ANTICANCER RESEARCH *35*: 6373-6378 (2015)

Review

Curcumin for the Treatment of Glioblastoma

LAURA A. SORDILLO, PETER P. SORDILLO and LAWRENCE HELSON

SignPath Pharma, Inc., Quakertown PA, U.S.A.

Abstract. *Glioblastoma multiforme is a highly aggressive primary cancer of the brain associated with a poor prognosis. Modest increases in survival can sometimes be achieved with the use of temozolomide and radiation therapy after surgery, but second-line therapy after recurrence has a limited efficacy. Curcumin has demonstrated promising results against this form of cancer in experimental models. The reported activity of curcumin against cancer stem cells, a major cause of glioblastoma resistance to therapy, and its ability to augment the apoptotic effects of ceramides, suggest it would have a synergistic effect with cytotoxic chemotherapy agents currently used in second-line therapy, such as lomustine.*

Glioblastoma [glioblastoma multiforme, (GBM)] is a highly malignant (grade IV) tumor arising from astrocytes. Approximately 15% of all primary brain tumors are GBM. GBM may arise *de novo* or, occasionally, from a low-grade astrocytoma. Genetic abnormalities are common (1-4). Median survival with treatment is 15 months, with a two-year survival rate of less than 25%. Survival without treatment is usually only a few months (5-8). Frequent presenting signs include headaches, nausea, seizures, blurred vision, vomiting, and personality changes. Standard treatment is a combination of surgery, radiotherapy, and chemotherapy. The effectiveness of surgery is limited by the difficulty of complete tumor resection and presence of residual tumor cells (9-11). If surgical ablation is not an option due to tumor size, tumor location, or very poor patient performance status, a combination of radiation and chemotherapy is used.

Correspondence to: Lawrence Helson, MD, SignPath Pharma, Inc., 1375 California Road, Quakertown PA 18951, U.S.A. Tel: +1 2155389996, Fax: +1 2155381245, e-mail: lhelson@comcast.net

Key Words: Glioblastoma, curcumin, lomustine, cancer stem cells, ceramide, blood–brain barrier, combination chemotherapy, lipophilic agent, review.

Standard Chemotherapy

Temozolomide is an oral alkylating agent which is an imidazotetrazine derivative of dacarbazine. It crosses the blood–brain barrier and is, in combination with radiation, the most frequently used first-line treatment given following surgery for malignant glioma (12-15). The addition of temozolomide to radiation therapy increases patient median survival by 2 to 3 months. In one randomized trial, median survival with this combination was 14.6 months compared to 12.1 months with radiation therapy alone (16-18). Two other agents, bevacizumab, which suppresses angiogenesis, and lomustine, have frequently been used as second-line therapy (19-23). Lomustine is a lipid-soluble, alkylating nitrosourea which also crosses the blood–brain barrier (21-25). However, treatment with these agents results in only minor increases in survival, and overall survival rates remain low, with fewer than 10% of patients alive at 5 years after diagnosis (18, 26). Due to the highly resistant and aggressive nature of GBM, new treatments are required.

Curcumin

Curcumin (diferuloylmethane) is the principal curcuminoid of turmeric, the Indian spice derived from the plant *Curcuma longa* Linn. Curcumin absorbs light with a wavelength maximum at approximately 420 nm, thus giving turmeric its yellow color. Curcumin has been shown to have antioxidant, anti-infective and anticancer effects, and its use is being investigated in diseases as diverse as diabetes (27), Alzheimer's disease (28), hepatitis (29) and rheumatoid arthritis (30). When orally administered, it is non-toxic and safe (31-35). Curcumin has numerous mechanisms of action, including suppression of pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)1, IL6, IL8, and affects multiple signaling pathways including wingless-related integration site (WNT), NOTCH, mitogen-activated protein kinase, hedgehog and Janus kinase/signal transducer and activator of transcription (JAK/STAT) (36-41). Curcumin is highly lipophilic, and crosses the blood–brain barrier (42, 43).

