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·生物信息学·

大 B 细胞性淋巴瘤化疗敏感性相关蛋白类型及信号通路的生物信息学研究 *

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摘要 目的:筛选化疗敏感性不同大 B 细胞淋巴瘤中差异表达蛋白,并分析其类型和相关信号通路,为淋巴瘤化疗敏感性的研究提供重要的靶蛋白。**方法:**通过肿瘤药物敏感试验选取化疗高敏感性和低敏感性大 B 细胞淋巴瘤组织,进行蛋白质组学比较研究后得出差异表达蛋白;应用 GO- 分析软件对差异表达蛋白进行分类和关系分析。**结果:**将大 B 细胞淋巴瘤化疗高敏感组和化疗低敏感组蛋白质经二维凝胶电泳分离的差异表达蛋白通过质谱和生物信息学分析鉴定的蛋白点 52 个, 按生化过程分为 12 种蛋白,其中与代谢过程有关的蛋白最多,其次是细胞过程蛋白;按信号通路分为 20 余条信号通路包括凋亡信号通路、细胞周期相关通路等。按分子功能分为 9 类蛋白,其中结合相关蛋白最多,其次是催化活性蛋白,第三为结构蛋白。按蛋白功能分为钙结合蛋白、水解酶、氧化还原酶、磷酸酶等。按细胞内定位分为细胞外区、细胞内、核糖核蛋白复合体三类蛋白,其中细胞内蛋白数量最多,其次是核糖核蛋白复合体。根据信号通路网络图,所有差异表达蛋白以三个复杂网络区为主和四个较为简单联系网络区。**结论:**大 B 细胞性淋巴瘤的化疗敏感性与多种蛋白功能和多条信号通路的改变有关,信号通路间也存在复杂的联系。

关键词:大 B 细胞淋巴瘤;化疗;蛋白质组学;信号通路

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Bioinformatic Study on Large B Cell Lymphoma Chemosensitivity Associated Proteins Classification and Signal Pathway*

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ABSTRACT Objective: To screen the differentially expressed proteins in large B cell lymphoma with different chemosensitivity, and analyze their types and related signaling pathways to provide the target protein involved chemotherapy sensitivity of lymphoma. **Methods:** The tumor drug sensitivity test was applied to distinguish high-chemosensitivity and low-chemosensitivity of large B cell lymphoma tissue for comparative proteomic study. Gene ontology (GO)analysis software was applied to analyze the differentially expressed protein classification and their relationships. **Results:** 52 differentially expressed proteins between high-chemosensitivity and low-chemosensitivity of large B cell lymphoma tissue were separated and identified by two-dimensional gel electrophoresis, mass spectrometry and bioinformatics analysis. The 52 proteins were classified according to the biochemical process and divided into 12 kinds of protein including metabolic processes related proteins to the most, followed by cell protein. The 52 proteins were classified according to the signal pathway and belonged to more than 20 signaling pathways, including apoptosis signaling pathway and cell cycle related pathway. Of the 52 proteins were classified according to molecular function and divided into 9 protein types with the binding related protein most, followed by the catalytic activity protein, third structural proteins. Of the 52 proteins, protein functional classification included calcium binding proteins, enzymes, redox enzyme, phosphatase. Based on intracellular localization, 52 proteins were divided into extracellular proteins, inner proteins, the ribonucleoprotein complex proteins including inner proteins to most, followed by the ribonucleoprotein complex. According to the signaling network diagram, all the differentially expressed proteins in three complex network area and four relatively simple network area. **Conclusions:** Chemotherapy sensitivity of large B cell lymphoma involved changes of many proteins and a plurality of signal pathway, among there are have complex relations.

Key words: Large B cell lymphoma; Chemotherapy; Proteomics; Bioinformatic

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前言

弥漫性大 B 细胞淋巴瘤(DLBCL)是非霍奇金淋巴瘤最常见类型,用得最多的化疗方案是环磷酰胺、多柔比星、长春新碱、泼尼松联合应用方案(CHOP 方案),该方案治疗的患者较多出现复发或再次化疗的耐药,所以区别化疗耐受患者和化疗敏感患者有重要的治疗意义。为了发现与化疗敏感性相关的肿瘤标志物,本研究小组前期应用蛋白质组学技术分离并鉴定在化疗敏感性不同大 B 细胞淋巴瘤中差异表达蛋白[1,2],在本文中将进一步对差异表达蛋白进行分类以及信号通路网络进行分析,这一研究将为弥漫性大 B 细胞淋巴瘤化疗耐药机制的阐明以及探索化疗增敏的靶分子提供重要依据。

