MOLECULAR RESPONSES OF U87-GLIOBLASTOMA MULTIFORM CANCER STEM CELLS TO HSV-G47Δ ONCOLYTIC VIRUS IN NORMOXIA AND HYPOXIA TUMOR MICROENVIRONMENTS

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Among young adults, Glioblastoma (GBM, WHO IV astrocytoma) is the most common and aggressive form of primary brain tumor and it is highly invasive with the potential to spread to the central nervous system. Despite the current standard therapies, which include surgery, chemotherapy and radiation, it is still considered a deadly disease. The mean survival rate of glioblastoma patients is 12-14 months. The GBM cancer stem cell subpopulation within tumor processes play a critical role in tumor initiation, progression, and local recurrence and which are resistant to standard therapies. Different genetic pathways such as *PI3K/AKT*, *RTK/RAS*, *p53*, *RB*, *PKR*, Apoptosis, telomerase, telomere length alterations, autophagy, mitophagy, angiogenesis and multiple functional of noncoding RNAs including microRNAs and Lung non coding RNAs are involved in GBM progression and its invasion. Resistance to chemotherapy treatment can occur in low tumor oxygenation environment (hypoxia). As a novel therapeutic strategy for GBM treatment, live and engineered oncolytic viruses such as HSV-G47 delta (a 3rd generation of HSV-1 with $ICP6^-$, $\gamma 34.5^-$, $\alpha47^-$, lac Z^+) with limited toxicity are applied, and they can specifically target apoptosis-resistance cancer stem cells without cross-resistance with existing therapies; hence, the normal cells are spared.

Although the HSV-G47Δ oncolytic virus has been applied to treat different kinds of solid tumors such as glioblastoma, its molecular targets in U87-GBM CSCs were in a Curtain of ambiguity. Therefore, PI3K/AKT, RTK/RAS, p53, RB, PKR, Apoptosis, telomerase, telomere length alterations, autophagy, mitophagy, angiogenesis, and non-coding RNAs were the main objective pathways that were evaluated by HSV-G47Δ oncolytic virus in normoxia and hypoxia tumor microenvironments. To achieve this purpose, First, GBM-CSCs neurospheres were isolated in DMEM/F12 serum free media and characterized using

monoclonal antibodies (CD133-PE, CD44-FITC and DAPI staining) by immunocytochemistry method. Flow cytometry was conducted for apoptosis and cell cycle distribution. Cell viability assay and CPE effects were performed using a standard protocol. Different genetic pathways (mentioned above) were evaluated at the level of mRNA expression in normoxia and hypoxia niches exposed to HSV-G47Δ oncolytic virus using a custom RT^{2}Profiler™ PCR Array and Q-PCR methods. In-silico pathway analysis was performed using online bioinformatics tool (GENE-MANIA) to detect physical and genetic interactions between dysregulated genes. Findings showed that GBM-CSCs could be specifically targeted by HSV-G47Δ oncolytic virus in both microenvironments and the cells were arrested at early stage of apoptosis and G0/G1 cell cycle. Furthermore, results indicated that HSV-G47Δ is more effective when the glioblastoma cancer stem cells are in hypoxic condition. Out of 169 evaluated genes of different pathways, 51genes were significantly in dysregulated pattern when GBM-CSCs exposed to HSV-G47Δ. One of the impressive results of the study was the effects of HSV-G47∆ virus on telomere length alterations with had increased under normoxic condition while a significant telomere shortening was observed when the U87-CSCs were exposed to HSV-G47∆ virus in hypoxic.

Data showed that out of forty three miRNAs, eight miRNAs including *miR-7-1, miR-let-7b, miR-130a, miR-137, miR-200b, miR-221, miR-222* and *miR-874* were significantly over expressed in normoxic microenvironment. Expression level of LncRNAs including *LEF1-AS1, MALAT1, LINC00470, TUSC7, HOTAIR*, *NEAT1* and *XIST* were significantly down regulated in hypoxic microenvironment and H19 did not have any dysregulated pattern in this niche. In normoxic condition, *LEF1-AS1, MALAT1, LINC00470, H19, HOTAIR, NEAT1* and *XIST* were under regulated and *TUSC7* was not targeted by HSV-G47∆. Furthermore, in hypoxic conditions, *PERK, ING-G, LC3, MFN2, PINK-1*, and *PARKIN* were significantly downregulated while *INF-G, P62, LC3,* and *PARKIN* were in the up-regulated pattern. The findings revealed that high-grade glioblastoma cancer stem cells were potentially controlled by HSV-G47∆ oncolytic virus in both autophagy and mitophagy pathways at hypoxic conditions. Our results also showed the expression of the majority of genes in MDR pathway (Exception *DKC1*down regulated) were significantly up in GBM-CSCs when the cells were inoculated with HSV-G47Δ (MOI=1,14h) in normoxic condition while most genes were down regulated under HSV-G47Δ (MOI=1,14h) in hypoxic condition. Pathway analysis showed genetic and physical interactions among dysregulated genes in both microenvironments in the most biological pathways.