Curcumin and GBM

The potential benefits of curcumin as a treatment for GBM have been studied by numerous groups (44-49). Aoki *et al*. showed that curcumin induced autophagy by suppression of the protein kinase B (AKT)/mammalian target of rapamycin (mTOR)/p70S6K and activation of the extracellular-signal-regulated kinase (ERK1/2) pathways in U87-MG and U373-MG human malignant glioma cells harboring a phosphatase and tensin homolog (*PTEN*) mutation. Similar results were seen in KBM-5 human leukemia cells (50). Choi *et al*. reported that curcumin activates p21 in U87-MG human GBM cells *via* ERK and c-JUN N-terminal protein kinase signaling (51). Senft *et al*. studied cell lines from human primary and recurrent GBM, and showed that curcumin reduced cell growth, inhibited migration and decreased invasiveness due to its inhibition of the JAK/STAT3 pathway (52). Similarly, Dhandapani *et al*. showed that curcumin enhanced cell death by reducing the activity of activator protein 1 and nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 binding in human and rat glioma cell lines (53). Zanotto-Filho *et al*. showed that in the C6 implant rat glioma model, curcumin caused reduction in brain tumor volume (54). Perry *et al*. showed that curcumin can suppress growth of human glioma U87 cells xenografted into athymic mice (55).

The effects of curcumin on GBM stem cells may also be important. Beier *et al*. showed that detoxifying enzymes such as O6-methylguanine-DNA-methyltransferase may confer intrinsic resistance of cancer stem cells to alkylating agents (56). Other researchers have also suggested a key role for stem cells in GBM formation and resistance to alkylating agent therapy (57, 58). Fong *et al*. studied rat C6 glioma cells, and showed that curcumin may have the potential to target cancer stem cells (59). Zhuang *et al*. found that curcumin induced differentiation of glioma-initiating cells and inhibited their growth *via* autophagy (60).

Curcumin: Alternate Delivery Mechanisms

Recently, new mechanisms have emerged, and engendered methods of improving the efficacy of curcumin (61-65). These methods may prove superior because of their ability to deliver greater doses of curcumin to the tumor. Nano-sized capsules of curcumin have been used as a treatment of GBM cells. Lim *et al*. have shown that curcumin nanoparticles can slow-down GBM growth through the inhibition of cell proliferation and a reduction in stem-like tumor cells (66). Langone *et al*. have shown that curcumin coupled to a monoclonal antibody caused a 120-fold increase in the death of human GBM cells in culture compared to curcumin alone. In addition, mice implanted with GBM cells had an extended survival time and a reduction in the size of the brain tumor mass with this treatment (67).

Rationale for Combination therapy

It is proposed that the optimal method of using curcumin is not as a single agent, but rather in combination with cytotoxic chemotherapy. Ramachandran *et al*. have shown that curcumin could be used to increase the therapeutic potential of temozolomide or of etoposide in brain tumor cell lines (68). Yin *et al*. investigated the use of a combination of curcumin and temozolomide in U87-MG GBM cell lines and in xenograft mouse models, and found that curcumin enhanced the effects of temozolomide by generating reactive oxygen species production, and by suppressing phosphorylated AKT and mTOR, thus causing cell death (69). Zanotto-Filho *et al*. showed that curcumin increased the cytotoxic effects of doxorubicin and cisplatin on GBM cells (70). Wu *et al*. showed that curcumin enhanced temozolomide cytotoxicity against human GBM cells (71). It has been reported that curcumin and paclitaxel act synergistically with much greater activity than seen with each individual agent in increasing the B-cell lymphoma like protein 4/B-cell lymphoma 2 ratio, increasing cytochrome *c*, reducing angiogenesis and causing apoptosis of HBTSC, LN18 and U138-MG cells (72).