1 材料与方法

1.1 主要材料与仪器

淋巴瘤组织样本取自湖南省肿瘤医院手术标本。收集新鲜淋巴结组织,标本以低温生理盐水冲洗干净,去除血液和污渍,分为两部分,一部分用于常规病理诊断,一部分置于液氮冷存,常规切片经免疫组织化学检测确诊为弥漫性大 B 细胞淋巴瘤,免疫标记 CD20,CD79 均为强阳性。

1.2 实验方法

1.2.1 化疗敏感性不同大 B 细胞淋巴瘤差异表达蛋白的质谱鉴定 针对前期双向凝胶电泳分离的大 B 细胞淋巴瘤高敏感组和低敏感组差异表达蛋白[1,2],选择更多差异超过 2 倍以上的蛋白质点进行质谱鉴定,进行脱色,透明,干燥,酶解,萃取,脱盐后用于质谱分析, 生物信息学分析, 将样品放入 MALDI-TOF-MS 质谱仪中,每个蛋白样品分别测定 3 次的质谱峰,所得数据通过 Data explorer TM4.0 收集。指纹图的数据输入 Mascot 蛋白质网站数据库中检索(www.matrixscience.com),Distiller 软件检索后,当匹配分数达到或超过 40 时,待测蛋白的氨基酸序列与数据库中某已知蛋白的氨基酸序列覆盖率较高,认为匹配的可能性很大,统计学上有意义。

1.2.2 Gene ontology 分析软件研究大 B 细胞淋巴瘤化疗敏感性相关蛋白相互关系的信号通路网络 Gene Ontology 软件具有分子功能(Molecular Function)、生物过程(biological process)和细胞组成(cellular component)三方面的分析功能,其中将位于不同数据库中的基因和基因产物进行联系, 形成网络,在本研究中它能将与蛋白质组学筛选的与淋巴瘤化疗敏感相关蛋白的功能和联系进行较好地分析。首先对差异基因进行相应的生物学功能分类, 采用 GO 数据库中的功能聚类注释结果,并根据统计检验方法(P-value)筛选显著差异的分类。GO 功能分类是在某一功能层次上统计蛋白的数目或组成。也可挑选一些 Term,而后统计直接对应到该 Term 的基因或蛋白数。结果一般以柱状图或者饼图表示。根据挑选出的差异蛋白,计算这些差异基因同 GO 分类中某(几)个特定的分支的超几何分布关系,GO 分析会对每个有差异蛋白存在的 GO 返回一个 p 值,小的 p 值表示差异基因在该 GO 中出现了富集。GO 分析对实验结果有提示的作用,通过差异基因的 GO 分析,可以找到富集差异基因的 GO 分类条目,寻找不同样品的差异基因可能和哪些基因功能的改变有关。

2 结果

2.1 蛋白质组学方法研究化疗敏感性不同大 B 细胞淋巴瘤中差异表达蛋白

将大 B 细胞淋巴瘤化疗高敏感组和化疗低敏感组蛋白质经二维凝胶电泳分离的差异表达蛋白通过质谱和生物信息学分析鉴定的蛋白点 52 个,其中应用 Gene ontology 软件对这些蛋白进行功能分类, 其中 GO 对分子功能的分类来自 SWISS-PROT、PIR、NCBI CGAP 等数据库,见表 1。

2.2 化疗敏感性不同大 B 细胞淋巴瘤差异表达蛋白的类别分析

应用 Gene ontology 软件分别从生化过程、信号通路、分子功能、蛋白功能、细胞成分几个方面进行分类。

按生化过程可分为 12 种蛋白: 与细胞凋亡、细胞粘附、细胞通讯、细胞周期、细胞成分、细胞过程、发育过程、免疫系统过程、代谢过程、应激反应、系统进程、细胞转运相关的蛋白,见图 1。其中与代谢过程有关的蛋白最多,其次是细胞过程蛋白。

