JBUON 2021; 26(6): 2218-2221
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

REVIEW ARTICLE

Caspases –related apoptosis in meningiomas

Dimitrios Roukas[1]*, Stylianos Mastronikolis[2], Evangelos Tsiambas[3,6,9]*, Despoina Spyropoulou[4], Ioannis Stavrakis[5], Vasileios Ragos[6], Pavlos Pantos[7], Anastasios Kouzoupis[8], Nikolaos Kavantzas[9], Andreas Lazaris[9]

[1]Department of Psychiatry, 417 VA (NIMTS) Hospital, Athens, Greece; [2]Medical School, University of Heraklion, Crete; [3]Department of Cytology, 417 VA (NIMTS) Hospital, Athens, Greece; [4]Department of Radiology, Medical School, University of Patras; [5]ENT Department, ''Sotiria'' General Hospital, Athens, Greece; [6]Departmant of Maxillofacial Surgery, Medical School, University of Ioannina, Greece; [7]1ST ENT Department, Hippokration Hospital, National and Kapodistrian University of Athens, Athens, Greece; [8]Department of Psychiatry, Medical School, University of Athens, Greece; [9]Department of Pathology, Medical School, University of Athens, Greece

*These authors contributed equally to this work

Summary

Meningiomas are the second most common brain tumours and the most common intracranial primary central nervous system (CNS) tumours in adults. Recurrence of these tumours – especially in higher grade meningiomas - is correlated with an aggressive biological behaviour affecting the response rates to surgery/radiation applied therapeutic regimens. Caspases (cysteine-aspartic proteases) represent a family of enzymes that modify several functions crucial for cell homeostasis such as inflammation and apoptosis. According to their implication in the apoptotic pathways, caspases are characterized as initiators and executioners, respectively. All these normal actions of the caspase complex that induce apoptosis are altered in epithelial malignancies. In cancerous tissues, programmed cell death is inhibited due to a deregulation in expression of apo- and anti-apoptotic proteins. This genetic imbalance drives the cancer cell to immortalization which reflects the aberrant tissue proliferation. For this reason, caspases and the other apoptotic molecules are considered as important targets for specific targeted therapeutic strategies enhancing the apoptotic levels of tumor cells. In the current review, we explored the role of caspases' modifications in meningiomas and their potential impact as biomarkers and targets for applying specific therapeutic strategies in the corresponding tumours.

Key words: *apoptosis, meningioma, caspase, targeted therapies, brain*

Introduction

Apoptosis corresponds to the genetically programmed variant of cell death mediated by a complex of proteins which influence positively or negatively intrinsic and extrinsic pathways [1]. In this energy consumption (ATP-dependent) based procedure, enzymes such as proteases and endonucleases split and break down the main domains of the cell entity: cytoplasm and nucleus. The morphological result of this activity is shrinkage of the cell volume combined with condensation of the cytoplasmic micro-environment. Nuclear pyknosis due to chromatin condensation and also DNA fragmentation follows cytoskeleton disorganization and disruption. Finally, the cell is transformed to apoptotic bodies enclosing cellular components exposed to phagocytosis mediated by macrophages [2]. Two main pathways are involved in the previous described apoptotic procedure: intrinsic and extrinsic, respectively. In both of them several proteins are characterized as inducers or inhibi-

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. 17 Patriarchou Grigoriou E´ Street, Ag. Paraskevi, 153 41 Athens, Greece.
Fax: +30 210 6526259, Email: tsiambasecyto@yahoo.gr
Received: 21/11/2020; Accepted: 07/01/2021

tors of apoptosis [3]. The first uses mitochondrial proteins with prominent the cytochrome c from the inter-membrane space of the organelle. Its activity in cytoplasm activates caspases (especially caspase-9) complex under the control of p53 and Bcl-2 (B-cell lymphoma-2) proteins. In this version, the apoptotic signal is triggered by inside the cell stress conditions including hypoxia, DNA damage, and altered protein accumulation. Concerning the extrinsic pathway, it is based on receptor-ligand complexes that are activated when the cell receives on its surface (membrane) the corresponding signals from the intercellular environment. The main receptors and their ligand binding molecules are Tumor Necrosis Factor Receptor-1(TNFR-1)/ Tumor necrosis factor (TNF-alpha) and Fas Receptor (FasR)/ Fas ligand (FasL). In fact, biochemically apoptosis, as a natural cell death mechanism is characterized by the production and development of an intracellular domain called "apoptosome" [4]. It can be described as a multi-protein complex structure including cytochrome c and Apaf-1 (apoptotic protease activating factor-1) which activates caspases – a critical positive apoptotic protein family interacting also with Bcl proteins [5]. In the current review we explored the role of caspase complex in meningiomas.

