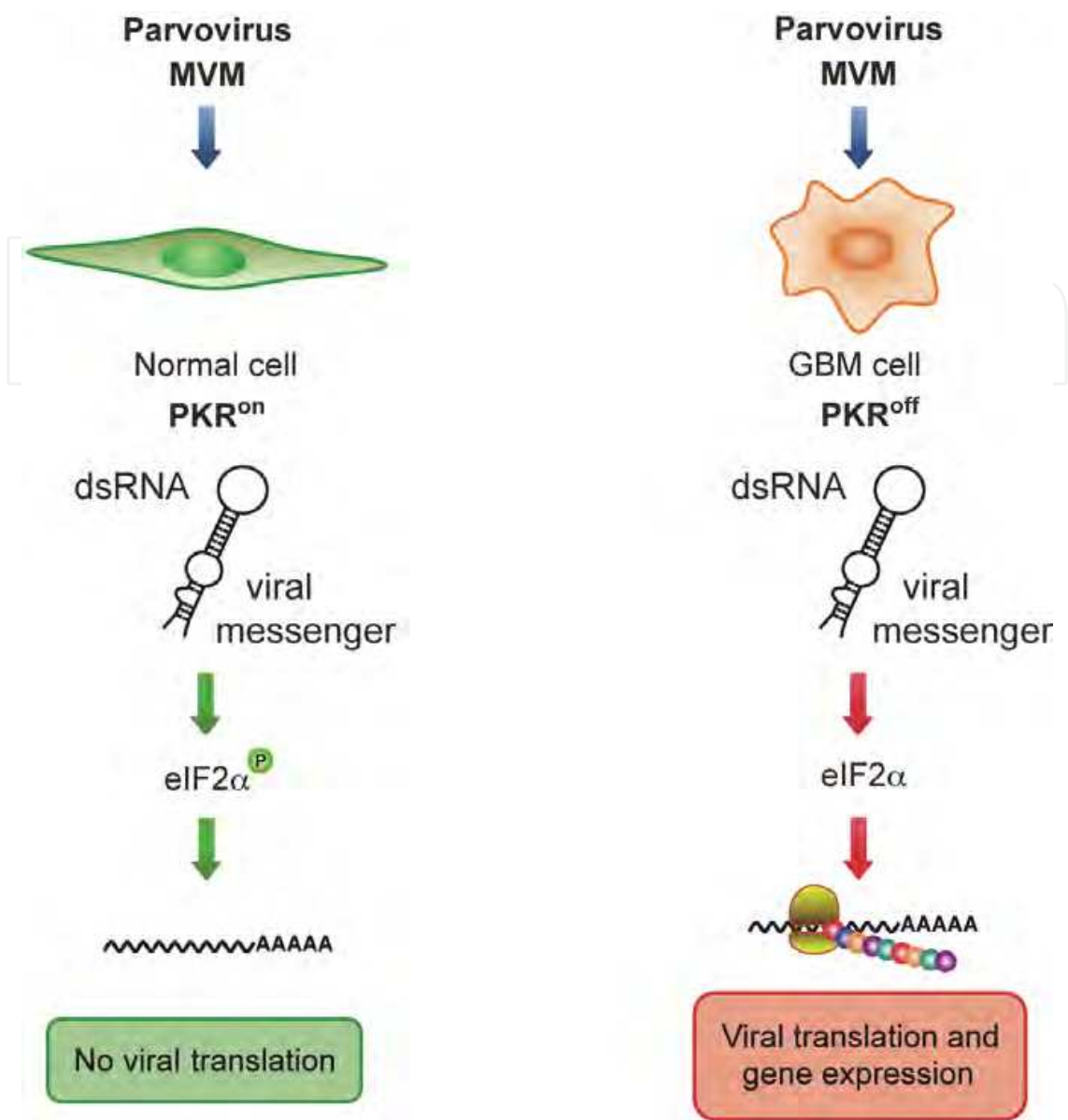


Fig. 3. Translational control of MVM gene expression in GBM based on PKR activity. Virus entry and traffic into the nucleus is followed by transcription of the early NS gene. Folding of viral messenger RNAs produces regions of dsRNA secondary structure with variable length and complexity. In most normal cells (left), the presence of dsRNA in the cytoplasm leads to PKR activation and eIF2 α phosphorylation, which inhibits cap-dependent mRNA translation. In GBM (right), the failure of PKR activation in response to infection allows viral mRNA translation and replication to proceed (based on Ventoso et al. 2010).

cell lines have lost the PKR gene (Beretta et al. 1996), whereas PKR activation, but not expression, was hampered in H-Ras transformed fibroblasts (Mundschau and Faller 1992), and PKR plays a role in the tumour-suppressor function of p53 (Yoon et al. 2009). Other transformed cells however, as some human glioblastoma cells, harbor functional PKR that can be activated by specific dsRNA to promote selective killing (Shir and Levitzki 2002; Friedrich et al. 2005). Therefore, in most cell transformation processes viruses find a favoured environment for messenger translation and gene expression. The defective

translational control in cancer cells have been exploited by different virotherapy systems (reviewed in Parato et al. 2005), as those conducted with naturally oncotropic VSV and Reovirus (Strong et al. 1998; Balachandran and Barber 2004), or with genetically engineered oncolytic Adenovirus and Herpesvirus (Farassati et al. 2001; Cascallo et al. 2003), which replicate inefficiently in cells with intact PKR pathways, but may complete gene expression and replication in malignant gliomas (Shah et al. 2007).

