Research Article

Analysis of Several PLA₂ mRNA in Human Meningiomas

Yves Denizot,¹ Rafael De Armas,² Karine Durand,² Sandrine Robert,² Jean-Jacques Moreau,³ François Caire,³ Nicolas Weinbreck,² and François Labrousse²

¹UMR CNRS 6101, Centre National de la Recherche Scientifique, Faculté de Médecine, Université de Limoges, 2 rue Dr. Marcland, 87025 Limoges, France
²Service d’Anatomie Pathologique, CHU Dupuytren, 87045 Limoges, France
³Service de Neurochirurgie, CHU Dupuytren, 87045 Limoges, France

Correspondence should be addressed to Yves Denizot, yves.denizot@unilim.fr

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In view of the important oncogenic action of phospholipase A₂ (PLA₂) we investigated PLA₂ transcripts in human meningiomas. Real-time PCR was used to investigate PLA₂ transcripts in 26 human meningioma tumors. Results indicated that three Ca²⁺-dependent high molecular weight PLA₂ (PLA₂-IV A, PLA₂-IVB, PLA₂-IVC), one Ca²⁺-independent high molecular weight PLA₂ (PLA₂-VI) and five low molecular weight secreted forms of PLA₂ (PLA₂-IB, PLA₂-IIA, PLA₂-III, PLA₂-V, and PLA₂-XII) are expressed with PLA₂-IV A, PLA₂-IVB, PLA₂-VI, and PLA₂-XIIA as the major expressed forms. PLA₂-IIE, PLA₂-IIF, PLA₂-IVD, and PLA₂-XIIB are not detected. Plasma (PLA₂-VIIA) and intracellular (PLA₂-VIIB) platelet-activating factor acetylhydrolase transcripts are expressed in human meningiomas. However no difference was found for PLA₂ transcript amounts in relation to the tumor grade, the subtype of meningiomas, the presence of inflammatory infiltrated cells, of an associated edema, mitosis, brain invasion, vascularisation or necrosis. In conclusion numerous genes encoding multiples forms of PLA₂ are expressed in meningiomas where they might act on the phospholipid remodeling and on the local eicosanoid and/or cytokine networks.

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1. Introduction

Meningiomas are the second most common primary intracranial tumor. Meningiomas present clinically by causing focal or generalized seizure disorders, focal neurological deficits or neuropsychological decline [1]. A large number of molecular and genetic pathways that are altered in brain tumor cells have been identified. Among them, a possible role for the eicosanoid cascade has been suggested in meningiomas [2]. Phospholipase A₂ (PLA₂) is the key enzyme involved in eicosanoid generation [3–5]. PLA₂ catalyzes the hydrolysis of the sn-2 position of membrane glycerophospholipids to liberate the eicosanoid precursor arachidonic acid (AA) [3–5]. Four distinct families have been documented: low molecular weight secreted forms of PLA₂ (sPLA₂), Ca²⁺-dependent high molecular weight PLA₂ (cPLA₂), Ca²⁺-independent high molecular weight PLA₂ (iPLA₂), and the platelet-activating factor acetylhydrolase (PAF-AH). The sPLA₂ family is implicated in several biological processes such as inflammation and host defense [3, 4].

Nine isoenzymes have been identified in human: PLA₂-IB, PLA₂-IIA, PLA₂-IIID, PLA₂-IIE, PLA₂-III, PLA₂-V, PLA₂-X, PLA₂-XIIA, and PLA₂-XIII. In addition to their function in digestion of dietary phospholipids, host defense against bacteria and AA release from cellular phospholipids for eicosanoid synthesis, two classes of receptors (M and N) and several extracellular binding proteins have been identified indicating that sPLA₂ might signal through receptor activation [3–5]. In human the cPLA₂ family consists of four members, PLA₂-IVA, PLA₂-IVB, PLA₂-IVC, and PLA₂-IVD; PLA₂-IVA being the central regulator of stimulus-coupled cellular AA release [3–5]. In human the iPLA₂ group consists of seven members, iPLA₂ (PLA₂-VIA-1) currently being the best known member and playing major role in phospholipids remodeling and cancer [3, 5]. Beside its important place for eicosanoid generation, PLA₂ is also the key enzyme for the generation of the pro-inflammatory lipid mediator PAF recently documented in human meningioma [6]. PAF-AH activity which hydrolyses PAF into the inactive PAF precursor, lyso-PAF is detected in meningioma [6].
However no results reported whether this enzymatic activity originated from PLA2-VIIA and/or PLA2-VIIB, the plasma PAF-AH and the intracellular PAF-AH forms, respectively. Currently the contribution of PLA2 in meningiomas is poorly documented despite the fact that PLA2 inhibition decreased the growth of cultured meningioma cells [7]. In view of the potentially important oncogenic action of the various PLA2 species, we investigated, at the mRNA levels, which of them were expressed in intracranial human meningiomas.