Caspase protein family: structure and functions

Caspases are significant proteins acting as strong apoptotic death promoters. Caspases (cysteine-aspartic proteases) represent a family of enzymes that influence several functions crucial for cell homeostasis such as inflammation, pyroptosis (a distinct aspect of programmed cell death mediated by microbial infection that triggers also an immune response), necroptosis, tissue differentiation and development in the embryonic early stages of life [6]. They also act as tumor suppressor genes, whereas their role in the ageing process is under investigation. Approximately, fifteen protease proteins have been identified and cloned implicating eight chromosomes (1, 2, 4, 7, 10, 11, 16, and 19). The corresponding protein products are initially inactive (pro-caspases) enzymes. Their dimerization or oligomerization create the final functional heterotetramer domain due to a cleavage process which develops an active heterodimer complex consisting of two units: a small and large one. According to their implication in the apoptotic pathways, caspases are characterized as initiators and executioners, respectively. In the first group have been inserted caspase-2,-8,-9, and -10, whereas caspase-3,-6, and-7 belong to the second category [7]. Concerning the previous described intrinsic apoptotic pathway, the most important protease is caspase-9 which is recruited and activated by cytochrome c/APAF-1 complex. Caspase-9 triggers the activation of the executioner caspases-3 and -7, leading finally to many proteins' cleavage inside the cytoplasm. In contrast, another critical protein, caspase-8, is activated in extrinsic pathway by the FasL binding to FasR leading also to recruitment and over expression of executioner caspases-3,-6, and -7. The result is the degradation of cellular proteins and organelles destruction similarly to the previous referred action of caspase-9 [8]. Novel studies have also shown that caspase-8 is implicated in cell adhesion and migration increasing its role in cell homeostasis and interactions inside the tissues [9]. As it has been mentioned before- besides apoptosis- caspases are involved also in the pyroptosis process. Caspase-1,-4,-5, and-11 are involved in this inflammatory procedure. Especially, caspase-1 activates a variety of pro-inflammatory cytokines and then secretes their mature products, interleukins (IL) IL-1α, IL-1β, and IL-18. Additionally, there is initial evidence that the complex caspase-1/caspase-7 activates the transcription of nuclear factor-κB (NF-κB), a molecule that modifies the function of TNF, IL-6, and IL-8 [10]. All of these normal actions of the caspase complex that induce apoptosis are altered in carcinoma progression and establishment. In cancerous tissues, programmed cell death is inhibited due to a deregulation in expression of apo- and anti-apoptotic proteins. This genetic imbalance drives the cancerous cell to immortalization which reflects the aberrant tissue proliferation. For this reason, caspases are considered as important targets for specific targeted therapeutic strategies by enhancing the apoptotic levels inside the neoplastic cell cores in a variety of solid malignancies [11,12].

Targeting caspases in meningioma

Meningiomas' histological substrate is the arachnoid cap cells of the meninges on the periphery of the brain. Brain tissue invasion is the most critical histopathological evidence of aggressive biological behavior of the tumor. Furthermore, meningiomas' extra-cranial metastatic potential is low and its metastatic activity and penetration is extremely rare. Significant series of meningiomas and detected gross chromosomal and specific gene aberrations (rearrangements/intra- or inter- translocations, gains, frame-shift deletions/insertions, point-driver mutations or in-frame fusions) also reflect the grades of differentiation (Grade I-III) in them [13]. Gene expression analyses focused on

apoptotic pathways including c-FLIP, XIAP, Bcl-2, caspase 3, 8 and 9, cytochrome c, APAF 1 and Smac/DIABLO molecules detected low protein levels regarding caspases. The study group observed a potential blocking of these apoptotic inducers mediated by c-FLIP inhibition on them [14]. Similarly, overexpression of tumor necrosis factor-related apoptosis-inducing ligand R2 (TRAIL-R2) combined with low levels of caspase 8 has been also detected in a series of meningiomas [15]. In contrast to caspase 8, caspase 3 has been found to be overexpressed more frequently in meningiomas. A combined calpain and caspase-3 upregulation has been detected in a series of brain tumors including transitional meningiomas [16]. It is also important to be mentioned that survivin, an inhibitor of apoptosis that binds to caspases-3 and -7 external domains is overxepressed in meningiomas down regulating their function [17]. Another molecule which interacts with caspase-3 is the midkine, a heparin-binding growth factor that acts as an inducer for growth, survival, migration, and differentiation of various cells. A study group co-analyzed their expression showed that midkine reduced active caspase-3 levels negatively affecting the response rates to camptothecin-mediated apoptotic cell death in meningioma cells *in vitro* cultures leading to increased chemoptherapeutic regimens resistance [18]. Based on this increased need for enhancing apoptotic rates in meningiomas, novel studies have focused on specific agents. One of them is fenretinide. This is a synthetic retinoid promoting apoptosis in tumor cell cultures in several malignancies. A study group reported significant levels of caspase activation in meningiomas mediated by fenretinide. Interestingly, the agent provided apoptosis in all three grades of meningioma primary cells cultures [19]. Additionally, valproic acid (VPA), a commonly used anti-epileptic drug, seems to induce apoptosis by increasing cleaved caspase-3 and PARP apoptotic molecules in meningiomas stem cells cultures providing also elevated radio-sensitivity to them [20].