In recent years, the important role that translational control plays in the gene expression and natural oncotropism of the ssDNA virus members of the *Parvoviridae* has been recognized. In the Adeno-Associated Virus type 5 (AAV5), a member of the Dependovirus genus, viral replication and protein synthesis was highly enhanced by the co-expression of an adenovirus VA I RNA (Nayak and Pintel 2007a) that, by binding to PKR, prevents its otherwise activation by a short RNA sequence of AAV5 messengers (Nayak and Pintel 2007b). The infection of untransformed fibroblast cells by MVM of the Parvovirus genus, activated PKR and subsequently phosphorylated eIF2 α (Ventoso et al. 2010). This mechanism drastically inhibited the synthesis of the NS1 protein, which controls the expression of the viral late messengers and genome replication, leading to a drastic inhibition of virus gene expression and multiplication in culture (see Figure 3, left). In support of this phenomenon observed in cells, purified PKR was highly activated by the R1 genomic messenger of MVM *in vitro*, leading to phosphorylation of the eIF2 α translation initiation factor. In contrast, the human glioblastoma U373MG cells showed basal levels of eIF2 α phosphorylation, and moreover failed to increase PKR-mediated eIF2 α phosphorylation in response to MVM infection, thereby allowing viral gene expression to proceed (Figure 3, right). Therefore, the oncolytic capacity of MVM, H-1, and other parvoviruses against glioblastoma may be largely related to the failure of PKR activation. This conclusion is consistent with the widely studied permissiveness to parvovirus gene expression and toxicity of multiple human cells transformed by oncogenes and tumour suppressors genes (Mousset and Rommelaere 1982; Salome et al. 1990; Telerman et al. 1993), which disturb PKR-based antiviral innate immunity.

