·全科医学论著·

应用 iTRAQ 技术筛选 DNT 与低级别胶质瘤差异表达蛋白

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摘要:目的 应用同位素标记相对和绝对定量蛋白质组学技术(iTRAQ)联合液相串联质谱筛选胚胎发育不良性神经上皮肿瘤与低级别胶质瘤的差异表达蛋白。**方法** 收集胚胎发育不良性神经上皮肿瘤(编号 113)与低级别胶质瘤(编号 114)各 6 例实体组织冻存新鲜标本,各组标本混合,通过蛋白质提取,蛋白质浓度测量(采用 Bradford 定量),聚丙烯酰胺凝胶电泳,蛋白质酶解,iTRAQ 标记,SCX 分离,再进行基于 QE 的液质联用分析,得到信息数据。使用蛋白质鉴定软件 Mascot 2.3.02,选择 UniProt-Human 数据库,然后进行数据库搜索和生物信息学分析。依据蛋白质丰度水平,当差异倍数达到 1.3 倍以上,且经统计检验其 $P<0.05$ 时,视为差异蛋白。**结果** 鉴定出了中国大陆黄种人 DNT 相对于低级别胶质瘤的差异蛋白质 88 个,其中上调蛋白质 44 个,下调蛋白质 44 个。这些差异蛋白具有不同生物学活性,并参与多种代谢及信号通路。其中重要的蛋白有水通道膜内在蛋白 1、丝氨酸/苏氨酸激酶、细胞内氯离子通道蛋白 1、膜联蛋白 A1、谷氨酰胺合成酶、硫酸软骨素多糖蛋白 4、S100A9、S100A16、S100A13、异柠檬酸脱氢酶等。**结论** iTRAQ 技术实用可靠,有效筛选出胚胎发育不良性神经上皮肿瘤与低级别胶质瘤的差异表达蛋白。

关键词:胚胎发育不良性神经上皮肿瘤;低级别胶质瘤;蛋白质组学;同位素标记相对和绝对定量技术;生物标记物

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iTRAQ technology for differentially expressed proteins screening in dysembryoplastic neuroepithelial tumor and low grade glioma

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Abstract: Objective To screen differentially expressed proteins in dysembryoplastic neuroepithelial tumor (DNT) and low grade glioma (LGG) by the proteomics analysis using isobaric tags for relative and absolute quantification (iTRAQ) combined with liquid chromatography-tandem mass spectrometry (LC-MS/MS). **Methods** The fresh frozen solid tissues of DNT (6 cases) and LGG (6 cases) were sampled and mixed. Then the protein extraction from admix specimens, protein concentration measurement (Bradford), SDS electrophoresis, protein enzymolysis, iTRAQ mark, SCX, 2D and LC-MS/MS were performed to get the data. The MS/MS data were searched against the International UniProt-Human using the Mascot 2.3.02 for peptide identification and quantification. According to protein abundance, differentially expressed proteins were determined when difference was more than 1.3 times and $P<0.05$. **Results** Total 88 differentially expressed proteins were identified between DNT and LGG in China Yellow. 44 proteins were significantly up-regulated (>1.3-fold) and also 44 were significantly down-regulated. These proteins had different of biologic activity and participated many metabolisms and signal pathways. The important proteins include aquaporin 1, serine/threonine-protein kinase, chloride intracellular channel 1, annexin A1, glutamine synthetase, chondroitin sulfate proteoglycan 4, S100A9, S100A16, S100A13, isocitrate dehydrogenase and so on. **Conclusion** The differentially expressed proteins of DNT and LGG identified by proteomic analysis using iTRAQ are reliable. The iTRAQ technology can provide a good platform to identify moresignificant molecule difference biomarkers of DNT and LGG.

Key words: Dysembryoplastic neuroepithelial tumor; Low grade glioma; Proteomics; Isobaric tags for relative and absolute quantitation; Biomarker

胚胎发育不良性神经上皮肿瘤(dysembryoplastic neuroepithelial tumor, DNT)是位于幕上的胶质神经元混合性肿瘤,主要发生在大脑皮质,WHO 分级Ⅰ级,属于良性肿瘤。组织学上分为单纯型、复合型和非特异型 3 个亚型,后两者形态学与星形细胞瘤、少突胶质细胞瘤十分相似,鉴别困难。目前缺乏特异的 DNT 诊断标记物,病理医师在面对复杂型和非特异型 DNT 的诊断时仍存在很大的挑战。

同位素标记相对和绝对定量技术(isobaric tags for relative and absolute quantitation, iTRAQ)是一种进行定量研究的蛋白质组学新兴技术,相对于其他蛋白质组学技术在定量可信度、覆盖度及定量精度方面都有明显的优势。本研究利用 iTRAQ 结合液相串联质谱(liquid chromatography coupled with tandem mass spec-