2. Materials and Methods

2.1. Patients. The procedure of the present study followed the rules edited by the French National Ethics. Ethics approval was obtained from the ethics committee of our hospital (CHU Dupuytren, Limoges, France). Twenty six patients who underwent surgery for intracranial meningiomas from 1998 to 2004 were investigated. Tumors were originated from PLA2-VIIA and/or PLA2-VIIB, the plasma PAF-AH, and the intracellular PAF-AH forms, respectively.

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2.2. RNA Extraction. Total RNA was extracted using the “RNeasy Lipid Tissue mini kit” (Qiagen, Courtaboeuf, France) from 10–15 mg of tumor tissue. Before RNA extraction, tumor fragments were incubated with 14 mm ceramic beads “Lysing matrix D” (Bertin Technologies, Montigny-Le-Bretonneux, France) in 1 mL QIAzol lysis reagent and homogenized at 5500 rpm during 2-fold 40 sec in the automated mixer Precellys (Bertin Technologies). Then homogenized samples were used for RNA purification according to the manufacturer’s protocol. A DNase I digestion step was included for each extraction to avoid RNA contamination by genomic DNA. RNA integrity was checked by capillary electrophoresis on the Bioanalyzer 2100 (Agilent Technologies, Massy, France). Only RNA with an RNA Integrity Number (R.I.N) higher than 5.5 was used for reverse transcription. Total RNA concentration was determined by measuring absorbance at 260 nm with a spectrophotometer NanoDrop ND-1000 (Labtech, Paris, France).

2.3. Reverse Transcription. Total RNA was reverse transcribed in single strand cDNA using random hexamers and as described in the protocol of the “SuperScript III First-Strand Synthesis System for RT-PCR” (Invitrogen, Cergy-Pontoise, France). Briefly, 1 μg total RNA was incubated with 200 U M-MLV reverse transcriptase in the presence of 0.5 mM dNTPs, 50 ng random hexamers, 5 mM MgCl2, 10 mM dithiotreitol, and 40 U RNase inhibitor, in a final volume of 20 μL 1X RT buffer. Reverse transcription was performed as follows in a thermocycler Gold 9700 (Applied Biosystem): denaturation during 5 min at 95°C and chilling 1 min on ice, hybridization during 10 min at 55°C followed by cDNA synthesis during 50 min at 50°C; enzyme was inactivated by a 5 min incubation at 85°C and chilling on ice; finally the destruction of the RNA portion of the RNA: cDNA hybrids was performed by 2 U RNase H during 20 min at 37°C. Reactions were frozen at –20°C until quantitative real-time PCR realisation.