These results suggest that the use of curcumin should be investigated in clinical trials of patients with GBM, ideally as a second-line therapy after failure of radiation therapy and temozolomide, and that the optimal method for using curcumin in this setting may be in combination with an established cytotoxic chemotherapy agent with activity against GBM such as carmustine or lomustine. As noted, it appears that a major reason for the very limited efficacy of alkylating agents in established tumors is the resistance of GBM stem cells to therapy. Our previous work and those of others has suggested that curcumin may be effective in reducing or eliminating the population of cancer stem cells, either by causing apoptosis or differentiation (73-76), while conventional chemotherapy alone is ineffective against stem cells, resulting in tumor recurrence even following initial response (77). Furthermore, curcumin may also increase the activity of cytotoxic chemotherapy against mature tumor cells. Curcumin has been shown to enhance ceramide production by increasing the activity of enzyme ceramide synthase (78). It has been suggested that the progression of GBM is caused by a decrease in ceramide levels (79). Increased activity of glucosylceramide synthase, an enzyme that causes a decrease in ceramides, has been associated with GBM progression and resistance to temozolomide (80). In contrast, acid sphingomyelinase, which hydrolyzes sphingomyelin to ceramide and phosphorylcholine, has been shown to sensitize glioma cell lines to chemotherapy or radiation therapy (81, 82). The combination of curcumin and chemotherapy has also been shown to have a synergistic effect on the generation of reactive oxygen species in GBM cell lines and in mouse xenografts (69). This may be an

additional mechanism by which GBM cell destruction might be enhanced, since reactive oxygen species are known to increase acid sphingomyelinase activity and, in consequence, ceramide levels (83-85).

Conflicts of Interest

Dr. Peter Sordillo is a member of the Scientific Advisory Board of SignPath Pharma, a developmental stage biotechnology company that is studying liposomal curcumin, liposomes and other agents. Dr. Helson is CEO of SignPath Pharma. Laura Sordillo reports no conflicts.

References

1 Virk SM, Gibson RM, Quinones-Mateu ME and Barnholtz-Sloan JS: Identification of variants in primary and recurrent glioblastoma using a cancer-specific gene panel and whole exome sequencing. PLos ONE *10(5)*: e0124174, 2015.

2 Tang C, Guo J, Chen H, Yao C, Zhuang D, Wang Y, Tang W, Ren G, Wu J, Mao Y and Zhou L: Gene mutation profiling of primary glioblastoma through multiple tumor biopsy guided by 1H-magnetic resonance spectroscopy. Int J Clin Exp Pathol *8(5)*: 5327-5335, 2015.

3 Taylor T, Fumari F and Cavenee W: Targeting EGFR for treatment of glioblastoma: molecular basis to overcome resistance. Curr Cancer Drug Targets *12(3)*: 197-209, 2012.

4 Arif SH, Pandith AA, Bhat AR, Ramzan AU, Malik NK, Chibber SS, Wani AA, Tabasum R and Kirmani A: EGFR and PTEN gene mutation status in glioblastoma patients and their prognostic impact on patient's survival. J Carcinog Mutagen 6:218, 2015.

5 American Brain Tumor Association. http://www.abta.org/brain-tumor-information/types-of-tumors/glioblastoma.html

6 National Brain Tumor Society. http://braintumor.org/brain-tumor-information/understanding-brain-tumors/tumor-types/

7 Shahar T, Nossek E, Steinberg DM, Rozovski U, Blumenthal DT, Bokstein F, Sitt R, Freedman S, Corn BW, Kanner AA, Ram Z: The impact of enrollment in clinical trials on survival of patients with glioblastoma. J Clin Neurosci *19*: 1530-1534, 2012.

8 Park JK, Hodges T, Arko L, Shen M, Iacono DD, McNabb A, Bailey NO, Kreisl TN, Iwamoto FM, Sul J, Auh S, Park GE, Fine HA, Black PM: Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clinical Oncology *28(24)*: 3838-3843, 2010.

