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The human medulloblastoma cell line TE671 expresses a muscle-like acetylcholine receptor

Cloning of the α-subunit cDNA

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Nicotinic acetylcholine receptors (AChRs) from muscle bind α-bungarotoxin (αBgt) and are composed of four kinds of subunits, whereas AChRs from mammalian brains do not bind αBgt and are composed of two kinds of subunits. αBgt-binding proteins whose function is unknown are also found in brain. All these proteins belong to the same gene family. The human medulloblastoma cell line TE671 expresses a functional AChR which binds αBgt. Surprisingly, the AChR of this neuron-derived cell line has electrophysiological, immunological and biochemical properties different from neuronal AChRs and very similar to muscle AChRs. The TE671 AChR binds αBgt, but is different from αBgt-binding proteins in brain. Here we show that TE671 expresses the α-subunit mRNA coding for the muscle AChR, thereby proving that TE671 expresses a muscle-type AChR that is not expressed in adult brain. The isolated cDNA clones should prove useful for expression of large amounts of human muscle-type AChR α-subunit protein for studies of the autoimmune response to muscle AChRs in human myasthenia gravis.

Acetylcholine receptor; Myasthenia gravis; cDNA; (TE671 cell line)

1. INTRODUCTION

The nicotinic acetylcholine receptor (AChR) gene family includes AChRs from skeletal muscle, neurons, the neuronal α-bungarotoxin (αBgt)-binding component and the more distantly related receptors for γ-aminobutyric acid and glycine (review [1]).

AChRs from muscle are thought to closely resemble AChRs from *Torpedo* electric organ, which are formed from four different subunits (α, β, γ and δ). These are organized in the order αβαγδ, like barrel staves around a central cation channel [2]. The sites which bind acetylcholine (ACh) and αBgt and regulate channel opening are located on the α-subunits, near cysteines α192 and 193 [3–5].

AChRs purified from brain have been found to consist of only two kinds of subunits [6,7]. Although their ACh-binding subunits have cysteines homologous to α192–193 of AChRs from muscle [8–10], neuronal AChRs do not bind αBgt [6–12].

αBgt-binding proteins are found on neurons of ganglia [11,13] and brain [7,14,15], but αBgt does not block AChR-induced depolarization in these neuronal preparations [11,13].

The human medulloblastoma cell line TE671 [16] has been reported to have functional AChRs which are blocked by αBgt [17]. It was assumed

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The nucleotide sequence presented here has been submitted to the EMBL/GenBank database under the accession number no. Y00762

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Fig.1. Northern blot analysis of TE671 poly(A)$^+$ RNA probed with mouse muscle AChR α-subunit cDNA.

that these were a neuronal AChR type which could be blocked by αBgt [17–19].

Previously, we observed that AChRs from TE671 cells were immunologically similar to the AChR from human muscle [20,21] and immunologically distinct from both human brain AChRs which did not bind αBgt and human αBgt-binding proteins [21]. Specifically, we observed that autoantibodies from myasthenia gravis (MG) patients reacted essentially as well as with AChR from TE671 cells as they did with AChRs from human muscle [20]. However, the MG patient sera did not react with either AChRs or αBgt-binding proteins from human brains [21]. Recently we observed that, at the level of single channel function, AChRs in TE671 cells resemble those found in muscle and that AChRs purified from TE671 cells have four kinds of subunits which closely resemble those of AChRs from *Torpedo* electric organ (Luther, M. et al., in preparation).

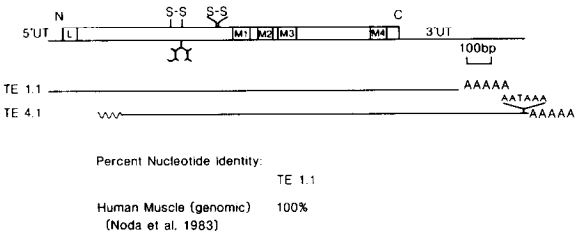


Fig.2. Analysis of TE 1.1 and TE 4.1 with deduced structural features of the AChR α-subunit. ☆, glycosylation site at Asn-141; UT, untranslated region; L, leader peptide; M1–M4, hydrophobic segments; ∿∿, intron sequence.

Here we report the cloning and sequencing of a cDNA for the α-subunit of AChRs from TE671 cells. The sequence shows extensive identity to α-subunits of muscle AChRs from several species, and is identical to the sequence predicted by a human genomic clone previously reported by Numa and co-workers [22]. This proves that this neuronal cell line is expressing α-subunits identical to those of AChRs in muscle rather than a neuronal-type AChR which is blocked by αBgt.

