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·临床研究·

鼻咽癌组织中核磷蛋白表达水平与患者疗效的关系

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[摘 要] **目的:**探讨核磷蛋白(nucleophosmin, NPM、B23、NO38或NPM1)在鼻咽癌活检组织中的表达水平与增殖指数和患者个体化治疗后疗效的关系。**方法:**采用免疫组织化学法检测157例鼻咽癌活检石蜡组织中NPM1和Ki67的表达,并结合相应临床病理资料,应用统计学方法对结果进行分析。**结果:**NPM1的表达水平与Ki67的表达水平呈正相关(r=0.445, P<0.01),与淋巴结分期呈负相关(N0, N1, N2, and N3; r=−0.235,P<0.01),但与原发灶分期(T1, T2, T3 and T4; r=0.006, P>0.05)和临床分期(r=−0.74, P>0.05)无相关性。NPM1表达水平与有淋巴结转移组治疗后淋巴结情况呈负相关(r=−0.196, P<0.05),与无淋巴结转移组治疗后原发灶情况呈负相关(r=−0.349,P<0.05)。NPM1表达水平与预后无明显相关性。**结论:**NPM1在鼻咽癌组织中高表达并与Ki67的表达水平呈正相关,再次证明NPM1有促进细胞增殖的作用且可能作为一个评估个体化治疗疗效的评价指标。

[关键词] 核磷蛋白;鼻咽癌;免疫组织化学;疗效评价指标
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Relation between nucleophosmin/B23 expression level in nasopharyngeal carcinoma tissues and therapeutic efficacy

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[Abstract] Objective: To correlate the nucleophosmin (NPM, B23, NO38 or NPM1) expression levels with tumor cell proliferation indices in biopsy tissues, and investigate their significance in predicting the therapeutic efficacy for nasopharyngeal carcinoma (NPC) patients. **Methods:** One hundred and fifty seven paraffin-embedded biopsy blocks of nasopharyngeal non-keratinizing carcinoma were collected from the Department of Pathology, Sun Yat-sen cancer center during the period from January 1, 2001 till December 31, 2003. Besides H&E, the tissue sections were stained immunohistochemically with Ki-67 and NPM1 antibodies, respectively. The Ki-67 score was divided into 4 grades according to the percentages of positive tumor cells presented in the slide. Three levels of staining intensity of NPM1 were defined basing upon the painting colors exhibited in the tumor cells. The clinical data of patients were reviewed in detail, and the patients were to be followed up to July 29, 2008 by phone. The SPSS-16 soft ware was adopted for statistical analysis. **Results:** The levels of NPM1 staining intensity were positively correlated with Ki-67 scores in nasopharyngeal non-keratinizing carcinoma cells significantly (r=0.445, P<0.01). They were also correlated with regional lymph node status (N0, N1, N2, and N3; r=−0.235, P<0.01), especially the greatest dimension of the metastatic lymph node (N1 vs. N3:Z=−2.994, p<0.01, and N2 vs. N3: Z=−1.365, P<0.05) though not correlated with primary tumor (T1, T2, T3 and T4; r=0.006, P>0.05) as well as clinical staging (r=−0.74, P>0.05). The primary tumor of 31 out of 35 patients without regional lymph node metastasis (91.18%) was disappeared from sight after a set of individually designed therapy (mainly radiotherapy), and the NPM1 expression levels were correlated with whether the primary tumor could be disappeared (r=−0.349, P<0.05). After a set of individually designed

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therapy, the regional lymph node(s) could not be palpable in 84 out of 119 patients (70.59%), who had lymph node (s) metastasis before therapy already; and the expression levels of NPM1 were negatively correlated with the palpable rate of lymph node(s) (r=−0.196, P<0.05). The expression levels of NPM1 were not correlated with the survival time of patients after therapy. **Conclusions:** The NPM1 expression levels were positively correlated with nasopharyngeal carcinoma cell proliferation indices, once again confirming that NPM1 overexpression leads to increased cell growth and proliferation as reported in cancers other than nasopharyngeal carcinoma. The expression levels of NPM1 in neoplastic cells of nasopharyngeal carcinoma biopsies could be used as an indicator for predicting the efficacy of therapeutic efficacy for nasopharyngeal carcinoma patients. The high level expression of NPM1 implicates better prognosis.

[Key words] nucleophosmin; nasopharyngeal carcinoma; immunohistochemistry; therapeutic evaluation

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核磷蛋白(nucleophosmin, NPM、B23、NO38或NPM1)的编码基因定位于5q35，全长约23 kb，含12个外显子。NPM1是一种多功能的细胞磷酸化的穿梭蛋白，参与mRNA运输、染色质重塑、基因组稳定[1]、核糖体生物合成、中心体复制调控[2]、细胞凋亡调控[1]等，还参与控制和调节ARF-p53肿瘤抑制通路[2]，有癌基因和抑癌基因的双重性质。NPM1在肿瘤细胞和生长期细胞中的含量明显高于静止期细胞。近年来国内外研究表明，在多种肿瘤组织中呈高表达，如胃癌[3]、结直肠癌[4]、膀胱癌[5]、肝癌[6]、甲状腺癌[7]等。