9 Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, Raza SM, Pascual-Gallego M, Ibrahim A, Hernandez-Hermann M, Gomez L, Ye X, Weingart JD, Olivi A, Blakeley J, Gallia GL, Lim M, Brem H and Quinones-Hinojosa A: Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol *16*: 113-122, 2013.

10 McGirt MJ, Mukherjee D, Chaichana KL, Than KD, Weingart JD and Quinones-Hinojosa A: Association of surgically acquired motor and language deficits on overall survival after resection of glioblastoma multiforme. Neurosurgery *65(3)*: 463-469; discussion 469-470, 2009.

11 Brown PD, Maurer MJ, Rummans TA, Pollock BE, Ballman KV, Sloan JA, Boeve BF, Arusell RM, Clark MM, Buckner JC: A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. Neurosurgery *57(3)*: 495-504, 2005.

12 Mason WP and Cairncross JG: Drug insight: temozolomide as a treatment for malignant glioma--impact of a recent trial. Nat Clin Pract Neurol *1*: 88-95, 2005.

13 Nagasawa DT, Chow F, Yew A, Kim W, Cremer N and Yang I: Temozolomide and other potential agents for the treatment of glioblastoma multiforme. Neurosurg Clin N Am *23*: 307-322, 2012.

14 Cohen MH, Johnson JR and Pazdur R: Food and drug administration drug approval summary: temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme. Clin Cancer Res *11*: 6767-6771, 2005.

15 Rosso L, Brock CS, Gallo JM, Saleem A, Price PM, Turkheimer FE and Aboagye EO: A new model for prediction of drug distribution in tumor and normal tissues: Pharmacokinetics of temozolomide in glioma patients. Cancer Res *69*: 120-127, 2009.

16 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Eng J Med *352*: 987-996, 2005.

17 Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG and Mirimanoff RO: Effects of radiotherapy with concomitant and adjuvant temozolomide *versus* radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol *10(5)*: 459-466, 2009.

18 Darefsky AS, King JT Jr. and Dubrow R. Adult glioblastoma multiforme survival in the temozolomide era: a population-based analysis of surveillance, epidemiology, and end results registries. Cancer *118*: 2163-2172, 2011.

19 Lund EL, Spang-Thomsen M, Skovgaard-Poulsen H and Kristjansen PE: Tumor angiogenesis – a new therapeutic target in gliomas. Acta Neurol Scand *97*: 52-62, 1998.

20 Jain RK, di Tomaso E, Duda DG, Loeffler JS, Sorensen AG and Batchelor TT: Angiogenesis in brain tumours. Nat Rev Neurosci *8*: 610-622, 2007.

21 Taal W, OOsterkamp H, Walenkamp AM, Dubbink HJ, Beerepoot LV, Hanse MC, Buter J, Honkoop AH, Boerman D, de Vos FY, Dinjens WN, Enting RH, Taphoorn MJ, van den Berkmortel FW, Jansen RL, Brandsma D, Bromberg JE, van Heuvel I, Vernhout RM, van der Holt B and van den Bent MJ: Single-agent bevacizumab or lomustine *versus* a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase II trial. Lancet Oncology *15*: 943-953, 2014.

22 Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R, Brown PD, Jaeckle KA, Schiff D, Stieber VW, Brachman DG, Werner-Wasik M, Tremont-Lukats IW, Sulman EP, Aldape KD, Curran WJ Jr. and Mehta MP: A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med *370*: 699-708, 2014.

23 Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA, Hilton M, Abrey L and Cloughesy T: Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma. N Engl J Med *370*: 709-722, 2014.

24 Schabel FM Jr: Nitrosoureas: a review of experimental antitumor activity. Cancer Treat Rep *60(6)*: 665-698, 1976.

25 Agarwal S, Chadha D and Mehrotra R: Molecular modeling and spectroscopic studies of semustine binding with DNA and its comparison with lomustine–DNA adduct formation. J Biomol Struct Dyn *33(8)*: 1653-1668, 2015.