2. MATERIALS AND METHODS

2.1. *Cell cultures*

TE671 cells were grown in Iscove's modified Dulbecco's minimal essential medium (Irvine Scientific) supplemented with 10% fetal bovine serum.

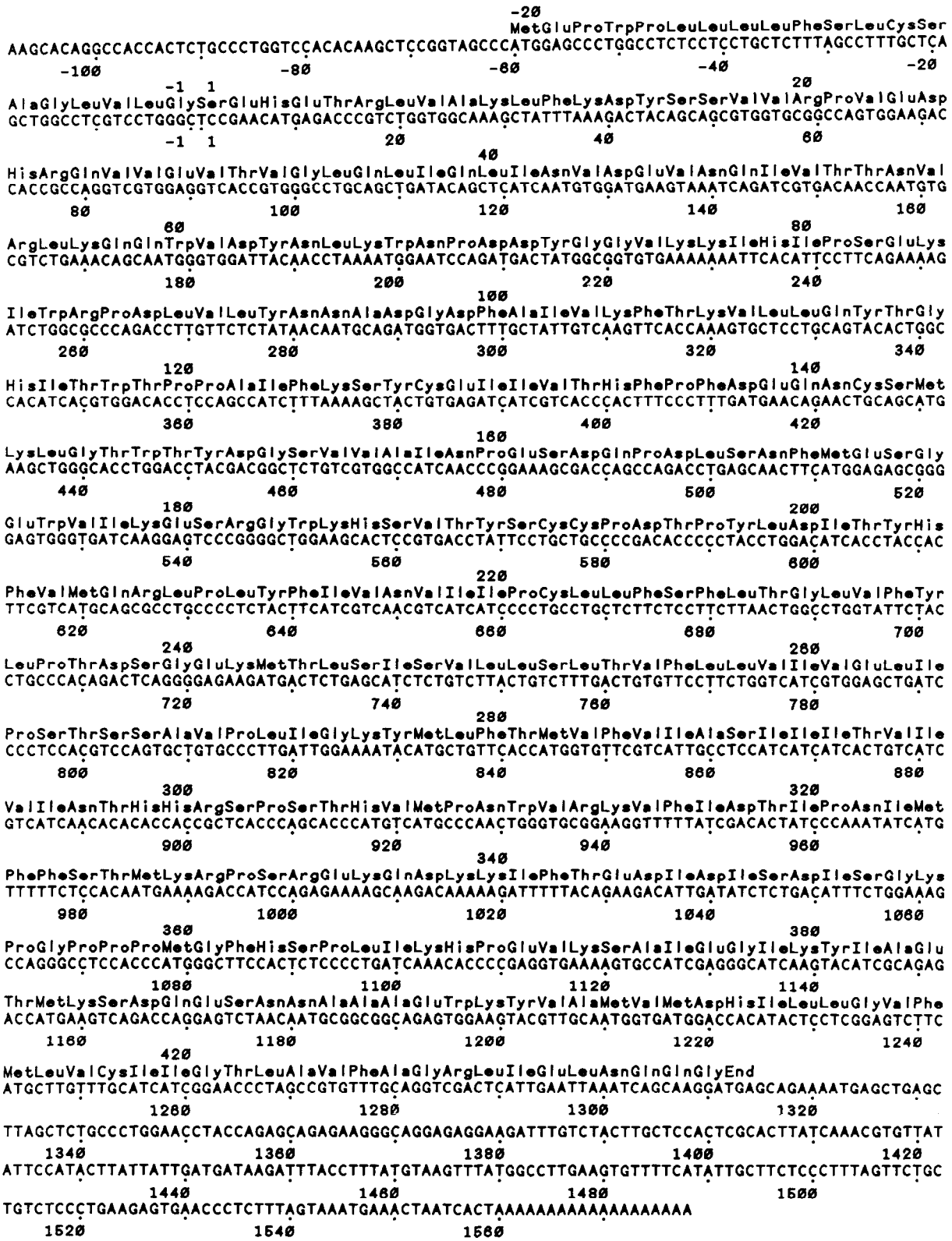
2.2. *Northern blot analysis*

DNA/RNA experiments were carried out, following standard procedures [23]. RNA isolation and Northern blot analysis were performed as described in [24] except that RNA was blotted onto Hybond-N nylon membranes (Amersham) and UV-crosslinked. Poly(A)$^+$ RNA was obtained by oligo(dT) chromatography.