5. Parvovirus capsid assembly targets deregulated Raf signaling in glioblastoma

A virotherapy of glioma with potential clinical benefit should exploit synergy interactions between molecular targets upregulated in glioma cells, and viral factors involved in the replication or maturation of the therapeutic candidate. The genetic alterations undergoing malignant gliomas are multiple and complex, although some signaling pathways play major roles. Alterations in tyrosine kinase growth factor receptors (EGFR, PDGFR, MET and ERBB2), as those found in almost all World Health Organization (WHO) grade II, III and IV astrocytomas, result in constitutive downstream signaling of the RAS/RAF/MEK/ERK (MAPK) and PI3K/AKT pathways. The MAPK pathway is also important for glioma development as it is activated in most WHO grade I tumours. These epidemiological studies are consistent with experimental evidences in mouse models showing that the expression of activated KRAS, CRAF or BRAF in neural progenitor cells combined with either AKT activation, or Ink4aArf loss, leads to the development of high-grade gliomas *in vivo* (Robinson et al. 2010). In the MAPK signal cascade (see Figure 4), assembled membrane-associated complex formed by kinases and scaffold proteins transduces mitogenic and other stimuli from the cell surface to the nucleus (Marais and Marshall 1996).

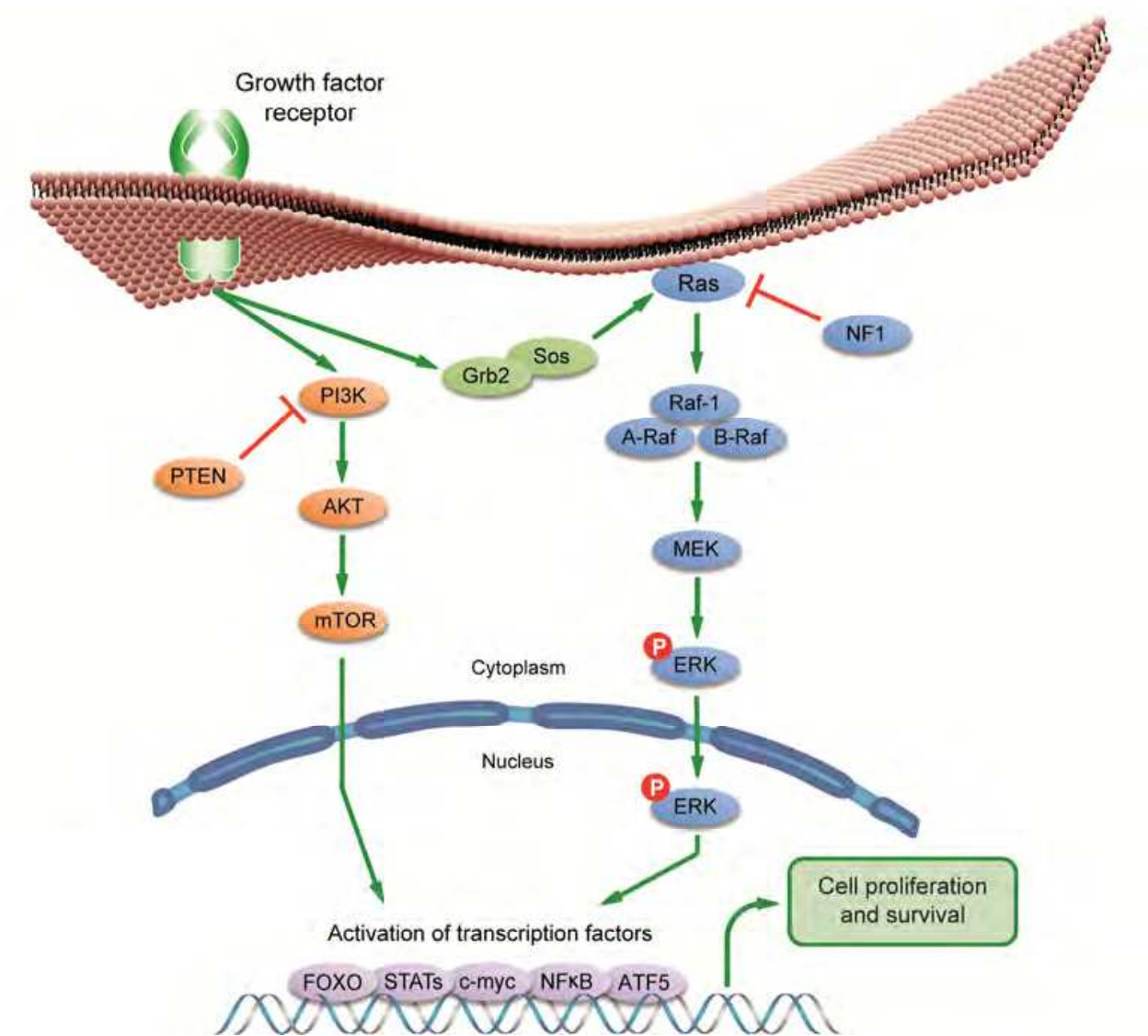


Fig. 4. Principal protein effectors of the signaling pathways altered in GBM. The two major pathways altered in GBM, the PI3K/ AKT/ mTOR and Ras/RAF/MEK/ MAPK, may be activated from the membrane-coupled receptor. Arrows designate the activation cascades mainly due to phosphorylation. Two inhibitors, PTEN and NF1 (Van Meir et al. 2010), relevant for GBM development, are also outlined. Note the key role of RAF proteins complex as regulator of ERK nuclear translocation (references in the text).