26 Patel MA, Kim JE, Ruzevick J, Li G and Lim M: The future of glioblastoma therapy: synergism of standard of care and immunotherapy. Cancers *6*: 1953-1985, 2014.

27 Meng B, Li J and Cao H: Antioxidant and antiinflammatory activities of curcumin on diabetes mellitus and its complications. Curr Pharm Des *19(11)*: 2101-2113, 2013.

28 Mishra A and Palanivelu K: The effect of curcumin (turmeric) on Alzheimer's disease: an overview. Ann Indian Acad Neurol *11(1)*: 13-19, 2008.

29 Anggakusma, Colpitts CC, Schang LM, Rachmawati H, Frentzen A, Pfaender A, Behrendt A, Behrendt P, Brown RJ, Bankwitz D, Steinmann J, Ott M, Meuleman P, Rice CM, Ploss A, Pieschmann T and Steinmann E: Turmeric curcumin inhibits entry of all hepatitis C virus genotypes into human liver cells. Gut *63(7)*: 1137:1149, 2014.

30 Chandran B and Goel A: A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res *26(11)*: 1719:1725, 2012.

31 Wahlstrom B and Blennow G: A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol (Copenh) *43*: 86-92, 1978.

32 Storka A, Vcelar B, Klickovic U, Gouya G, Weisshaar S, Aschauer S, Bolger G, Helson L and Wolzt M: Safety, tolerability and pharmacokinetics of liposomal curcumin in healthy humans. Int J Clin Pharmacol Ther *53(1)*: 54-65, 2015.

33 Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, Marczylo TH, Morgan B, Hemingway D, Plummer SM, Pirmohamed M, Gescher AJ and Steward WP: Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res *10*: 6847-6854, 2004.

34 Aggarwal BB, Kumar A and Bharti AC: Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res *23(1A)*: 363-398, 2003.

35 Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, Ko JY, Lin JT, Lin BR, Ming-Shiang W, Yu HS, Jee SH, Chen GS, Chen TM, Chen CA, Lai MK, Pu YS, Pan MH, Wang YJ, Tsai CC and Hsieh CY: Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res *21(4B)*: 2895-2900, 2001.

36 Sordillo PP and Helson L: Suppression of cytokine release and cytokine storm: a potential therapy for patients with Ebola and other viral infections. In Vivo *29*: 1-4, 2015.

37 Chan MM: Inhibition of tumor necrosis factor by curcumin, a phytochemical. Biochem Pharmacol *49*: 1551-1556, 1995.

38 Leow PC, Tian Q, Ong ZY, Yang Z and Ee PL: Antitumor activity of natural compounds, curcumin and PKF118-310, as Wnt/β-catenin antagonists against human osteosarcoma cells. Invest New Drugs *28*: 766-782, 2010.

39 Subramaniam D, Ponnurangam S, Ramamoorthy P, Standling D, Battafarano RJ, Anant S and Sharma P: Curcumin induces cell death in esophageal cancer cells through modulating notch signaling. PloS One *7*: e30590, 2012.

40 Elamin MH, Shinwari Z, Hendrayani SF, Al-Hindi H, Al-Shail E, Khafaga Y, Al-Kofide A and Aboussekhra A: Curcumin inhibits the Sonic Hedgehog signaling pathway and triggers apoptosis in medulloblastoma cells. Mol Carcinog *49*: 302-314, 2010.

41 Alexandrow MG, Song LJ, Altiok S, Haura EB and Kumar NB: Curcumin: a novel STAT3 pathway inhibitor for chemoprevention of lung cancer. Eur J Cancer Prev *21(5)*: 407-412, 2012.

42 Chiu SS, Liu E, Majeed M, Vishwanatha JK, Ranjan AP, Maitra A, Pramanik D, Smith JA and Helson L: Differential distribution of intravenous curcumin formulations in the rat brain. Anticancer Res *31(3)*: 907-911, 2011.