2.4. Real-Time PCR Analysis. PLA2-IB, PLA2-IIA, PLA2-IIID, PLA2-IIIE, PLA2-III, PLA2-IVA, PLA2-IVB, PLA2-IVC, PLA2-IVD, PLA2-V, PLA2-VI, PLA2-X, PLA2-XIIA, PLA2-XIIB, PLA2-VI (plasma PAF-AH), PLA2-VIIB (intracellular PAF-AH), and PLA2R transcripts were analyzed using real-time polymerase chain reaction (PCR). PCR was performed in duplicate by using TaqMan assay reagents (Applied Biosystems, Foster City, CA) [9, 10]. Product references were the following: PLA2-IB: Hs00386701-m1; PLA2-IIA: Hs00179898-m1; PLA2-IIID: Hs00173860-m1; PLA2-IIIE: Hs00173897-m1; PLA2-III: Hs00224482-m1; PLA2-IVB: Hs00210447-m1; PLA2-IVA: Hs00233352-m1; PLA2-IVC: Hs00234345-m1; PLA2-IVD: Hs00603557-m1; PLA2-V: Hs00173472-m1; PLA2-VI: Hs0085926-m1; PLA2-X: Hs00358567-m1; PLA2-XIIA: Hs00831006-s1; PLA2-XIIB: Hs00261432-m1; PLA2-VIIA: Hs00968593-m1; PLA2-VIIIB: Hs01042135-m1; PLA2-R: Hs00234853-m1. Real-time PCR were performed following the recommendations of the manufacturer in a final volume of 20 μL with 10 μL of 2X Universal PCR Master Mix, 20 ng of cDNA in a volume of 9 μL (the amount of cDNA is an equivalent based on the initial amount of RNA used for the RT reaction and 1 μL of a 20X TaqMan gene expression specific probe. PCR parameters were the following: 95°C for 10 min and forty cycles of 95°C/15 sec and 60°C/60 sec. Amplification products were analyzed on an ABI Prism 7000 system (Applied Biosystems) [9, 10]. Gene expression levels were normalized to 18S RNA (product reference: Hs99999901-s1) according to the manufacturer’s recommendation. Amounts of various transcripts were compared to sample with the lowest level of transcripts (a patient who was arbitrary quoted 1). The relative quantification of gene expression was performed using the comparative C_T method (△△C_T) (Figure 1(a)).

Experiments were made
in duplicate. Mean \( C_T \) values were used in the \( \Delta \Delta C_T \) calculation by using the “relative quantitation calculation and analysis software for Applied Biosystems real-time PCR systems”. NonRT controls (only with RNA) and blank RT controls (RT without RNA) were run to make sure the amplifications were specifics.

2.5. Data Analysis. Significance was assessed by using the Kruskal-Wallis test followed by a Mann-Whitney \( U \)-test.

3. Results and Discussion

In a first set of experiments we investigated if mRNAs derived from the five intracellular PLA\(_2\) genes (four cPLA\(_2\) and iPLA\(_2\)) were detected in meningiomas. As shown in Figure 1(b), mRNAs derived from four of these five cloned PLA\(_2\) genes are detected. Mean \( C_T \) values are reported in Table 1. PLA\(_2\)-IVD transcripts were not present at detectable levels. In contrast, PLA\(_2\)-IVA, PLA\(_2\)-IVB, PLA\(_2\)-IVC, and PLA\(_2\)-VI were detected in 96% (25/26), 100% (26/26), 92% (24/26), and 100% (26/26) of tumors, respectively (Figure 2). These results confirm a previous study highlighting PLA\(_2\) activity in 100% of human meningiomas [6]. No difference (\( P > .05 \), Mann Whitney \( U \)-test) was found for PLA\(_2\) transcript amounts in relation to the tumor grade (Figure 1), nor the subtype of meningiomas, the presence of inflammatory infiltrated cells, of an associated edema, mitosis, brain invasion, vascularisation or necrosis (data not shown).

The analysis of twenty six patients indicated the following rank of magnitude in human meningiomas: PLA\(_2\)-VI = PLA\(_2\)-IVB > PLA\(_2\)-IVA > PLA\(_2\)-IVC (Table 1). PLA\(_2\)-IVB and PLA\(_2\)-IVC had little specificity for the sn-2 fatty acid as compared with PLA\(_2\)-IVA which preferentially hydrolyses
phospholipids containing AA at the sn-2 position [3–5]. PLA2-VI was originally reported to mediate phospholipid remodeling and, thus, to act as a housekeeping protein without significant role in cell growth [3, 4]. However, several recent studies have demonstrated that PLA2-VI exhibited roles in cell regulation, growth, and death. Especially, one mechanism by which PLA2-VI mediates cell growth involves regulation of AA release, p53, and MAPK activation [11]. Of interest, involvements of p53 and MAPK kinase have been recently reported in the pathology of human meningiomas [12, 13]. A role for PLA2-VI may, thus, be suggested in meningioma tumor growth. Together, these observations might suggest PLA2-VI as a novel and interesting target for drug development for meningioma therapy. However, given the ubiquitous expression of PLA2-VI and its role in glycerophospholipid metabolism, drug strategies targeting PLA2-VI must exhibit selectivity to avoid undesired side effects.