按信号通路进行分类,分属 20 余条信号通路,5- 羟色胺降解通路 (P04372)、血管生成相关通路、凋亡信号通路、细胞周期相关通路、RHO GTPase 介导的细胞骨架调节、DNA 修复相关通路、EGFR 信号通路、Fas 信号通路,FGF 信号通路、醣酵解相关通路、Huntington 病、趋化因子和细胞因子信号通路介导的炎症通路、胰岛素 /IGF 通路 -MAPKK/MAPK 级联反应通路、胰岛素 /IGF 通路 -PKB 信号级联反应通路、整合素信号通路、PI3 激酶通路、帕金森病相关通路、苯(基)乙胺降解通路、VEGF 信号通路、MAPK 通路、P53 通路, 见图 2。其中整合素信号通路、趋化因子和细胞因子信号通路介导的炎症通路、FGF 信号通路、帕金森病相关通路的相关蛋白是主要类型蛋白,其它类型蛋白数量较为一致。

按分子功能进行分类,分为 9 类蛋白:与结合、催化活性、酶调节活性、肌动活动、受体活性、结构分子活性、转录调节活性、翻译调节活性、转运活性相关的蛋白,见图 3。其中结合相关蛋白最多,其次是催化活性蛋白,第三为结构分子活性,其它类型蛋白数量较少。

按蛋白功能进行分类,分为 21 种蛋白,属于钙结合蛋白、伴侣蛋白、细胞骨架蛋白、酶调节蛋白、细胞外间质蛋白、水解酶、异构酶、连接酶、膜交通蛋白、核酸结合蛋白、氧化还原酶、磷酸酶、蛋白酶、受体、信号分子、储存蛋白、转录因子、转运 / 携带蛋白、转移酶、转运体,见图 4。

按细胞成分进行分类,分为 3 类蛋白:细胞外区、细胞内、核糖核蛋白复合体。细胞内蛋白数量最多,其次是核糖核蛋白复合体,细胞外区蛋白最少,见图 5。

2.2 GO 分析软件分析大 B 细胞淋巴瘤化疗敏感性相关蛋白的信号通路网络

表 1 化疗敏感性不同的大 B 细胞淋巴瘤中部分差异表达蛋白及其功能分类

Table 1 Part of differentially expressed proteins and Functional classification in large B cell lymphoma with different chemosensitivity

NO	Gene ID	Gene Name	Molecular Function
1	P09211	Glutathione S-transferase P	transferase activity
2	Q9Y265	RUVBL1	DNA helicase activity; transcription factor activity
3	P04406	Glyceraldehyde-3-phosphate	oxidoreductase activity Dehydrogenase, GAPDH
4	Q99714	3-hydroxyacyl-CoA dehydrogenase	oxidoreductase activity type-2, HSD17B10
5	P05387	60S acidic ribosomal protein P2, RPLP2	structural constituent of ribosome
6	P62081	40S ribosomal protein S7, RPS7	structural constituent of ribosome
7	Q9UL46	Proteasome activator complex	proteolysis subunit 2,PSME2
8	P08758	Annexin A5	calcium-dependent phospholipid binding
9	P11717	Cation-independent mannose-6-phosphate	receptor activity Receptor,IGF2R
10	O15511	Actin-related protein 2/3 complex subunit 5,ARPC5	structural constituent of cytoskeleton
11	P04792	Heat shock protein beta-1,HSPB1	immune system process;protein folding response to stress
12	P50395	Rab GDP dissociation inhibitor beta,GDI2	acyltransferase activity; protein binding; small GTPase regulator activity
13	O43598	c-Myc-responsive protein Rcl,;RCL	
14	P02647	Apolipoprotein A-I(1-242),APOA1	lipid transporter activity transmembrane transporter activity
15	P00915	Carbonic anhydrase 1,CA1	hydro-lyase activity
16	P05388	60S acidic ribosomal protein P0, RPLP0	structural constituent of ribosome nucleic acid binding
17	P07951	Tropomyosin beta chain, TPM2	structural constituent of cytoskeleton motor activity
18	P09493	Tropomyosin alpha-1 chain, TPM1	structural constituent of cytoskeleton motor activity
19	P31146	Coronin-1A,CORO1A	structural constituent of cytoskeleton actin binding
20	P00352	Retinal dehydrogenase 1, ALDH1A1	oxidoreductase activity
21	Q99497	Protein DJ-1, PARK7	RNA binding
22	P62258	14-3-3 protein epsilon	cell cycle, signal transduction
23	P30040	Endoplasmic reticulum protein ERp29	intracellular protein transport;exocytosis
24	P04908	Histone H2A type 1-B/E	DNA binding
25	Q9NRX4	14 kDa phosphohistidine phosphatase, PHPT1	
26	Q9UMS4	Pre-mRNA-processing factor 19,PRPF19	RNA splicing factor activity transesterification mechanism; mRNA binding
27	P15311	Ezrin,EZR	structural constituent of cytoskeleton
28	Q9C000	LRR and PYD domains-containing protein 1,NLRP1	immune system process induction of apoptosis
29	P23527	Histone H2B type 1-O, HIST1H2BO	
30	P60660	Myosin light polypeptide 6, MYL6	structural constituent of cytoskeleton; calcium ion binding; calmodulin binding
31	P52565	Rho GDP-dissociation inhibitor 1,ARHGDIA	small GTPase regulator activity receptor binding;
32	P12109	Collagen alpha-1(VI) chain,COL6A1	extracellular matrix structural constituent
33	P04908	Histone H2A type 1-B/E,HIST1H2AE	
34	P28838	Cytosol aminopeptidase, LAP3	metallopeptidase activity
35	Q9UHD8	Septin-9	tructural constituent of cytoskeleton protein binding, GTPase activity;s
36	P07195	L-lactate dehydrogenase B chain,;LDHB	oxidoreductase activity
37	P06702	Protein S100-A9	calcium ion binding, calmodulin binding