43 Priyadarsini KI: The chemistry of curcumin: from extraction to therapeutic agent. Molecules *19*: 20091-20112, 2014.

44 Gao X, Deeb D, Jiang H, Liu YB, Dulchavsky AS and Gautam SC: Curcumin differentially sensitizes malignant glioma cells to TRAIL/APO2L-mediated apoptosis through activation of procaspases and release of cytochrome c from mitochondria. J Exp Ther Oncol *5*: 39-48, 2005.

45 Kim SY, Jung SH and Kim HS. Curcumin is a potent broad spectrum inhibitor of matrix metalloproteinase gene expression in human astroglioma cells. Biochem Biophys Res Commun *337*: 510-516, 2005.

46 Nagai S, Kurimoto M, Washiyama K, Hirashima Y, Kumanishi Y and Endo S: Inhibition of cellular proliferation and induction of apoptosis by curcumin in human malignant astrocytoma cell lines. J Neurooncol *74*: 105-111, 2005.

47 Woo MS, Jung SH, Kim SY, Hyun JW, Ko KH, Kim WK, Kim HS: Curcumin suppresses phorbol ester-induced matrix metalloproteinase-9 expression by inhibiting the PKC to MAPK signaling pathways in human astroglioma cells. Biochem Biophys Res Commun *335*: 1017-1025, 2005.

48 Belkaid A, Copland IB, Massillon D and Annabi B: Silencing of the human microsomal glucose-6-phosphate translocase induces glioma cell death: potential new anticancer target for curcumin. FEBS Lett *580*: 3746-3752, 2006.

49 Karmakar S, Banik NL, Patel SJ and Ray SK: Curcumin activated both receptor mediated and mitochondria-mediated proteolytic pathways for apoptosis in human glioblastoma T98G cells. Neurosci Lett *407*: 53-58, 2006.

50 Aoki H, Takada Y, Kondo S, Sawaya R, Aggarwal BB and Kondo Y: Evidence that curcumin suppresses the growth of malignant gliomas *in vitro* and *in vivo* through induction of autophagy: role of Akt and extracellular signal-regulated kinase signaling pathways. Mol Pharmacol *72*: 29-39, 2007.

51 Choi BH, Kim CG, Bae Y, Lim Y, Lee YH, and Shin SY: $p21^{WAF1/CIP1}$ expression by curcumin in U-87MG human glioma cells: role of early growth response-1 expression. Cancer Res *68*: 1369-1377, 2008.

52 Senft C, Polacin M, Priester M, Seifer V, Kögel D and Weissenberger J: The nontoxic natural compound curcumin exerts antiproliferative, antimigratory, and anti-invasive properties against malignant gliomas. Cancer *10*: 491-498, 2010.

53 Dhandapani KM, Mahesh VB and Brann DW: Curcumin suppresses growth and chemoresistance of human glioblastoma cells *via* AP-1 and NFκB transcription factors. J Neurochem *102*: 522-538, 2007.

54 Zanotto-Filho A, Braganhol E, Edelweiss MI, Behr GA, Zanin R, Schröder R, Simões-Pires A, Battastini AM and Moreira JC: The curry spice curcumin selectively inhibits cancer cells growth *in vitro* and in preclinical model of glioblastoma. J Nutr Biochem *23(6)*: 591-601, 2012.

55 Perry MC, Demeule M, Régina A, Moumdjian R and Béliveau R: Curcumin inhibits tumor growth and angiogenesis in glioblastoma xenografts. Mol Nutr Food Res *54(8)*: 1192-1201, 2010.

56 Beier D, Schulz JB and Beier CP: Chemoresistance of glioblastoma cancer stem cells–much more complex than expected. Mol Cancer *10*: 128, 2011.

57 Bleau AM, Hambardzumyan D, Ozawa, T, Fomchenko EI, Huse JT, Brennan CW and Holland EC: PTEN/PI3K/AKT pathway regulates the side population phenotype and ABCG2 activity in glioma tumor stem-like cells. Cell Stem Cell *4*: 226-235, 2009.