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trometry, LC-MS/MS) 对 DNT 与低级别胶质瘤组织标本进行蛋白质组学分析，鉴定出 DNT 与低级别胶质瘤的差异表达蛋白。

1　资料与方法

1.1　资料来源　选取广州军区广州总医院神经外科脑手术分装冻存标本，其中胚胎发育不良性神经上皮肿瘤 6 例，年龄 15～56 岁，男女各 3 例。低级别胶质瘤 6 例，年龄 20～63 岁，男女各 3 例，其中星形细胞瘤 3 例，少突胶质细胞瘤 2 例，混合性星形-少突胶质细胞瘤 1 例。

1.2　检测方法　①蛋白质提取过程：称取适量的样品；②蛋白质浓度测量（采用 Bradford 定量），依据标准曲线计算出样品浓度；③聚丙烯酰胺凝胶电泳；④蛋白质酶解；⑤iTRAQ 标记；⑥用强阳离子交换色谱（strong cation exchange chromatography, SCX）进行液相分离；⑦液相串联质谱分析。

1.3　生物信息学分析　使用蛋白质鉴定软件 Mascot 2.3.02。操作时以 mgf 文件为原始文件，选择 UniProt-Human 数据库，然后进行数据库搜索。

1.4　统计学方法　使用 SPSS 19.0 统计学软件，依据蛋白质丰度水平，当差异倍数达到 1.3 倍以上，且 $P < 0.05$ 时，视为差异蛋白。

2　结　果

2.1　蛋白质定量　当蛋白的丰度比即差异倍数达到 1.3 倍以上，且经统计检验，$P < 0.05$ 视该蛋白为差异蛋白。鉴定出 DNT 与 LGG 差异蛋白 88 个，其中上调蛋白 44 个（见表 1），下调蛋白 44 个（见表 2）。

2.2　差异蛋白的 GO 富集分析　针对鉴定出的所有差异蛋白进行 GO 功能注释分析，从而给出差异蛋白质与哪些生物学功能显著相关。本实验鉴定出的差异蛋白涉及钙离子结合、柠檬酸盐跨膜转运蛋白活性、三羧酸跨膜转运蛋白活性、类脂运载体活性、有机酸跨膜转运蛋白活性、羧酸跨膜转运蛋白活性、结构分子活性等多种生物学活性。

2.3　差异蛋白的 Pathway 富集分析　通路显著性富集分析方法同基因本体论功能富集分析，是以 KEGG 公共数据库里的代谢通路为单位，应用超几何检验，找出与所有鉴定到蛋白背景相比，在差异蛋白中显著性富集的通路。通过通路显著性富集分析确定这些差异蛋白参与细胞分裂周期、凋亡、细胞色素 P450 对外源性化学物质代谢、谷光苷肽代谢、血管内皮生长因子信号通路、过氧化物酶体等多种代谢及信号通道。

3　讨　论

经实验鉴定出的上调蛋白质中，水通道膜内在蛋白 1（AQP1）是特异性跨膜转运水分子的蛋白，在中枢神经系统主要表达在脉络丛上皮细胞，参与脑脊液的形成。在胶质瘤中，AQP1 主要在星形胶质细胞瘤细胞和血管内皮细胞中表达，并且随着肿瘤级别的升高 AQP1 表达增加[1]。