38	Q15056	Eukaryotic translation initiation factor 4H, EIF4H	translation factor activity, nucleic acid binding; translation initiation factor activity
39	Q96AE4	Far upstream element-binding protein 1, FUBP1	RNA splicing factor activity, transesterification mechanism; mRNA binding
40	P13693	Translationally-controlled tumor protein,TPT1	microtubule binding structural constituent of cytoskeleton;
41	P02647	Apolipoprotein A-I(1-242);APOA1	
42	P42126	3,2-trans-enoyl-CoA isomerase, mitochondrial	oxidoreductase activity;acetyltransferase activity; hydro-lyase activity; racemase and epimerase activity; ligase activity
43	P07910	Heterogeneous nuclear ribonucleoproteins C1/C2; HNRNPC	mRNA binding
44	O95336	6-phosphogluconolactonase;PGLS	hydrolase activit
45	P30153	Serine/threonine-protein phosphatase 2A 65 kDa	phosphoprotein phosphatase activity regulatory subunit A alpha isoform; PPP2R1A
46	P02792	Ferritin light chain; FTL	cation transport
47	P31942	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN (HNRNP)	structural constituent of ribosome; nucleic acid binding
48	Q92558	Wiskott-Aldrich syndrome protein family member 1; WASF1	actin binding structural constituent of cytoskeleton
49	P08567	Pleckstrin; PLEK	
50	Q96I24	Far upstream element-binding protein 3; FUBP3	RNA splicing factor activity transesterification mechanism; mRNA binding
51	P12004	Proliferating cell nuclear antigen; PCNA	nucleic acid binding; DNA polymerase processivity factor activity
52	P04179	Superoxide dismutase [Mn], mitochondrial	oxidoreductase activity