The MEK1/2 proteins are the main downstream effectors of the activated RAF protein kinases, and subsequently they phosphorylate ERK, which dissociates from the complex and translocates into the nucleus (Khokhlatchev et al. 1998). Active ERK induces many transcription factors including ATF5, which expression inversely correlates with malignant glioma prognosis (Sheng et al. 2010). In glioma, the RAF kinase isoforms are constitutively activated, overexpressed, or mutated (Wellbrock et al. 2004; Lyustikman et al. 2008), and although most mutations map to BRAF (Davies et al. 2002), the activity of the complex may be regulated by CRAF, as it also acts as an effector of BRAF (Wan et al. 2004). Therefore, finding viral proteins that become specific substrate of the RAF kinases in infected cells may support anti-glioma therapeutic virotherapies.

The parvovirus capsid is composed of 60 protein subunits (named VP) folded in an eight-stranded antiparallel β -barrel motif (Tsao et al. 1991). From their synthesis in the cytoplasm, the VP proteins undergo a well-regulated assembly process that leads to the maturation of the infectious particle in the nucleus of permissive cells. In MVM, the VP1/VP2 capsid proteins are synthesized at an approximate 1/5 ratio, and rapidly assemble into two types of trimers in the cytoplasm at stoichiometric amounts (Rioloobos et al. 2006). As outlined in Figure 5, in mammalian permissive cells these trimers are translocated into the nucleus driven by two nuclear-targeting sequences: (i) a non-conventional structured nuclear localization motif (NLM) evolutionary conserved in the parvovirus β -barrel (Lombardo et al. 2000); and (ii) a conventional nuclear localization sequence (NLS) found in the VP1 N-terminus (Lombardo et al. 2002; Vihinen-Ranta et al. 2002).