2.3. *cDNA library*

cDNA was synthesized by the RNase H method [25], following the protocol of Watson and Jackson [26]. cDNA >1 kb was ligated into the cloning vector λ-zap (Stratagene). Approx. 10^5

Fig.3. Nucleotide sequence of TE 1.1 with deduced amino acid sequence. The mature protein starts at position 1.


-20
MetGluProTrpProLeuLeuLeuLeuPheSerLeuCysSer
AAGCACAGGCCACCACTCTGCCCTGGTCCACACAAGCTCCGGTAGCCCATGGAGCCCTGGCCTCTCCTCCTGCTCTTTAGCCTTTGCTCA
-100 -80 -60 -40 -20
-1 1 20
AlaGlyLeuValLeuGlySerGluHisGluThrArgLeuValAlaLysLeuPheLysAspTyrSerSerValValArgProValGluAsp
GCTGGCCTCGTCCTGGGCTCCGAACATGAGACCCGTCTGGTGGCAAAGCTATTTAAAGACTACAGCAGCGTGGTGCGGCCAGTGGAAGAC
-1 1 20 40 60
40
HisArgGlnValValGluValThrValGlyLeuGlnLeuIleGlnLeuIleAsnValAspGluValAsnGlnIleValThrThrAsnVal
CACCGCCAGGTCGTGGAGGTCACCGTGGGCCTGCAGCTGATACAGCTCATCAATGTGGATGAAGTAAATCAGATCGTGACAACCAATGTG
80 100 120 140 160
60 80
ArgLeuLysGlnGlnTrpValAspTyrAsnLeuLysTrpAsnProAspAspTyrGlyGlyValLysLysIleHisIleProSerGluLys
CGTCTGAAACAGCAATGGGTGGATTACAACCTAAAATGGAATCCAGATGACTATGGCGGTGTGAAAAAAATTCACATTCCTTCAGAAAAG
180 200 220 240
100
IleTrpArgProAspLeuValLeuTyrAsnAsnAlaAspGlyAspPheAlaIleValLysPheThrLysValLeuLeuGlnTyrThrGly
ATCTGGCGCCCAGACCTTGTTCTCTATAACAATGCAGATGGTGACTTTGCTATTGTCAAGTTCACCAAAGTGCTCCTGCAGTACACTGGC
260 280 300 320 340
120 140
HisIleThrTrpThrProProAlaIlePheLysSerTyrCysGluIleIleValThrHisPheProPheAspGluGlnAsnCysSerMet
CACATCACGTGGACACCTCCAGCCATCTTTAAAAGCTACTGTGAGATCATCGTCACCCACTTTCCCTTTGATGAACAGAACTGCAGCATG
360 380 400 420
160
LysLeuGlyThrTrpThrTyrAspGlySerValValAlaIleAsnProGluSerAspGlnProAspLeuSerAsnPheMetGluSerGly
AAGCTGGGCACCTGGACCTACGACGGCTCTGTCGTGGCCATCAACCCGGAAAGCGACCAGCCAGACCTGAGCAACTTCATGGAGAGCGGG
440 460 480 500 520
180 200
GluTrpValIleLysGluSerArgGlyTrpLysHisSerValThrTyrSerCysCysProAspThrProTyrLeuAspIleThrTyrHis
GAGTGGGTGATCAAGGAGTCCCGGGGCTGGAAGCACTCCGTGACCTATTCCTGCTGCCCCGACACCCCCTACCTGGACATCACCTACCAC
540 560 580 600
220
PheValMetGlnArgLeuProLeuTyrPheIleValAsnValIleIleProCysLeuLeuPheSerPheLeuThrGlyLeuValPheTyr
TTCGTCATGCAGCGCCTGCCCCTCTACTTCATCGTCAACGTCATCATCCCCTGCCTGCTCTTCTCCTTCTTAACTGGCCTGGTATTCTAC
620 640 660 680 700
240 260
LeuProThrAspSerGlyGluLysMetThrLeuSerIleSerValLeuLeuSerLeuThrValPheLeuLeuValIleValGluLeuIle
CTGCCCACAGACTCAGGGGAGAAGATGACTCTGAGCATCTCTGTCTTACTGTCTTTGACTGTGTTCCTTCTGGTCATCGTGGAGCTGATC
720 740 760 780
280
ProSerThrSerSerAlaValProLeuIleGlyLysTyrMetLeuPheThrMetValPheValIleAlaSerIleIleIleThrValIle
CCCTCCACGTCCAGTGCTGTGCCCTTGATTGGAAAATACATGCTGTTCACCATGGTGTTCGTCATTGCCTCCATCATCATCACTGTCATC
800 820 840 860 880
300 320
ValIleAsnThrHisHisArgSerProSerThrHisValMetProAsnTrpValArgLysValPheIleAspThrIleProAsnIleMet
GTCATCAACACACACCACCGCTCACCCAGCACCCATGTCATGCCCAACTGGGTGCGGAAGGTTTTTATCGACACTATCCCAAATATCATG
900 920 940 960
340
PhePheSerThrMetLysArgProSerArgGluLysGlnAspLysLysIlePheThrGluAspIleAspIleSerAspIleSerGlyLys
TTTTTCTCCACAATGAAAAGACCATCCAGAGAAAAGCAAGACAAAAAGATTTTTACAGAAGACATTGATATCTCTGACATTTCTGGAAAG
980 1000 1020 1040 1060
360 380
ProGlyProProProMetGlyPheHisSerProLeuIleLysHisProGluValLysSerAlaIleGluGlyIleLysTyrIleAlaGlu
CCAGGGCCTCCACCCATGGGCTTCCACTCTCCCCTGATCAAACACCCCGAGGTGAAAAGTGCCATCGAGGGCATCAAGTACATCGCAGAG
1080 1100 1120 1140
ThrMetLysSerAspGlnGluSerAsnAsnAlaAlaAlaGluTrpLysTyrValAlaMetValMetAspHisIleLeuLeuGlyValPhe
ACCATGAAGTCAGACCAGGAGTCTAACAATGCGGCGGCAGAGTGGAAGTACGTTGCAATGGTGATGGACCACATACTCCTCGGAGTCTTC
1160 1180 1200 1220 1240
420
MetLeuValCysIleIleGlyThrLeuAlaValPheAlaGlyArgLeuIleGluLeuAsnGlnGlnGlyEnd
ATGCTTGTTTGCATCATCGGAACCCTAGCCGTGTTTGCAGGTCGACTCATTGAATTAAATCAGCAAGGATGAGCAGAAAATGAGCTGAGC
1260 1280 1300 1320
TTAGCTCTGCCCTGGAACCTACCAGAGCAGAGAAGGGCAGGAGAGGAAGATTTGTCTACTTGCTCCACTCGCACTTATCAAACGTGTTAT
1340 1360 1380 1400 1420
ATTCCATACTTATTATTGATGATAAGATTTACCTTTATGTAAGTTTATGGCCTTGAAGTGTTTTCATATTGCTTCTCCCTTTAGTTCTGC
1440 1460 1480 1500
TGTCTCCCTGAAGAGTGAACCCTCTTTAGTAAATGAAACTAATCACTAAAAAAAAAAAAAAAAAAAA
1520 1540 1560