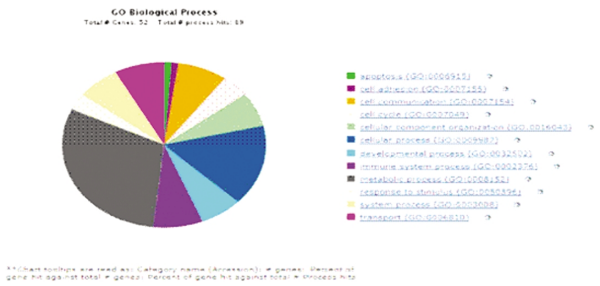

图 1 根据生化过程对蛋白进行分类

Fig.1 Classification of proteins according to biological process

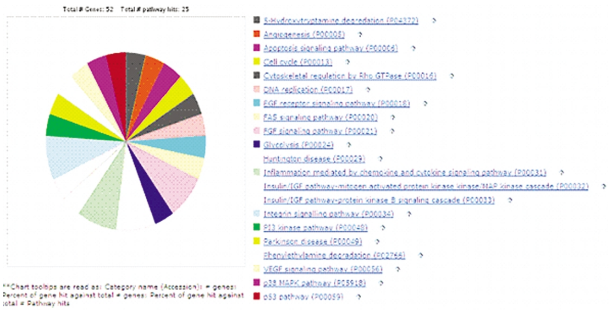

图 2 根据信号通路对蛋白进行分类

Fig.2 Classification of proteins according to signal pathway

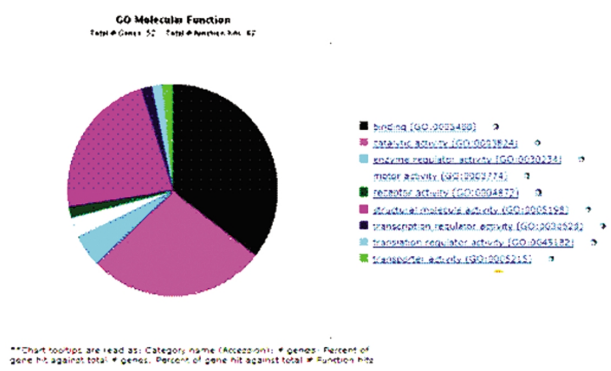

图 3 根据分子功能对蛋白进行分类

Fig.3 Classification of proteins according to molecular function

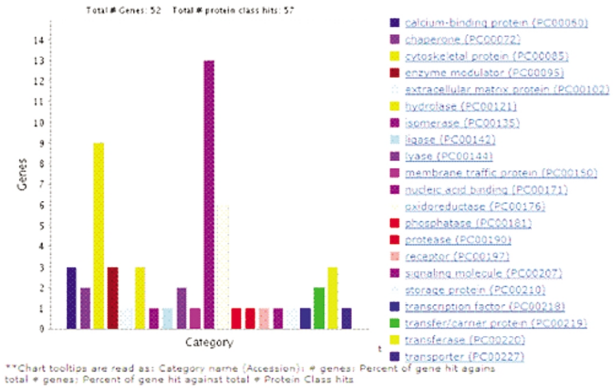

图 4 根据蛋白类型对蛋白进行分类

Fig.4 Classification of proteins according to protein class

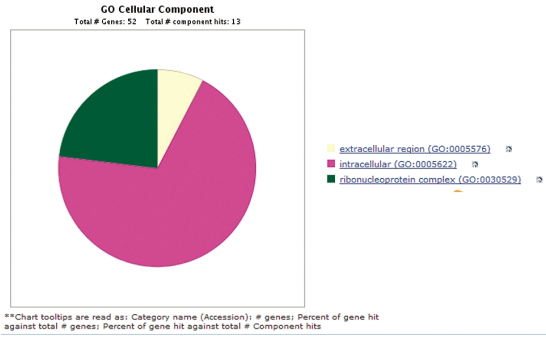

图 5 根据细胞成分对蛋白进行分类

Fig.5 Classification of proteins according to cellular component

根据信号通路网络图,所有差异表达蛋白以三个复杂网络区为主，一区包括蛋白有 RUVBL2、RFC2、REC5、RFC4、RFC3、POLD1,2,3,4、FEN1、RFC1、GADD45A、CDK4、CDK2、CDT1、CDK6、CDKN1A、CCND1、YWHAE、PPPAR1A(IGF2)、PPPAR2A、PPP2CA、TP53、PARK7、SOD2、GSTP1、HSPB1、ANXA5，二区包括蛋白有 PSME2、LAP3、PAK1、RAC1、ZER、ARH、ARHGAP1、LDHB、RHOA、IQGAP1、PLEK,三区包括蛋白有 TPT1、RPL12、RPLPO、RP57、RPLP2、RPL27A、EIF4H、S100A9、RUVBL1。其它四个较为简单联系网络区,一个蛋白有 HNRNPH3、TPM2、TPM1、MYL6，一个包括蛋白有 ARPC5 和 ARC20，一个包括蛋白有 PGLS 和 ERP29，一个包括蛋白有 HNRNPC 和 GD12,见图 6。

3 讨论

鉴于蛋白质组学筛选的大 B 细胞淋巴瘤化疗敏感相关蛋白的复杂性,本研究从生物信息学的角度对所筛选的蛋白进行类别和信号通路的分析,重点关注与大 B 细胞淋巴瘤化疗敏感相关蛋白的功能分类和相互关系,这一研究结果可为淋巴瘤化疗敏感性相关靶点和功能联系提供重要依据。