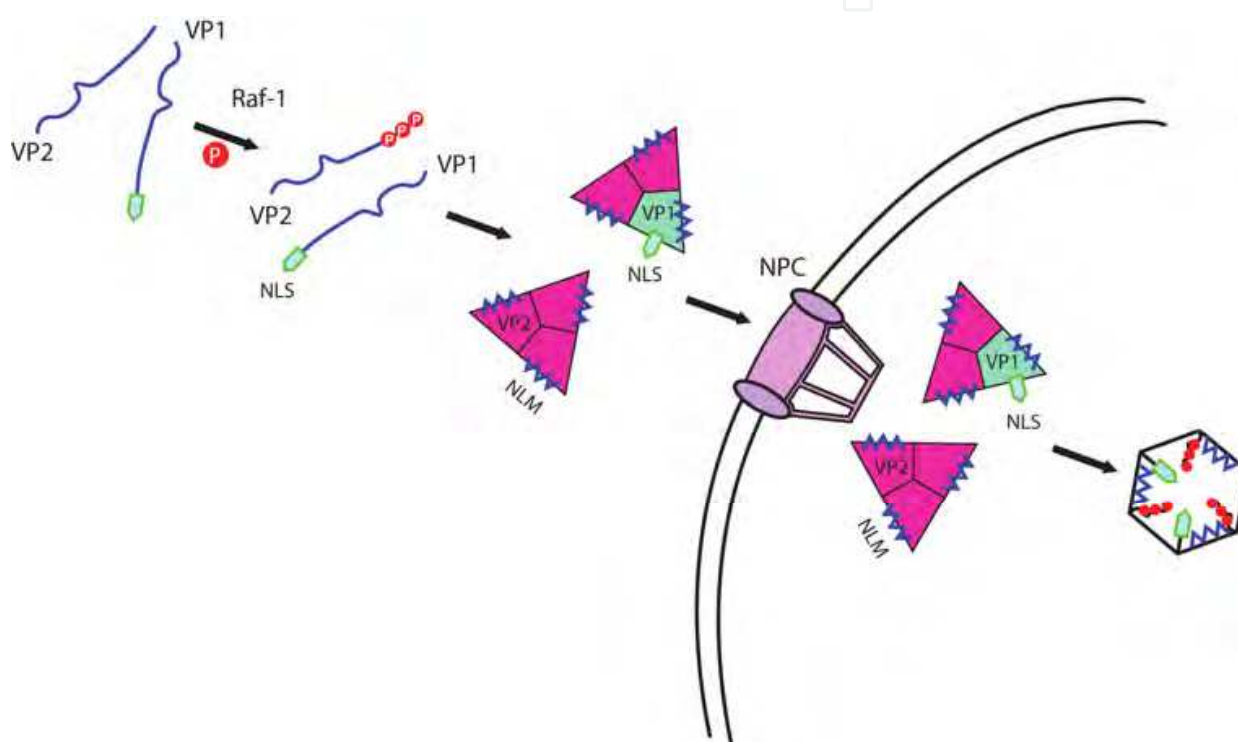


Fig. 5. Role of Raf-1 (C-Raf) in the nuclear transport of MVM capsid assembly intermediates. MVM capsid proteins (VP1 and VP2) assemble into two types of trimers at their 1/5 stoichiometry of synthesis. Trimers gain nuclear transport competence upon cytoplasmic Raf-1 phosphorylation (VP2 N-terminus is a major phosphorylated domain), and are driven into the nucleus by the NLM and NLS sequences exposed to the transport machinery. Inside the nucleus the fully assembled icosahedral capsid harbors the NLS and NLM facing to the particle inward. Abbreviations: NPC, nuclear pore complex; NLM, nuclear localization motif; NLS, nuclear localization sequence (based on Lombardo et al. 2000; Maroto et al. 2000; Rioloobos et al. 2006; Rioloobos et al. 2010).

The VP proteins of MVM undergo cytoplasmic phosphorylation by the Raf-1 kinase (Rioloobos et al. 2010). Raf-1 (or C-RAF) (72-74 kDa) is a cytoplasmic major protein isoform of the conserved MAPK signaling module with intrinsic serine-threonine kinase activity. The phosphorylation of the VP capsid subunits by Raf-1 occurs at specific Ser/Thr sites *in vitro* yielding a characteristic 2-D phosphopeptides map found in the MVM infections (Maroto et

al. 2000). The important role of Raf-1 phosphorylation in VP nuclear transport is best illustrated in heterologous cell systems devoid of Raf-1. For example, the expression of parvovirus VP proteins in insect cells resulted in non-phosphorylated VP trimers and aggregates (Riolobos et al. 2010) that, although at low efficiency, self-assembled into virus-like particles (VLPs) accumulating in the perinuclear region of the cytoplasm (Hernando et al. 2000; Yuan and Parrish 2001). However the co-expression of a constitutively active Raf-1 kinase in the insect cells, as the truncated mutant Raf-22W with transforming activity (Stanton et al. 1989), restored the phosphorylation and nuclear transport competence of the VP trimer (Riolobos et al. 2010).