In conclusion, HSV-G47Δ has a therapeutic potential to control crucial mechanisms in GBM-CSCs progression and could be considered as a promising strategy in GBM treatment, especially when the cells have a high grade of tumorigenicity in hypoxic niche.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

TINDAKBALAS MOLEKULAR STEM SEL KANSER U87-GLIOBLASTOMA PELBAGAI TERHADAP VIRUS ONKOLITIK HSV-G47Δ DI PERSEKITARAN NORMOKSIA DAN HIPOKSIA

Oleh

REZA VAZIFEHMAND RODPOSHTEI

April 2021

Pengerusi : Profesor Zamberi bin Sekawi, PhD
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Di kalangan orang muda, Glioblastoma (GBM, WHO IV astrocytoma) adalah sejenisketumbuhan otak asas yang paling biasa dan agresif. Ia mempunyaipotensi untuk merebak dengan cepat sehingga mencapai sistem saraf pusat. Walaupun pembedahan, kemoterapi dan radiasi digunakan sebagai terapi umum, glioblastoma masih dianggap sebagai penyakit yang boleh membawa maut. Purata Kadar kelangsungan hidup pesakit glioblastoma adalah 12-14 bulan. Subpopulasi sel stem kanser GBM dalam proses ketumbuhan memainkan peranan penting dalam permulaan tumor, perkembangan, dan pengulangan tempatan (local recurrence) and rawatan standard tidak memberi keputusan yang baik. Laluan genetik yang berbeza seperti *PI3K / AKT, RTK / RAS, p53, RB, PKR,* Apoptosis, telomeras, kepanjangan telomer, autopagi, mitopagi, angiogenesis dan pelbagai fungsi RNA bukan pengekodan termasuk microRNAs dan RNA bukan pengkod paru-paru terlibat dalam perkembangan dan perebakan GBM . Rawatan menggunakan kemoterapi sering tidak berjaya dan ini berlaku di persekitaran oksigenasi ketumbuhan kecil (hipoksia). Sebagai strategi terapi baru untuk rawatan GBM, virus onkolik hidup dan rekayasa seperti HSV-G47 delta (generasi ke-3 HSV-1 dengan ICP6-, ɣ 34.5-, α47-, lac Z +) yang mempunyai toksik rendah digunakan, dan mereka mensasar sel stem barah ketahanan apoptosis tanpa rintangan silang menggunakan terapi yang sediaada; oleh itu, sel normal tidak terjejas.

Walaupun virus onkolitik HSV-G47Δ telah diterapkan untuk merawat pelbagai jenis ketumbuhan padat seperti glioblastoma, sasaran molekulnya dalam CSC U87-GBM tidak begitu jelas. Oleh itu, *PI3K / AKT, RTK / RAS, p53, RB, PKR*, Apoptosis, telomeras, perubahan dalam kepanjangan telome, autopagi, mitopagi, angiogenesis, dan non-coding RNAs adalah jalan masuk (pathway) yang dinilai oleh virus onkolitik= HSV-G47Δ dalam persekitaran ketumbuhan