对所筛选的蛋白按分子功能分为 9 类蛋白,最多的三类蛋白为结合相关蛋白、催化活性蛋白、结构分子。按蛋白功能分为 21 种蛋白包括酶类、信号分子、转录因子等。按细胞内定位进分为 3 类蛋白,其中按数量多少依次为细胞内蛋白、核糖核蛋白复合体、细胞外区蛋白。虽然这些蛋白的类别较多,可能涉及的功能较复杂,但相对于整个人体的复杂性而言,这些分类有助于阐明淋巴瘤化疗敏感性相关蛋白间的功能联系。

本研究最为关注的蛋白生化过程与化疗敏感性的相互关系，对 12 个蛋白类别进行分析发现其中与代谢过程有关的蛋白最多,其次是细胞过程蛋白,其它相关蛋白有细胞凋亡、细胞粘附、细胞周期、应激反应等。研究发现谷胱甘肽 S- 转移酶 P (Glutathione S-transferase P, GSTP1）参与免疫系统反应和对毒素的代谢。研究发现在大肠癌患者中 GSTP1 105Val/105Val 基因型对顺铂类药物有更好的反应性且患者生存期更长[3]。在骨肉瘤细胞中 GSTP1 过表达引起对 doxorubicin 和顺铂的耐受增加，而抑制 GSTP1 增加化疗药物诱导瘤细胞凋亡和广泛的 DNA 损伤,也可抑制瘤细胞生长[4]。RUVBL1 具有 DNA 解旋酶活性和转录因子活性等功能,在单纯疱疹病毒感染的肝癌细胞蛋白质组学研究发现凋亡通路的延迟激活，其中有 Ru-

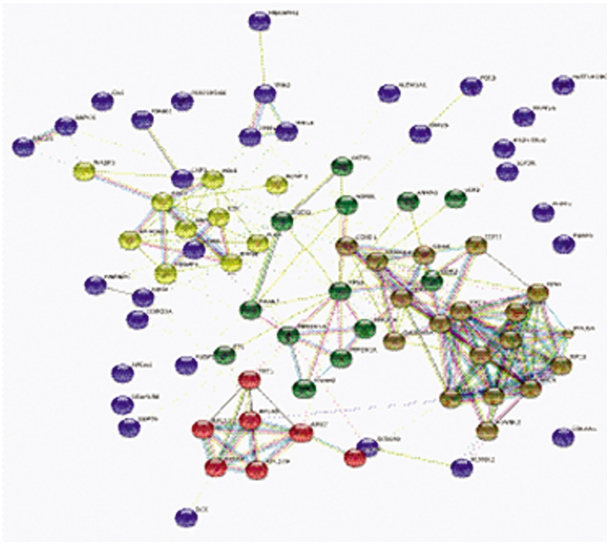

图 6 大 B 细胞淋巴瘤化疗敏感性相关蛋白间信号通路联系

Fig. 6 Signal pathway connection among large B cell lymphoma chemosensitivity associated proteins

vB-like 2 蛋白的改变 [5]。RUVBL2 在大部分肝细胞性肝癌中过表达,可能参与肝癌发生,主要涉及肿瘤细胞存活[6]。热休克蛋白 β1(Heat shock protein beta-1, HSPB1)参与免疫系统过程、蛋白折叠和对应激反应等。在卵巢癌对紫杉醇反应性体外研究中发现，阻断 HSP27 表达增加癌细胞对紫杉醇的敏感性并增加紫杉醇诱导的凋亡和活性氧产生[7]。HSP27 表达抑制可显著促进胃癌细胞对 vincristine 和 adriamycin 化疗敏感性[8]。研究显示碳酸酐酶 9 为对人舌癌细胞平阳霉素诱导耐药的原因,碳酸酐酶(CA)抑制剂乙酰唑胺和 CA9 CA9 沉默与反义寡核苷酸的应用有助于舌鳞癌 Tca8113 细胞和增强平阳霉素 / 平阳霉素化疗敏感性介质 pH 的增加[9]。14-3-3ζ 蛋白在肝癌细胞中过表达，阻断其表达可通过激活 JNK 和 P38MAPK 抑制细胞增殖,也会增加 cis-diammined dichloridoplatium (CDDP)的抗癌作用[10]。14-3-3σ 是 n-3 多不饱和脂肪酸(PUFA)可增强结肠癌细胞的化疗和放疗敏感性中的效应分子[11]。在软组织肉瘤中 14-3-3tau 的单核苷酸多态性与生存率和化疗反应性密切相关[12]。内质网蛋白(Endoplasmic reticulum protein, ERp29)在鼠肝癌细胞中 ERp29 与 BiP/GRP78 间的相互作用在衣霉素等作用后显著增强[13]。ezrin-radixin-moesin 结合磷蛋白 50(EBP50)基因 ezrin-radixin-moesin-binding phosphoprotein 50 (EBP50)稳定转染的胃癌细胞对 5-FU 诱导的凋亡率增加[14]。Rho GDP-dissociation inhibitor 1 在肺癌细胞中阻断 RhoGDIα 可增强紫杉醇诱导的凋亡并抑制细胞生存 [15]。细胞质中的氨肽酶(Cytosol aminopeptidase,LAP3)与化疗的关系没有直接报道,但 LAP 家族成员 P-LAP8 过表达的子宫内膜癌细胞对 paclitaxel 和 carboplatin 的反应性增加[16]。S100A9 是卵巢癌化疗后表达增加的基因[17]。6- 磷酸葡糖酸内酯酶(6-phosphogluconolactonase)在决定胰腺癌对吉西他滨敏感性中起着重要作用 [18]。铁蛋白轻链(Ferritin light chain)是阳离子转运和储存蛋白、储存蛋白。阻断铁蛋白重链能有效增加化疗敏感性[19]。miR-200b 介导的乳腺癌细胞中 ferritin heavy chain 下调，伴有癌细胞对阿霉素敏感性增加 [20]。WASF1 是威 - 奥德里奇综合征蛋白家族