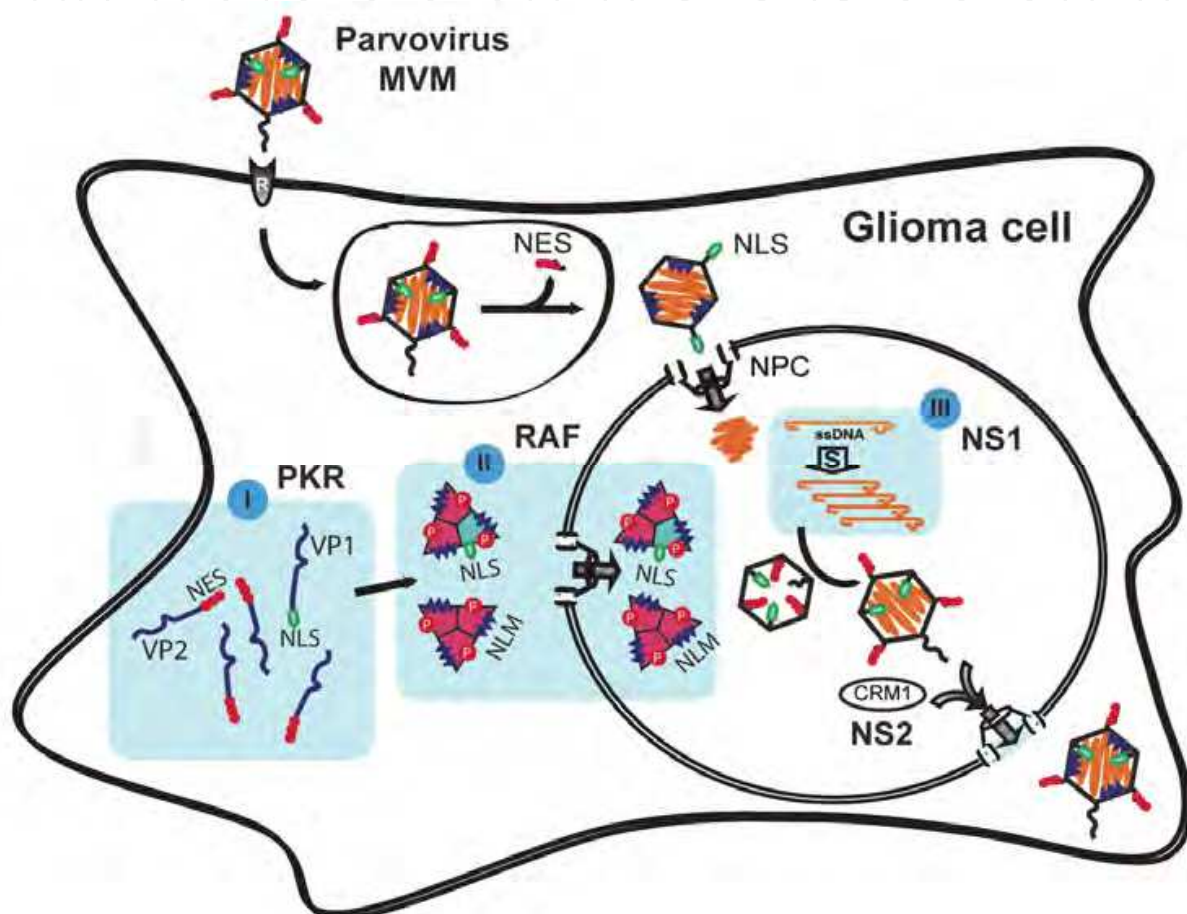


Fig. 6. Molecular overview of parvovirus MVM life cycle steps in glioma cells. **Virus Entry:** VP2 cleavage, Phospholipase activity and VP1 NLS externalization are required to deliver the genome across the NPC. **Capsid Assembly:** VP synthesis, phosphorylation and assembly into trimers lead to translocation into the nucleus by the NLM and NLS signals. **Maturation and Egress:** Viral DNA is amplified in the S phase and encapsidation presumably occurs in pre-assembled empty capsids. DNA-filled virions actively egress from the nucleus by the NES at VP2 n-terminus and CRM1-NS2-Nucleoporins mediation. For three processes (I, II, III), the cellular and viral factors found involved in the regulation of glioma-parvovirus interactions, are highlighted. NLS, nuclear localization sequence; NLM, nuclear localization motif; S, cell cycle dependent DNA synthesis; NES, nuclear export sequence; NPC, nuclear pore complex. CRM1, nuclear export factor (adapted with modifications from Maroto et al. 2004, and Valle et al. 2006).

The enhanced VP nuclear transport and MVM capsid assembly by oncogenic deregulated Raf-1 should facilitate parvovirus maturation in cancer cells. Indeed, in rat C6 and human U373MG glioblastoma cells infected with MVM, the characteristic pattern of VP phosphorylation by Raf-1 was conserved, correlating with a high activity of the MAPK signaling pathway (Riolobos et al. 2010). Moreover these glioblastomas were efficiently killed by MVM and the virus underwent productive maturation to high yields (Rubio et al. 2001). Given the difficulties encountered in searching effective chemotherapies against the Raf signaling cascade for cancer treatment (Madhunapantula and Robertson 2008; Newton 2010), the above mentioned findings may support MVM and related parvoviruses as replicative inhibitors specifically targeting glioblastomas with deregulated Raf signaling.