In conclusion, caspase complex -as a critical apoptotic pathway- demonstrates alterations in meningiomas. Especially, caspase -3 and -8 should be potential targets for novel therapeutic strategies in meningiomas for enhancing apoptotic death and response rates to specific chemo-radiation regimens.

Conflict of interests

The authors declare no conflict of interests.

References

1. Chung C. Restoring the switch for cancer cell death: Targeting the apoptosis signaling pathway. Am J Health Syst Pharm 2018;75:945-52.
2. Pfeffer CM, Singh ATK. Apoptosis: A Target for Anticancer Therapy. Int J Mol Sci 2018;19:E448-454.
3. Banoth B, Cassel SL. Mitochondria in innate immune signaling. Transl Res 2018; 5244:30115-4.
4. Dorstyn L, Akey CW, Kumar S. New insights into apoptosome structure and function. Cell Death Differ 2018;25:1194-208.
5. Arumugam A, Abdull Razis AF. Apoptosis as a Mechanism of the Cancer Chemopreventive Activity of Glucosinolates: a Review. Asian Pac J Cancer Prev 2018;19:1439-48.
6. Anja P, Anahid J, Janko K. Cysteine cathepsins: Their biological and molecular significance in cancer stem cells. Semin Cancer Biol 2018;S1044-579X(18)30028-2.
7. Kopeina GS, Prokhorova EA, Lavrik IN, Zhivotovsky B. Alterations in the nucleocytoplasmic transport in apoptosis: Caspases lead the way. Cell Prolif 2018; e12467-77.
8. Wilson CH, Kumar S. Caspases in metabolic disease and their therapeutic potential. Cell Death Differ 2018;25:1010-24.
9. Keller N, Ozmadenci D, Ichim G, Stupack D. Caspase-8 function, and phosphorylation, in cell migration. Semin Cell Dev Biol 2018;82:105-7.
10. Yuan YY, Xie KX, Wang SL, Yuan LW. Inflammatory caspase-related pyroptosis: mechanism, regulation and therapeutic potential for inflammatory bowel disease. Gastroenterol Rep (Oxf) 2018;6:167-76.
11. McArthur K, Kile BT. Apoptotic Caspases: Multiple or Mistaken Identities? Trends Cell Biol 2018;28:475-93.
12. Chrysovergis A, Papanikolaou VS, Tsiambas E et al. Caspase complex in laryngeal squamous cell carcinoma. JBUON 2019; 24: 1-4.
13. Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. Brain Tumor Pathol 2016; 33:237-47.
14. Tirapelli DP, Menezes SB, Franco IM et al. High expression of anti-apoptotic genes in grade I and II meningiomas. Arq Neuropsiquiatr 2017;75:209-15.
15. Koschny R, Krupp W, Xu LX et al. WHO grade related expression of TRAIL-receptors and apoptosis regulators in meningioma. Pathol Res Pract 2015;211:109-16.

16. Ray SK, Patel SJ, Welsh CT et al. Molecular evidence of apoptotic death in malignant brain tumors including glioblastoma multiforme: upregulation of calpain and caspase-3. J Neurosci Res. 2002;69:197-206.
17. Sasaki T, Lopes MB, Hankins GR, Helm GA. Expression of survivin, an inhibitor of apoptosis protein, in tumors of the nervous system. Acta Neuropathol 2002;104:105-9.
18. Tong Y, Mentlein R, Buhl R et al. Overexpression of midkine contributes to anti-apoptotic effects in humanmeningiomas. J Neurochem 2007;100:1097-107.
19. Puduvalli VK, Li JT, Chen L, McCutcheon IE. Induction of apoptosis in primary meningioma cultures by fenretinide. Cancer Res 2005;65:1547-53.
20. Chiou HY, Lai WK, Huang LC et al. Valproic acid promotes radiosensitization in meningioma stem-like cells. Oncotarget 2015; 6:9959-69.