(Wiskott-Aldrich syndrome protein family)表达增加可以使白血病细胞对化疗药物诱导的凋亡产生更强的抵抗,而抑制该蛋白则对化疗药物诱导的凋亡更敏感[21]。研究显示新的 AKT 中 pleckstrin 同源区(pleckstrin homology domain)抑制剂在鼠模型中显示出抗肿瘤活性,且与放疗和化疗有协同作用[22-24]。乳腺癌新辅助化疗后 PCNA 水平增加[25]。锰超氧化物歧化酶调节乳腺癌中 p53 活化和 PRIMA-1 毒性,PRIMA-1 可能有助于防止缺氧介导肿瘤化疗耐药[26]。视网膜脱氢酶 1 (Retinal dehydrogenase 1) 和 Far upstream element-binding protein 3(FUBP3)蛋白与肿瘤化疗的关系目前还未见报道。以上对文献报道的复习显示所筛选的蛋白大部分与化疗及化疗敏感性有关,说明本研究前期比较蛋白质组学研究结果能较可靠地反映淋巴瘤化疗敏感性相关蛋白的变化,也说明淋巴瘤化疗敏感性的生物过程涉及效应分子的复杂性。

对差异表达蛋白按信号通路进行分类发现这些蛋白涉及 20 余条信号通路,包括一些经典的生化代谢通路如 5-羟色胺降解通路、醣酵解相关通路、苯(基)乙胺降解通路;生长因子相关通路如 EGFR 信号通路、FGF 信号通路、胰岛素 /IGF 通路 -PKB 信号级联反应通路、胰岛素 /IGF 通路 -MAPKK/MAPK 级联反应通路;细胞周期和凋亡通路如 P53 通路;激酶通路如 PI3 激酶通路、MAPK 通路等。其中整合素信号通路,趋化因子和细胞因子信号通路介导的炎症通路,FGF 信号通路,帕金森病相关通路的相关蛋白是主要类型蛋白,其它类型蛋白数量较为一致。已有一些研究对凋亡通路、细胞周期相关通路、MAPK 通路等在化疗中的意义进行了研究和证实[27-29]。根据信号通路网络图,所有差异表达蛋白以三个复杂网络区为主,其它四个较为简单联系网络区。这些结果说明在对化疗敏感性的调节中涉及多个相对独立的信号通路网络,而每个网络中包括以上的多条信号通路,但目前关于不同信号通路间关系的研究还缺乏足够的研究。

综上所述,本研究通过对化疗敏感性不同的淋巴瘤的生物信息学分析发现在大 B 细胞性淋巴瘤中,化疗敏感性涉及多种蛋白、多条信号通路的改变,信号通路分子间也存在复杂的功能联系,这一研究提示对化疗敏感性的研究应用以往常规的单因子研究可能难以揭示该生物过程的复杂性,以信号通路及信号通路间的相互作用(Cross-talk)为研究对象可能会取得更为有意义的结果。

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