recombinants were screened at high stringency with the 430 bp *Pst*I fragment of pMARα15 [27], containing the sequences for the N-terminal of the mouse muscle α-AChR subunit. Positive clones were plaque purified, and insert bearing plasmids were obtained using a helper phage following the supplier's protocol.

2.4. *Analysis of cDNA clones*

Plasmid DNA was characterized by restriction enzyme digestion, followed by agarose gel electrophoresis and Southern blotting.

For DNA sequencing, nested deletions were produced by the EXO III/Mung Bean protocol (Stratagene) in both orientations. DNA sequencing was performed using a modification of the dideoxynucleotide chain termination method of Sanger et al. [28].

3. RESULTS

Northern blot analysis of total cellular poly(A)$^+$ RNA (fig.1) revealed a single RNA species of approx. 2 kb when probed with the mouse muscle AChR subunit cDNA clone pMARα15 [27] at high stringency (final washing 0.3 × SSPE at 65°C). Three larger RNA species >4 kb were visible after longer exposure (not shown). Hybridization with probes derived from cDNAs coding for the β-, γ- and δ-subunits of the mouse muscle AChR also revealed one major RNA species for each probe, suggesting that β-, γ- and δ-subunits are also expressed (Luther, M. et al., in preparation).

To analyze the primary structure of the α-subunit, a cDNA library was constructed. Screening of approx. 10^5 recombinants allowed the isolation of four overlapping clones harboring inserts >1.3 kb. Two clones, TE 1.1 and TE 4.1 (fig.2), were analyzed by DNA sequencing. The 3′-end of the 1686 bp insert of TE 1.1 is probably the result of an oligo(A) stretch present in the genomic sequence [22] that might have been the priming site for the cDNA synthesis. The poly(A) tail in TE 4.1 follows the polyadenylation signal AATAAA. The 5′-end of TE 4.1 represents sequences of intron 3. Nucleotide sequence (fig.3) comparison of TE 1.1 with the predicted exons of the human muscle genomic α-subunit sequence [22] revealed 100% identity. This confirms that TE671 expresses exactly the same human gene which is thought to code for the functional muscle α-subunit. This is based on the >95% sequence identity of the human muscle α-subunit with those from calf and mouse muscle α-subunits, both of which have been shown to function in oocyte expression systems [29,30].