mikro normoxia dan hipoksia. Untuk mencapai objektif ini, pertama, neurosfera GBM-CSC diasingkan dalam media bebas serum DMEM / F12 dan dicirikan menggunakan antibodi monoklonal (pewarnaan CD133-PE, CD44-FITC dan DAPI) menggunakan kaedah imunokimia. Sitometri aliran digunakan untuk apoptosis dan taburan kitaran sel. Ujian daya maju sel dan kesan CPE dilakukan menggunakan protokol umum. Jalur genetik yang berbeza (seperti di atas) dinilai pada tahap ekspresi mRNA pada persekitaran normoksia dan hipoksia yang terdedah kepada virus onkolitik HSV-G47Δ menggunakan kaedah RT^{2}Profiler ™ PCR Array dan Q-PCR khusus. Analisis jalur 'in-silico' dilakukan menggunakan bioinformatik dalam talian (GENE-MANIA) untuk mengesan interaksi fizikal dan genetik antara gen yang tidak teratur. Hasil kajian menunjukkan bahawa GBM-CSC secara khusus disasarkan oleh virus onkolitik HSV-G47Δ di lingkungan mikro dan sel-sel ditangkap pada tahap awal apoptosis dan kitaran sel G0 / G1. Selanjutnya, hasil menunjukkan bahawa HSV-G47Δ lebih berkesan apabila sel stem kanser glioblastoma berada dalam keadaan hipoksia. Daripada 169 gen yang dievaluasi dari jalur yang berbeza, 51 gen secara signifikan berada dalam keadaan tidak teratur ketika GBM-CSC terdedah kepada HSV-G47Δ. Salah satu hasil kajian yang signifikan adalah kesan virus HSV-G47Δ terhadap kepanjangan telomer dalam persekitaran normoksik dan pemendekan telomer yang ketara diperhatikan bila U87-CSC terdedah kepada virus HSV-G47Δ dalam persekitaran hipoksia.

Data menunjukkan daripada 43 (empat puluh tiga) miRNA, lapan miRNA termasuk *miR-7-1, miR-let-7b, miR-130a, miR-137, miR-200b, miR-221, miR-222* dan *miR-874* meningkat secara ketara dalam persekitaran normoksik mikro. Tahap ekspresi LncRNA termasuk *LEF1-AS1, MALAT1, LINC00470, TUSC7, HOTAIR, NEAT1* dan *XIST* di kawal selia dengan ketara dalam lingkungan mikro hipoksia dan H19 tidak mempunyai corak yang berbeza dalam ceruk ini. Di dalam persekitaran normoksik, *LEF1-AS1, MALAT1, LINC00470, H19, HOTAIR, NEAT1* dan *XIST* diatur dan *TUSC7* tidak disasarkan oleh HSV-G47Δ. Selanjutnya, dalam keadaan hipoksia, *PERK, ING-G, LC3, MFN2, PINK-1*, dan *PARKIN* disaksikan terteratur dengan ketara sementara *INF-G, P62, LC3*, dan *PARKIN* berada dalam corak yang dikawal selia. Hasil kajian menyaksikan sel stem barah glioblastoma peringkat tinggi mempunyai potensi dikendalikan oleh virus onkolitik HSV-G47Δ pada kedua-dua jalur autofagus dan mitofagi dalam persekitaran hipoksia. Hasil kajian kami juga menunjukkan ekspresi majoriti gen dalam jalur MDR meningkat secara signifikan dalam GBM-CSCs bila sel-sel dionokulasi dengan HSV-G47Δ (MOI = 1,14h) dalam keadaan normoksik sementara kebanyakan gen turun dikawal selia di bawah HSV-G47Δ (MOI = 1,14j) dalam persekitaran hipoksia. Analisis laluan menunjukkan interaksi genetik dan fizikal antara gen yang tidak terkawal (dysregulated genes) di kedua-dua persekitaran mikro di kebanyakan laluan biologi.

Kesimpulannya, HSV-G47Δ memiliki potensi terapeutik untuk mengawal mekanisme penting dalam perkembangan GBM-CSC dan ia boleh dianggap sebagai strategi baru yang mempunyai potensi dalam rawatan GBM, terutamanya bila sel-sel memiliki tingkat tumorigenitas yang tinggi dalam ceruk hipoksia.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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ATCC	American type culture collection
BBB	Blood brain barrier
cDNA	Complementary DNA
CSCs	Cancer stem cells
CPE	Cytopathic effects
D-Loop	Displacement loop
GBM	Glioblastoma Multiform
HGG	High grade glioblastoma
HIF	Hypoxia inducible factor
HSV	Herpes simplex virus
kb	Kilo bases
LGG	Low grade glioblastoma
lncRNAs	Long non coding RNAs
MDR	Multi drug resistance
MIP	Microscopic image processing
miRNAs	MicroRNAs
MOI	Multiplicity of infection
mRNA	Messenger ribonucleic acid
nc-RNAs	Non-coding RNAs
OVs	Oncolytic viruses
PCR	Polymerase chain reaction
SPA	Scatter plot analysis
T-Loop	Telomere loop
TMZ	Temozolomide
WHO	World health organization