表 1　DNT 相对于 LGG 上调蛋白

序号	蛋白编号	蛋白名称
1	B7Z3W8	Transporter
2	B2R6P2	aquaporin 1 (channel-forming integral protein, 28 kDa, AQP1)
3	A6NFQ9	Septin-8
4	CYTC	Cystatin-C
5	M0QZW8	RAC-beta serine/threonine-protein kinase
6	E7EWW9	Glutathione S-transferase Mu 1
7	S100B	Protein S100-B
8	Q5T7W3	Tropomodulin-1
9	CBR1	Carbonyl reductase [NADPH] 1
10	B4DSL6	Actin-binding protein anillin
11	Q53FB0	Chloride intracellular channel 1 variant
12	E7EPZ9	Tenascin-X
13	ANXA1	Annexin A1
14	GLNA	Glutamine synthetase
15	CSPG4	Chondroitin sulfate proteoglycan 4
16	MOES	Moesin
17	LRP1	Prolow-density lipoprotein receptor-related protein 1
18	H0YD13	CD44 antigen
19	C9JF17	Apolipoprotein D
20	OR1M1	Olfactory receptor 1M1
21	NB5R2	Isoform 2 of NADH-cytochrome b5 reductase 2
22	APOA4	Apolipoprotein A-IV
23	H6VRF8	Keratin 1
24	A0AVG7	Breast carcinoma amplified sequence 1
25	B4DV94	pre-B-cell leukemia transcription factor interacting protein1 (PBXIP1)
26	KAD4	Adenylate kinase 4, mitochondrial
27	A1A5C4	RRBP1 protein
28	K1C10	Keratin, type I cytoskeletal 10
29	Q6MZQ6	Putative uncharacterized protein DKFZp686G11190
30	B2R4M6	S100 calcium binding protein A9 (calgranulin B, S100A9)
31	SNP25	Isoform 2 of Synaptosomal-associated protein 25
32	S10AG	Protein S100-A16
33	ERMIN	Isoform 2 of Ermin
34	B1AVU8	Saposin-D
35	Q68DQ4	Putative uncharacterized protein DKFZp779L0468
36	A0A024QZX5	Serpin peptidase inhibitor, clade B (Ovalbumin), member 6, isoform CRA_d
37	S10AD	Protein S100-A13
38	B4DI81	Gap junction protein
39	Q9P1Y0	Histamine N-methyltransferase
40	Q5U068	Hippocalcin
41	V5LU97	Huntingtin interacting protein 1 variant
42	D3YTA9	Calcineurin subunit B type 1
43	E7EVA0	Microtubule-associated protein
44	HP1B3	Heterochromatin protein 1-binding protein 3

S100B 蛋白是神经胶质细胞的标志蛋白，其重要的生物学作用是调节神经胶质细胞及神经元中纤维蛋白及中间丝的合成，参与细胞内的分化、凋亡等生理过程[2]。此外，S100B 蛋白还具有神经营养[3]、信号调节因子[4]等作用。细胞内氯离子通道蛋白 1（chloride intracellular channel 1, CLIC1）是一种跨膜蛋白，氨基端在外、羧基端在内。现已发现CLIC1与多种肿瘤的发

表 2 DNT 相对于 LGG 下调蛋白

序号	蛋白编号	蛋白名称
1	B3KS75	Biglycan
2	B4DMY3	heterogeneous nuclear ribonucleoprotein A/B (HNRPAB), transcript variant 1
3	E9PBF6	Lamin-B1
4	A8K288	cDNA FLJ76322
5	Q6IBG1	MYL9 protein
6	Q96EB3	EEF1A1 protein
7	TAGL	Transgelin
8	Q1WWL2	PTGFRN protein
9	ECH1	Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial
10	F8VW96	Cysteine and glycine-rich protein 2
11	SETLP	Protein SETSIP
12	H0YKC5	Deoxyuridine 5 ~ -triphosphate nucleotidohydrolase, mitochondrial
13	G5E9L9	Doublecortin and CaM kinase-like 2, isoform CRA_c
14	H7C1S9	Sideroflexin-5
15	J3QT54	Cleavage and polyadenylation-specificity factor subunit 7
16	TMM65	Transmembrane protein 65
17	A8K3K1	cDNA FLJ78096, highly similar to Homo sapiens actin, alpha, cardiac muscle (ACTC)
18	STX1A	Syntaxin-1A
19	A8K1X2	Septin 3, isoform CRA_b
20	Q53F35	Acidic (Leucine-rich) nuclear phosphoprotein 32 family, member B variant
21	NECA2	N-terminal EF-hand calcium-binding protein 2
22	J3QRG6	Cyclin-dependent kinase inhibitor 2A, isoforms 1/2/3
23	SYPH	Synaptophysin
24	J3KR03	Rabphilin-3A
25	B3KVR1	Small nuclear ribonucleoprotein-associated protein
26	GHC1	Mitochondrial glutamate carrier 1
27	XRCC5	X-ray repair cross-complementing protein 5
28	D3DSM4	Collagen, type XVIII, alpha 1, isoform CRA_d
29	Q53GL5	Isocitrate dehydrogenase 2 (NADP +), mitochondrial variant
30	E7ETK0	40S ribosomal protein S24
31	SMOC1	Isoform 2 of SPARC-related modular calcium-binding protein 1
32	CO4B	Complement C4-B
33	Q05C31	Uncharacterized protein
34	SFXN1	Sideroflexin-1
35	A0A024R814	Ribosomal protein L7, isoform CRA_a
36	APOE	Apolipoprotein E
37	B3KXB8	Synaptopodin
38	B4DP62	Solute carrier family 25 (Mitochondrial carrier citrate transporter), member 1, isoform CRA_b
39	I3L397	Eukaryotic translation initiation factor 5A-1
40	ACTN2	Alpha-actinin-2
41	Q6FHG6	PRELP protein
42	B7Z1I4	Neurotrimin
43	CO6A1	Collagen alpha-1(VI) chain
44	RS9	ribosomal protein S9