58 Schiffer D, Mellai M, Annovazzi L, Piazzi A, Monzeglio O and Caldera V: Glioblastoma cancer stem cells: basis for a functional hypothesis. Stem Cell Discov *2(3)*: 122-131, 2012.

59 Fong D, Yeh A, Naftalovich R, Choi TH and Chan MM: Curcumin inhibits the side population (SP) phenotype of the rat C6 glioma cell line: towards targeting of cancer stem cells with phytochemicals. Cancer Lett *293(1)*: 65-72, 2010.

60 Zhuang W, Long L, Zheng B, Ji W, Yang N, Zhang Q and Liang Z: Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy. Cancer Sci *103(4)*: 684-690, 2012.

61 Ganta S and Amiji M: Coadministration of paclitaxel and curcumin in nanoemulsion formulations to overcome multidrug resistance in tumor cells. Mol Pharm *6*: 928-939, 2009.

62 Bisht S, Mizuma M, Feldmann G, Ottenhof NA, Hong SM, Pramanik D, Chenna V, Karikari C, Sharma R, Goggins MG, Rudek MA, Ravi R, Maitra A and Maitra A: Systemic administration of polymeric nanoparticle-encapsulated curcumin (NanoCurc) blocks tumor growth and metastases in preclinical models of pancreatic cancer. Mol Cancer Ther *9*: 2255-2264, 2010.

63 Helson L: Curcumin (diferoylmethane) delivery methods: a review. Biofactors *39*: 21-26, 2013.

64 Séhédic D, Cikankowitz A, Hindré F, Davodeau F and Garcion E: Nanomedicine to overcome radioresistance in glioblastoma stem-like cells and surviving clones. Trends Pharmacol Sci *36(4)*: 236-225, 2015.

65 Zanotto-Filho A, Coradini K, Braganhol E, Schröder R, de Oliveira CM, SimõesPires A, Battastini AM, Pohlmann AR, Guterres SS, Forcelini CM, Beck RC and Moreira JC: Curcumin-loaded lipid-core nanocapsules as a strategy to improve pharmacological efficacy of curcumin in glioblastoma treatment. Eur J Pharm Biopharm *83(2)*: 156-167, 2013.

66 Lim KJ, Maitra A, Bisht S, Eberhart C and Bar E: Using nanocurcumin to treat medulloblastoma and glioblastoma. Cancer Res *70*: 4440, 2010.

67 Langone P, Debata PR, Inigo Jdel R, Dolai S, Mukherjee S, Halat F, Mastroianni K, Curcio GM, Castellanos MR, Raja K and Banerjee P: Coupling to a glioblastoma directed antibody potentiates antitumor activity of curcumin. Int J Cancer *135(3)*: 7109, 2014.

68 Ramachandran C, Nair SM, Escalon E and Melnick SJ: Potentiation of etoposide and temozolomide cytotoxicity by curcumin and turmeric force in brain tumor cell lines. J Complement Integr Med *9*: Article 20, 2012.

69 Yin H , Zhou Y, Wen C , Zhou C , Zhang W , Hu X , Wang L , You C and Shao J: Curcumin sensitizes glioblastoma to temozolomide by simultaneously generating ROS and disrupting AKT/mTOR signaling. Oncol Rep *32(4)*: 1610-1616, 2014.

70 Zanotto-Filho A, Braganhol E, Edelweiss MI, Behr GA, Zanin R, Schröder R, Simões-Pires A, Battastini AM and Moreira JC: The curry spice curcumin selectively inhibits cancer cells growth *in vitro* and in preclinical model of glioblastoma. J Nutr Biochem *23(6)*: 591-601, 2012.

71 Wu H, Liu Q, Cai T, Chen YD and Wang ZF: Induction of microRNA-146a is involved in curcumin-mediated enhancement of temozolomide cytotoxicity against human glioblastoma. Mol Med Rep *12(4)*: 5461-5466, 2015.