CHAPTER 1

INTRODUCTION

In young adults, Glioblastoma (GBM, WHO IV astrocytoma) is the most common and active form of primary brain tumor which grows rapidly targeting the central nervous system (Hanif, Muzaffar, Perveen, Malhi, & Simjee, 2017). It is also highly invasive and heterogeneous influencing therapeutic responses (Neilsen et al., 2019). Exhaustive genetic analysis has shown a variety of deregulated pathways involved in GBM pathogenicity (Martínez, 2012). With the current standard therapies that include surgery, chemotherapy and radiation, the mean survival rate of glioblastoma patients is 12-14 months. (Ohka, Natsume, & Wakabayashi, 2012a). Despite treatment, their prognosis is very poor. The GBM cancer stem cells subpopulation within the tumor processes have the ability for infinite and multi potency thus it is assumed they play a critical role in the tumor initiation, progression, local recurrence of GBM cancer while being resistant to standard therapies (Codrici, Enciu, Popescu, Mihai, & Tanase, 2016). Hypoxia known as low oxygenation (Anoxic) of solid tumors (PO2 less than 2.5mmHG) is a major concern in glioblastoma cancer treatment since it promotes chemo-radiotherapy resistance (Vaupel & Mayer, 2007).

Telomeres and telomerase play a critical role in abnormal proliferations, metastasis and stemness maintenance (J. Lee et al., 2006). Evidences showed telomerase are expressed in GBM-CSCs and the telomere length are around 3.5kb - three times shorter than the normal human brain cells (Diane E. Handy, Rita Castro, 2011). Telomeres are located at both ends of a chromosome with a nucleoprotein structures composed of a non-coding, repetitive DNA sequence, and they have six kinds of proteins called shelterin complex (Blasco, 2007)(Blasco, 2007) These proteins control the length of the telomere and protect them from degradation(Blackburn, 2010).With the help of the shelterin complex overhanging the single stranded DNA at the very end of all telomeres, two structures known as T-loop (protective cap) and D-loop (displacement loop) are formed (Diotti & Loayza, 2011). De novo repetitive telomeric sequence add to telomeric ends via telomerase enzyme which is a unique transcriptase enzyme (Greider, 2010). Telomerase maintains the length of telomeres (Greider, 2010). It is well-known that different levels of hypoxia regulate telomere length and telomerase activity (Guan, Wei-Ping, Maeda, & Makino, 2011). A study has shown that telomerase activity and short telomere length in glio-asterocytoma tumors are significantly associated with histological potential progression and tumorigenicity (Hiraga et al., 1998a). Despite the existence of many therapies to fight glioblastoma multiform, it is still a deadly disease which has an extremely poor diagnosis (Hanif et al., 2017). Studies have revealed that telomeres and telomerase activity could be an attractive target for cancer therapy (Picariello, 2014).

A large number of studies have pointed to two groups of small non-coding RNAs (ncRNAs) including microRNAs (17-22 nucleotides) and long non-coding RNAs (ln RNAs) >200 nucleotides, deep involvement in glioblastoma global biological process, such as pathogenesis, tumor initiation, progression, proliferation, invasion, angiogenesis, apoptosis, and resistance to chemo-radiotherapy (Rynkeviciene et al., 2019; Stahlhut & Slack, 2013). MicroRNAs(miRNAs) are short, single stranded RNA that post-transcriptionally regulate gene expression (Y. S. Lee & Dutta, 2009; Londina et al., 2015). miRNAs produced in the nucleus are pri-miRNA and they are processed into pre-miRNA that is exported to the cytoplasm by exportin-5 and converted to a mature miRNA by Dicer complex and exert their action by targeting 3′ untranslated region (3′-UTR) of mRNA resulting in inhibition of protein synthesis (Bentwich et al., 2005; Berezikov et al., 2005). Figure 1 shows the biogenesis and function process of miRNAs. LncRNAs as non-coding protein exert their biological function at transcriptional, post-transcriptional and epigenetic levels (Mercer, Dinger, & Mattick, 2009). They are also involved in gene expression regulation via multiple mechanisms, such as chromatin modifications, alternative splicing, mRNA stability and interaction with miRNAs (Fernandes, Acuña, Aoki, Floeter-Winter, & Muxel, 2019). Dysregulation of specific lncRNAs play a crucial role in glioblastoma progression and malignancy (X. Zhang et al., 2012). Non-coding RNAs can potentially be applied as therapeutic targets for GBM treatment (Dews et al., 2006; X. Zhang et al., 2012; Qi & Du, 2013).