6. Conclusions

We have summarized in this chapter some molecular mechanisms involved in glioma-MVM interactions. Figure 6 illustrates some major events of MVM life cycle, highlighting those three steps at which the interaction of this parvovirus with glioma cells was found to be modulated. Final comments related to these findings are in brief : (i) Identifying the relevance of PKR translational control for MVM cytotoxic infection in U373MG glioblastoma, connects the parvoviral oncolysis with a common mechanism exhibited by other oncolytic viruses to preferentially infect tumour cells with deregulated IFN and other innate antiviral responses; (ii) Raf-1 requirement for MVM nuclear capsid assembly not only assigns parvoviral oncolysis to an important kinase upregulated in human cancer, but also underlies a novel general mechanism to be exploited in oncolytic virotherapy; (iii) the lack of correlation between NS1-mediated MVM replication and gene expression may be important to better understand the cellular machinery regulating these processes in normal vs. tumour cells. It is likely that other signals and mechanisms tightly regulated during MVM life cycle steps (see Figure 6) be also found perturbed in cancer cells, what could provide additional targets for anti-glioma intervention.

Finally, the dependence of parvovirus infection on cellular factors which are functionally dysregulated in a cancer-specific manner may bring two important benefits: (i) the use of parvoviruses as markers of host-cell perturbations (e.g. signaling) coupled to transformation, and (ii) it may allow to apply these simple viruses as specific therapeutic agents against precise types of glioblastomas showing permissive genetic profiles, toward a personalized parvoviral anti-cancer virotherapy.

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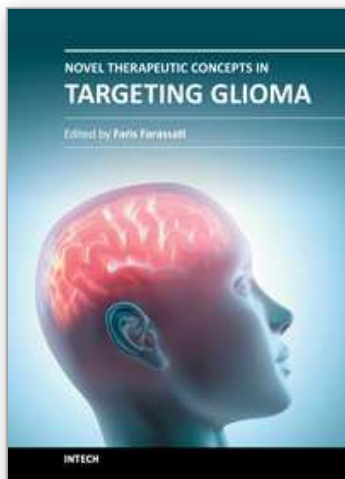
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