72 Hossain MM, Banik NK and Ray SK: Synergistic anticancer mechanisms of curcumin and paclitaxel for growth inhibition of human brain tumor stem cells and LN18 and U138-MG cells. Neurochem Int *61*: 1102-111, 2012.

73 Lim KJ, Bisht S, Bar EE, Maitra A and Eberhart CG: A polymeric nanoparticle formulation of curcumin inhibits growth, clonogenicity and stem-like fraction in malignant brain tumors. Cancer Biol Ther *11*: 464-473, 2011.

74 Sordillo PP and Helson L: Curcumin and cancer stem cells: curcumin has asymmetrical effects on cancer and normal stem cells. Anticancer Res *35*: 599-614, 2015.

75 Almanaa TN, Geusz ME and Jamasbi RJ: Effects of curcumin on stem-like cells in human esophageal squamous carcinoma cell lines. BMC Compl Altern Med *12*: 195, 2012.

76 Batth BK, Tripathi R and Srinivas UK: Curcumin-induced differentiation of mouse embryonal carcinoma PCC4 cells. Differentiation *68*: 133-140, 2001.

77 Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu MF, Hilsenbeck SG, Pavlick A, Zhang X, Chamness GC, Wong H, Rosen J and Chang JC: Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. J Natl Cancer Inst *100*: 672-679, 2008.

78 Moussavi M, Assi K, Gómez-Muñoz A and Salh B: Curcumin mediates ceramide generation *via* the *de novo* pathway in colon cancer cells. Carcinogenesis *27(8)*: 1636-44, 2006.

79 Grammatikos G, Teichgraber V, Carpinteiro A, Trarbach T, Weller M, Hengge UR and Gulbins E: Overexpression of acid sphingomyelinase sensitizes glioma cells to chemotherapy. Antioxid Redox Signal *9*: 1449-1456, 2007.

80 Hara S, Nakashima S, Kiyono T, Sawada M, Yoshimura S, Iwama T, Banno Y, Shinoda J and Sakai N: p53-Independent ceramide formation in human glioma cells during gamma-radiation-induced apoptosis. Cell Death Differ *11*: 853-861, 2004.

81 Riboni L, Campanella R, Bassi R, Villani R, Gaini SM, Martinelli-Boneschi F, Viani P and Tettamanti G: Ceramide levels are inversely associated with malignant progression of human glial tumors. Glia *39*: 105-113, 2002.

82 Giussani P, Bassi R, Anelli V, Brioschi L, De Zen F, Riccitelli E, Caroli M, Campanella R, Gaini SM, Viani P and Riboni L: Glucosylceramide synthase protects glioblastoma cells against autophagic and apoptotic death induced by temozolomide and Paclitaxel. Cancer Invest *30*: 27-37, 2012.

83 Manago A, Becker KA, Carpinteiro A, Wilker B, Soddemann M, Seitz AP, Edwards MJ, Grassme H, Szabo I and Gulbins E:

Pseudomonas aeruginosa pyocyanin induces neutrophil death *via* mitochondrial reactive oxygen species and mitochondrial acid sphingomyelinase. Antioxid Redox Signal *22*: 1097-1110, 2015.

84 Hatanaka Y, Fujii J, Fukutomi T, Watanabe T, Che W, Sanada Y, Igarashi Y and Taniguchi N: Reactive oxygen species enhances the induction of inducible nitric oxide synthase by sphingomyelinase in RAW264.7 cells. Biochem Biophs Acta *1393*: 203-210, 1998.

85 Castillo SS, Levy M, Thaikoottathil JV and Goldkorn T: Reactive nitrogen and oxygen species activate different sphingomyelinases to induce apoptosis in airway epithelial cells. Exp Cell Res *313*: 2680-2686, 2007.

Received September 22, 2015
Revised October 20, 2015
Accepted October 23, 2015