生、发展有关，并与肿瘤的侵袭及转移相关[5-6]。膜联蛋白 A1(Annexin A1, ANXA1)的表达在不同肿瘤组织中有差异，并且同一肿瘤不同类型中表达也不一样，其异常表达及细胞内定位改变可能跟多种恶性肿瘤的分化及转移相关。Annexin A1 与肿瘤关系密切，可能潜在的新的肿瘤标志物，为肿瘤的早期诊断、治疗及预后提供新的判断标准[7]。谷氨酰胺合成酶(Glutamine synthetase, GS)作为 Wnt 信号通路的靶基因，伴随 β-catenin 的异常激活而可导致许多疾病的发生，常表达于星形胶质细胞和少突胶质细胞，参与谷氨酸-谷氨酰胺的代谢循环，与胶质细胞的增殖和分化相关[8]。硫酸软骨素多糖蛋白 4(Chondroitin sulfate proteoglycan 4, CSPG4)在多种类型的肿瘤中表达异常，参与了多种肿瘤细胞的生长、黏附、运动和侵袭过程，其特异性单克隆抗体可抑制肿瘤细胞生长，是一个很有前途的潜在肿瘤治疗新靶点[9]。

S100A9 参与细胞分化、增殖、蛋白磷酸化、突变细胞的侵袭与转移等过程。已有研究发现，S100A9 在结肠癌、肺癌、甲状腺癌、膀胱癌、乳腺癌等多种肿瘤组织中呈高表达，且与肿瘤组织的分化程度呈负相关[10-11]。S100A16 在许多肿瘤组织中表达上调，表明该基因与肿瘤的进展和转移密切相关[12]。S100A13 属于钙结合蛋白家族的一个较新成员，与组织炎症反应、新管腔结构生成及肿瘤生长、浸润、转移关系密切[13]。

下调蛋白质中，异柠檬酸脱氢酶(isocitrate dehydrogenase, IDH)相对较为重要，其基因共有 5 种，编码 3 种不同的酶，分别称为 IDH1、IDH2 和 IDH3。测序分析发现 IDH1(2q33.3)和 IDH2(15q26.1)频发突变在Ⅱ、Ⅲ级胶质瘤，尤其是继发性胶质母细胞瘤[14]。IDH1/2 突变也发生在人类其他类型肿瘤，如黑色素瘤、前列腺癌、结肠癌、甲状腺癌和软骨肉瘤等[15]。至于 IDH3，至今尚未报道肿瘤中该基因突变。

本实验证明了 iTRAQ 技术为筛选出低级别胶质瘤的分子鉴别标记物提供了一个良好的平台。但对这些蛋白在 DNT 与低级别胶质瘤发生发展中的具体病理生理机制，其生物学功能及参与的信号通路对 DNT 与低级别胶质瘤的具体影响机制仍有待进一步研究。对备选的分子鉴别标记物仍有待进一步的实验验证。

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1 年内,也有多次复发的报道。约 15% ~35% 的 SFT 在初诊中诊断为恶性肿瘤,影响恶性 SFT 患者生存率的主要因素是肿瘤分期与完整的外科切除[14]。本组患者均完整切除,随访过程中,未见复发及转移,效果满意。即使外侵较重的肿瘤,如具有可切除的机会,仍应积极行手术治疗,术后可辅助放射治疗。纵膈 SFT 多体积巨大,靠近纵膈内脏器,特别是后纵膈肿瘤,手术难度及风险多较大,尤其是复杂性具有外侵的 SFT,主要风险为术中大出血[15]。术前选择手术入路及范围时,应针对肿瘤的生长特点进行充分考虑,主要原则是肿瘤易切除、暴露良好、干扰小。手术中,要特别注意完整切除,外侵部分应一并切除。对于巨大肿瘤,可采取分块切除。本组 1 例患者肿瘤环绕食管生长,侵犯食管肌层及心包,肿瘤体积较大(图 1C),采取分块切除的方式完整切除肿瘤,并将受侵心包及食管肌层一并切除。1 例患者因外侵左下肺,切除左下肺叶。

综上所述,复杂纵膈 SFT 是一种少见的纵膈肿瘤,属于部分可转移的中间型纤维母细胞/肌纤维母细胞来源肿瘤,影像学诊断误诊率较高,需经病理学及确诊免疫组织化学分析,首选外科手术治疗,完整切除预后良好,外侵严重患者术后需辅助放疗。术后需长期随访[16]。随着进一步积累临床病例数据,更加深入地认识此类肿瘤,将会进一步提高复杂性纵膈 SFT 的诊断和治疗方法。

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