4. DISCUSSION

The deduced amino acid sequence of TE 1.1 shows the typical features of an ACh-binding subunit of muscle AChRs. It exhibits 95% amino acid sequence identity to α-subunits of AChR from mouse muscle [27]. A hydrophobic leader sequence of twenty amino acids, four hydrophobic segments M1–M4, and two extracellular cysteines at 128 and 142 (presumably linked by a disulfide bridge) are

Table 1

Binding of mAbs on Western blots to *Torpedo* and human AChR α-subunits

mAb no.	mAb binding site	Sequence	Binding on Western blots to α-subunit
3,5	*Torpedo* α349–357	*Torpedo*: S D I S G K Q V T	+
		human: . . . . . P G P	–
142	*Torpedo* ~α353–359	*Torpedo*: G K Q V T G E	+
		human: . . P G P P P	–
152,153, 155,157, 164	*Torpedo* α371–378	*Torpedo*: D V K S A I E G	+
		human: E	+

mAb binding sites from [35]. (Dot) Amino acid as in *Torpedo* sequence

present. The adjacent disulfide linked cysteines 192–193 are unique to the α-subunit and can be affinity labeled with MBTA [3,31]. The α-subunit of the AChR of TE671 can also be affinity labeled with MBTA (Luther, M. et al., in preparation).

The sequence of the ACh-binding subunit of AChRs from TE671 is quite distinct from that of the ACh-binding subunit of rat neuronal AChRs, although they both have a leader sequence, hydrophobic segments M1–M4 and cysteines at 128, 142, 192 and 193. It exhibits only 51% amino acid sequence identity with a cDNA identified in PC12 cells [32] and 47% sequence identity with a cDNA identified in rat brain [10]. This rat brain cDNA is known to correspond to the ACh-binding subunit of AChR purified from rat brain [9]. Muscle-type AChR protein was not detected in human brain immunologically [21], nor has muscle α-subunit mRNA been detected in rat brain (Boulter, J., personal communication).

Why is muscle AChR expressed in a neuronal cell line? It is interesting to remember that the BC3H1 mouse cell line which is studied as a model muscle AChR was derived from a CNS tumor and only partially exhibits skeletal muscle morphology [33]. One possible explanation for why TE671 expresses muscle AChR may be that this cell line arises from the immortalization of a neuronal cell type expressed transiently during development, but not in adult brain. Conditions have been found which can either up-regulate AChR expression in this cell line or down-regulate expression of AChR while stopping division and inducing a neuronal morphology with greatly extended processes (Luther, M. et al., in preparation). This may be analogous to the effect of a normal developmental inducer which suppresses muscle AChR synthesis and induces terminal neuronal differentiation.

Although α-subunits of AChRs from *Torpedo* and human muscle have 80% amino acid sequence identity [22], AChRs from these species exhibit $<5\%$ serum antibody crossreactivity [34]. Monoclonal antibodies (mAbs) which bind to epitopes formed by contiguous amino acid sequences can also clearly discriminate between α-subunits of the two species, as shown by the examples in table 1.

Torpedo AChR α-subunit cDNA clones have been expressed in fragments in bacteria [36,37], as full-length clones in yeast [38] and cell lines [39,40]. The proteins in bacteria have been used to map the αBgt-binding site [36,37] and epitopes recognized by T cells in experimental autoimmune MG (EAMG) and MG (Melmes, A. et al., personal communication). Blount and Merlie [40] showed that the BC3H1 α-subunit expressed in quail fibroblast acquires the main immunogenic region (MIR), a highly conformation-dependent epitope against which the majority of antibodies in EAMG and MG are directed [41].

α-subunits are very important in the autoimmune response to AChR which occurs in MG because denatured α-subunit epitopes predominate in T lymphocyte recognition of AChRs [42,43], and because conformation-dependent α-subunit epitopes predominate in B lymphocyte recognition of AChRs ([41] and review [44]). Although electric organ provides large amounts of AChR for studies of EAMG, human AChR for studies of species-specific autoimmune responses in MG has been available in only negligible amounts from extracts of amputated leg muscle. TE671 cells provide a far richer source of human muscle AChR, but still submilligram amounts. From suitable expression systems, α-subunits from TE671 cells may in the future be prepared in both desirable conformations and large amounts, with great benefit for studies of MG.

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