In a second set of experiments we investigated if mRNAs derived from the nine sPLA2 genes (i.e., PLA2-IB, PLA2-IIA, PLA2-IID, PLA2-IIE, PLA2-IIF, PLA2-III, PLA2-V, PLA2-X, PLA2-XIIA, and PLA2-XIIB) were detected in human meningiomas. PLA2-IIE, PLA2-IIF, and PLA2-XIIB transcripts were not present at detectable levels in tumors while PLA2-IID and PLA2-X transcripts were detected in only a few number (4/26, 15%) of them. In contrast, PLA2-IB, PLA2-IIA, PLA2-III, PLA2-V and PLA2-XIIA were detected in 88% (23/26), 88% (23/26), 77% (20/26), 65% (17/26), and 96% (25/26) of tumors, respectively (Figure 3). Mean CT values are reported in Table 1. Results indicated the following rank of magnitude for sPLA2 transcripts in meningiomas: PLA2-XIIA > PLA2-IIA > PLA2-IB = PLA2-V = PLA2-III = PLA2-IID > PLA2-X. No difference (P > .05, Mann Whitney U-test) was found for sPLA2 transcript amounts in relation to the tumor grade (Figure 3), nor the subtype of meningiomas, the presence of inflammatory infiltrated cells, of an associated edema,
mitosis, brain invasion, vascularisation or necrosis (data not shown). PLA2-XIIA, PLA2-IIA, and PLA2-IB might be implicated in meningioma growth. The physiologic roles of PLA2-XIIA remain an open question. Whether PLA2-XIIA exhibits a weak AA catalytic activity [14], a potential role for this enzyme is suggested in membrane fusion or cell division [15]. PLA2-XIIA was reported to inhibit bone morphogenetic protein (BMP) through the loss of activated Smad1/4 complexes [16]; a result of importance since BMP inhibits the tumorigenic potential of human glioblastomas.

**Figure 3**: Secreted PLA2 transcripts in human meningiomas. Same legend as in Figure 2. (°) indicates patients with no detectable transcripts. No significant differences were documented between groups.
by triggering the Smad signaling cascade [17]. PLA2-IB expression is mainly neuronal in human brain [18]. Apart from its lipolytic and pro-inflammatory activities, PLA2-IB acts as receptor ligand to induce cell signaling and subsequent activation of cPLA2, thus indirectly contributing to AA production [19]. However the role of PLA2-IB as a ligand for the PLA2R is still controversial. PLA2-IIA elicits a mitogenic response and activates AA metabolism in astrocytoma cells [20], is critical for neuronal death via reactive oxygen species [21] and plays a role in cellular senescence [22]. Finally, studies have suggested the role of PLA2-IIA, PLA2-III, and PLA2-V as potential prognostic markers in colorectal adenocarcinomas and prostate cancer [23, 24]. The data reported in Figure 3 suggest that levels of PLA2-IIA, PLA2-III, and PLA2-V transcripts greatly varied between patients (see the Log scale). Would it be possible that their levels were related to patient outcomes in meningioma tumors? Clearly investigation of a larger number of patients would be of interest to test this hypothesis.