Under various stimulation factors, an autophagy pathway can be activated as a cytoprotective response to help cells overcome those stressful situations (Singh & Cuervo, 2011). It has been shown that glioblastoma promotes the survival and proliferation of tumor cells (Piao et al., 2012). Autophagy is a lysosome-dependent degradation pathway whereby the cells recycle their damaged cytoplasmic content, such as lipids, proteins and organelles (Vessoni, Muotri, & Okamoto, 2012). There is ample evidence that point to essential role of autophagy in the maintenance and self-renewal of glioblastoma cancer stem cells (Galavotti et al., 2013). Mitophagy on the other hand is a selective autophagy process that promotes cancer cell survival, tumorigenesis and chemo resistance phenotype by removing abnormal mitochondria, and reduction of overall mitochondrial mass in response to certain stress factors such as hypoxia (Chourasia, Boland, & Macleod, 2015; Vara-Perez, Felipe-Abrio, & Agostinis, 2019). Microvascular proliferation, Multi-drug resistance, epithelial-to-mesenchymal transition (EMT), tumor metabolic reprograming are various mechanisms by which GBM tumor stem cells avoid therapy (Iser, Pereira, Lenz, & Wink, 2017; Pengse Po1, Erin Delaney1, Howard Gamper2, Miklos Szanti-Kis3, Lee Speight3, LiWei Tu1, Andrey Kosolapov1, E. James Petersson3, Ya-Ming Hou2, 2017; Schmalz, Shen, & Park, 2011; W. Zhou & Wahl, 2019).

Despite promising therapies in GBM over the past three decades, there is a risk of relapse phenotype recurrence. Therefore, more effective therapeutic approaches to treat GBM is of critical importance. Among GBM treatment options, oncolytic virotherapy (OV) is promising (Wollmann, Ozduman, & Van Den Pol, 2012a).

Oncolytic viruses (OVs) are either genetically engineered or naturally occurring that selectively replicate in the cancer cells and kill them without harming normal tissues (Fukuhara, Ino, & Todo, 2016). HSV-G47Δ is an engineered oncolytic virus (3rd generation of HSV-1) with three different mutations including ICP6-, ɣ34.5-,α47- and lac Z+, that have been recently used to treat various tumors, particular brain tumors (Eissa et al., 2018).

Logical interaction between two or more genes can affects the phenotype of cells that can identified using various types of bioinformatics tools. The ultimate goals of gene-gene interactions are to recognize gene functions, identify pathways and discover potential drug targets(Koo, Liew, Mohamad, Hakim, & Salleh, 2013). GeneMANIA is a flexible, user-friendly web interface for generating hypotheses about gene function, analyzing gene lists and prioritizing genes for functional assays(Warde-farley, Donaldson, Comes, Zuberi, Badrawi, et al., 2010).The mechanism of molecular targeting of HSV-G47Δ is still in a grey zone and therefore, this study was undertaken to evaluate the expression pattern of genes involved in GBM progression pathways. Furthermore, Gene-gene interactions will be evaluated using GENEMANIA bioinformatics tool.

The objectives of the current research study were as follows:

1. To detect molecular responses of U87-GBM-CSCs to HSV-G47Δ oncolytic virus focusing on apoptosis, cell cycle distribution and PI3K /AKT, RTK/RAS, p53, RB, PKR signaling pathways using Flowcytometry and Array-PCR method.
2. To detect effects of HSV-G47Δ oncolytic virus on telomerase and telomere length alterations using Q-PCR method.
3. To detect noncoding RNA responses to HSV-G47Δ on GBM-CSCs in normoxia and hypoxia tumor environments using QPCR method.
4. To detect HSV-G47Δ effects on GBM-CSCs in autophagy and mitophagy pathways in normoxia and hypoxia microenvironments using Q-PCR method.
5. To detect molecular responses of GBM-CSCs to HSV-G47Δ oncolytic virus in normoxia and hypoxia tumor microenvironments, focusing on angiogenesis, multiple drug resistance, Epithelial-to-mesenchymal transition and metabolic pathways using Q-PCR method

Hypothesis

HSV-G47Δ oncolytic virus significantly targets U87-GBMCSCs in different GBM biological pathways and has ability to control GBM progression.

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