In a third set of experiments we investigated PAF-AH enzymes that constitute another PLA2 subfamily. As shown in Figure 4 (upper panel), PLA2-VIIA (the plasma PAF-AH form) and PLA2-VIIB (the intracellular PAF-AH form) were present in 100% (23/23) and 95% (22/23) meningioma tumors. Mean C\textsubscript{T} values are reported in Table 1. No difference (\textit{P}>0.05, Mann Whitney \textit{U}-test) was found for PAF-AH transcript amounts in relation to the tumor grade (Figure 4(a)), nor to other clinical data (data not shown). The present results confirm a previous study reporting PAF-AH enzymatic activity in meningioma homogenates [6]. The PAF-AH family exhibits unique substrate specificity toward PAF and oxidized phospholipids. Degradation of these bioactive phospholipids by PAF-AH may lead to the termination of inflammatory reaction. Its presence in human
Table 1: CT values obtained during real-time PCR analysis.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mean ± SEM CT (made on detectable samples)</th>
<th>Number of samples with a CT &gt; 40 (nondetectable samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18S</td>
<td>12.27 ± 0.18</td>
<td>0</td>
</tr>
<tr>
<td>PLA2-IB</td>
<td>35.35 ± 0.29</td>
<td>3</td>
</tr>
<tr>
<td>PLA2-IIA</td>
<td>33.69 ± 0.74</td>
<td>3</td>
</tr>
<tr>
<td>PLA2-IIID</td>
<td>34.91 ± 0.81</td>
<td>22</td>
</tr>
<tr>
<td>PLA2-IIIE</td>
<td>nd</td>
<td>26</td>
</tr>
<tr>
<td>PLA2-IIIF</td>
<td>nd</td>
<td>26</td>
</tr>
<tr>
<td>PLA2-III</td>
<td>35.28 ± 0.50</td>
<td>6</td>
</tr>
<tr>
<td>PLA2-IV</td>
<td>nd</td>
<td>6</td>
</tr>
<tr>
<td>PLA2-V</td>
<td>35.81 ± 0.61</td>
<td>9</td>
</tr>
<tr>
<td>PLA2-VI</td>
<td>30.78 ± 0.30</td>
<td>0</td>
</tr>
<tr>
<td>PLA2-VIIA</td>
<td>33.19 ± 0.48</td>
<td>0</td>
</tr>
<tr>
<td>PLA2-VIIB</td>
<td>30.25 ± 1.21</td>
<td>1</td>
</tr>
<tr>
<td>PLA2-VIIB</td>
<td>37.93 ± 0.26</td>
<td>22</td>
</tr>
<tr>
<td>PLA2-X</td>
<td>nd</td>
<td>26</td>
</tr>
<tr>
<td>PLA2-XIIA</td>
<td>32.86 ± 0.33</td>
<td>1</td>
</tr>
<tr>
<td>PLA2-XIIB</td>
<td>nd</td>
<td>26</td>
</tr>
</tbody>
</table>

Results are reported as mean ± SEM of 26 experiments excepted for PLA2-VIIA and PLA2-VIIB were 23 samples were analysed. nd: not detectable CT.

meningioma is consistent with the presence of PAF in meningioma tumors [6, 25].

Finally in a fourth set of experiments we focused our attention on PLA2R transcripts in human meningioma. As shown in Figure 4 (lower panel), PLA2R transcripts were detected in 100% (23/23) meningioma tumors but without significant link with the tumor grade. The PLA2R can act as a ligand for several sPLA2 thus mediating a variety of biological responses (such as cell proliferation, cell migration, hormone release, lipid mediator production and cytokine production). In turn, PLA2R can also play a negative role in sPLA2 functions by downregulating their exaggerated reactions as PLA2R is involved in the degradation/internalization of sPLA2 [26]. Particularly, PLA2R deficient mice exhibit resistance to endotoxic shock [27] and knockdown of the PLA2R prevents the onset of replicative senescence and diminishes stress-induced senescence [28]. Finally PLA2R was found to be upregulated in dermatofibrosarcoma [29].

In conclusion, numerous genes encoding multiple forms of cPLA2, sPLA2, and PAF-AH are expressed (at the mRNA level) in human meningiomas where they might act on tumor growth not only by acting on phospholipid remodeling but also by altering the local eicosanoid and/or cytokine networks. It is of evidence that immunhistochemistry would be of importance to confirm the relative expression of the different PLA2 forms in human meningioma tumors. The discovery of specific receptors that bind sPLA2 strongly indicate that these enzymes can exert various biological responses via binding to a receptor, in addition to their enzymatic activity. Of interest meningioma tumors expressed PLA2R transcripts. Further studies are clearly needed to elucidate the contributions of sPLA2, cPLA2, iPLA2, and PAF-AH in meningioma and to determine their possible relevance in the targeting of new therapeutic interventions.

Abbreviations

PLA2: phospholipase A2
sPLA2: secreted phospholipase A2
cPLA2: cytosolic phospholipase A2
iPLA2: calcium independent phospholipase A2
PCR: polymerase chain reaction.

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References

activity regulates Ca^{2+} storage-dependent cellular proliferation,”

D. N. Louis, H. Oghaki, O. D. Wiestler, and W. K. Cavenee,
WHO Classification of Tumours of the Central Nervous System,

C. Vincent, R. Fiancette, M. Donnard, et al., “5-LOX, 12-LOX
and 15-LOX in immature forms of human leukemic blasts,”

R. Fiancette, C. Vincent, M. Donnard, et al., “Genes encoding
multiple forms of phospholipase A_2 are expressed in immature
forms of human leukemic blasts,” Leukemia, vol. 23, no. 6,

S. B. Hooks and B. S. Cummings, “Role of Ca^{2+}-independent
phospholipase A_2 in cell growth and signaling,” 

M. D. Johnson, M. O’Connell, F. Vito, and R. S. Bakos,
“Increased STAT-3 and synchronous activation of Raf-1-MEK-1-MAPK,
and phosphatidylinositol 3-kinase-Akt-mTOR pathways in atypical
and anaplastic meningiomas,” 

Z. N. Chang, C.-L. Guo, I. Ahronowitz, A. O. Stemmer-Rachamimov,
M. MacCollin, and F. P. Nunes, “A role for the
p53 pathway in the pathology of meningiomas with NF2 loss,”

M. H. Gelm, E. Valentin, F. Ghomashchi, M. Lazdunski,
and G. Lambeau, “Cloning and recombinant expression of a
structurally novel human secreted phospholipase A_2,” 
Journal of Biological Chemistry, vol. 275, no. 51, pp. 39823–39826,
2000.

arachidonate-releasing function of novel classes of secretory
phospholipase A_2 (groups III and XII),” 

I. Munoz-Sanjuan and A. H. Brivanlou, “Induction of ectopic
olfactory structures and bone morphogenetic protein inhibi-
tion by Rossy, a group XII secreted phospholipase A_2,”
Molecular and Cellular Biology, vol. 25, no. 9, pp. 3608–3619,
2005.

morphogenetic proteins inhibit the tumorigenic potential of
human brain tumour-initiating cells,” 

M. Kolko, N. R. Christoffersen, H. Varoqui, and N. G. Bazan,
“Expression and induction of secretory phospholipase A_2
group IB in brain,” 

E. Valentin and G. Lambeau, “Increasing molecular diversity
of secreted phospholipases A_2 and their receptors and binding
proteins,” 

L. Fuentes, M. Hernandez, M. L. Nieto, and M. Sanchez
Crespo, “Biological effects of group IIA secreted phospholipase A_2,” 

G. H. Mathisen, I. H. Thorkildsen, and R. E. Paulsen,
“Secretory PLA_2-IB and ROS generation in peripheral mitoch-
donia are critical for neuronal death,” 

senescence by secretory phospholipase A_2 in human dermal
fibroblasts through an ROS-mediated p53 pathway,” 

phospholipase A_2 as a prognostic marker in prostate cancer: relevance
to clinicopathological variables and disease-specific mortality,” 
Acta Pathologica Microbiologica and Immunologica,

C. M. Mounier, D. Wendum, E. Greenspan, J.-F. Fléjou, D. W. Rosenberg,
and G. Lambeau, “Distinct expression pattern of the
full set of secreted phospholipases A_2 in human colorectal
adenocarcinomas: sPLA_2-III as a biomarker candidate,” 

Y. Hirashima, N. Hayashi, O. Fukuda, H. Ito, S. Endo,
and A. Takaku, “Platelet-activating factor and edema surrounding
meningiomas,” 
Journal of Neurosurgery, vol. 88, no. 2, pp. 304–

K. Hanasaki, “Mammalian phospholipase A_2: phospholipase
A_2 receptor,” 

K. Hanasaki, Y. Yokota, J. Ishizaki, T. Itoh, and H. Arita,
“Resistance to endotoxic shock in phospholipase A_2 receptor-
deficient mice,” 

A. Augert, C. Payré, Y. de Launoit, J. Gil, G. Lambeau,
and D. Bernard, “The M-type receptor PLA_2R regulates senescence
through the p53 pathway,” 

patterns and gene copy number changes in dermatofibrosar-
coma protuberas,” 
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