鼻咽癌(nasopharyngeal carcinoma，NPC)为我国两广地区常见的头颈肿瘤之一，有“广州瘤”(Canton tumour)之称。中国两广地区的发病率约为25~50人/10万人[8]，几乎所有的病例均与EB病毒有密切关系[9]。放射治疗被公认为首选的治疗方法[10]，近30年来随着疾病管理的改进、诊断影像学水平的提高、放疗技术发展和系统性治疗的广泛应用，鼻咽癌的疗效有了明显提高[11]。目前，临床分期是指导临床治疗和判断病人预后主要依据，但即使具有相同的临床分期，疗效也存在较大差异，其原因可能是由于肿瘤的异质性造成其生物学行为的不同。因此，目前鼻咽癌研究方向之一是寻找某些能够预测鼻咽癌治疗疗效和预后的生物学指标，而NPM1蛋白在人体鼻咽癌组织中的表达情况目前国内外均未有文章报道。本研究旨在探讨核磷蛋白(nucleophosmin/B23，NPM1)在鼻咽癌活检组织中的表达水平与增殖指数和患者个体化治疗后疗效的关系。

1　材料与方法

1.1　组织标本及病例资料

随机选取中山大学肿瘤防治中心2001年1月1日至2003年12月31日期间收治的、目前还保存有治疗前活检蜡块的初诊鼻咽癌患者157例，均有完整临床和病理档案资料。其中男性患者123例，女性患者34例，年龄13～75岁，中位年龄46岁。所选取的该157例鼻咽癌根据最新的WHO病理诊断标准均诊断非角化性癌。根据WHO TNM分期标准，Ⅰ期6例，Ⅱ期24例，Ⅲ期73例，Ⅳ期54例。个体化治疗根据病人具体情况设计治疗方案，包括放疗加化疗或单纯放疗两种。放疗均采用直线加速器或钴机照射，鼻咽总量60～82 Gy，颈部区域淋巴结总量40～78 Gy。经过1个疗程的治疗后，由鼻咽科医生在鼻咽镜直视下判断原发灶的情况，再通过触摸患者颈部判断淋巴结的情况，并结合患者治疗前后的MR情况，两者均分为残留、消失、未评价、不明四种情况。157例鼻咽癌患者中，治疗1个疗程后原发灶残留的有24例，消失127例，4例未评价或不明；治疗前有淋巴结转移组(119例)治疗1个疗程后残留的有35例，消失84例。

1.2　免疫组织化学检测

上述鼻咽癌活检组织石蜡标本做4 μm连续切片，经脱蜡、微波修复抗原及血清封闭，分别孵育NPM1单克隆一抗(1∶400稀释)和Ki67(中衫金桥公司，即用型)过夜，DAB显色,苏木精对比染色，中性树脂封片。

1.3　评分标准

NPM1的评分标准：阳性染色为浅棕色、棕黄色或深褐色，定位于细胞核和核仁，呈颗粒状或团块状。采用染色强度判断结果：浅棕色为1分，染色呈细颗粒状或粉尘样，胞核部分区域着浅棕色，部分区域仍被苏木精染成蓝色；棕黄色为2分，染色呈颗粒状或团块样，胞核部分区域仍可见蓝色；深褐色为3分，染色呈团块状，完全遮盖整个胞核。

Ki67的评分：每张切片随机计数5个视野，计算1 000~1 500个肿瘤细胞中的阳性细胞百分比。Ki67阳性细胞的判定标准：只要细胞核着棕褐色即可判断为阳性，不论染色强度强或弱。Ki67根据阳性细胞百分数划分为四个等级：Grade I: 0~<25%; Grade

Ⅱ: 25%~<50%; Grade Ⅲ: 50%~<75%; Grade Ⅳ: 75%~100%。

1.4 随访方式

从该157例鼻咽癌患者接受第一次个体化治疗结束后开始进行定期随访,随访方式为书信访问、电话访问或门诊复查,随访至2008年7月29日截止,其中死亡病例37例,失访病例34例。失访的34例患者列入预后统计分析。随访时间平均为61.5个月,最长达90.1个月。

1.5 统计学处理

采用SPSS 16.0统计软件进行分析。其中等级资料采用Spearman等级相关分析,Kruskal-wallis检验和Mann-Whitney检验。生存分析采用Kaplan-Meier法,并用Log-rank检验分析生存曲线的差异统计。以$P<0.05$或$P<0.01$表示差异具有统计学意义。

2 结 果

2.1 NPM1及Ki67在鼻咽癌组织中的表达

免疫组化结果(图1、2)显示,NPM1表达定位于胞核与核仁,在鼻咽癌组织中呈高表达,阳性率达100%,统计显示157例鼻咽癌组织中强阳性病例33例(21.0%),阳性病例65例(41.4%),弱阳性病例59例(37.6%)。Ki67表达定位于细胞核,根据阳性细胞百分数划分为四个等级,其中Grade I 101例,Grade II 22例,Grade III 14例,Grade IV 20例。

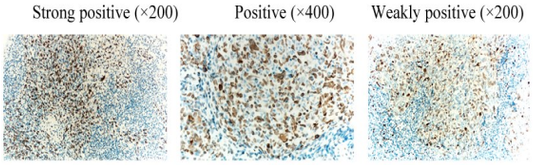

图1 NPM1在鼻咽癌组织中表达于细胞核及核仁

Fig. 1 NPM1 localed in cell nucleus and nucleolus of nasopharyngeal carcinoma tissues

2.2 NPM1在鼻咽癌组织中的表达水平与临床病理参数的关系

在157例鼻咽癌病例中,根据不同临床病理参数进行分组,比较NPM1的表达差异,统计结果(表1)表明,NPM1的表达水平与Ki67的表达水平呈正相关(r=0.445, P=0.000),与淋巴结分期呈负相关(r=−0.235, P=0.003),但与原发灶分期(r=0.006, P=0.940)和临床分期(r=−0.74, P=0.358)无相关性。NPM1的表达水平与有淋巴结转移组的治疗后淋巴结的情况呈负相关(r=−0.196, P=0.033),与无淋巴结转移组治疗后的原发灶情况呈负相关(r=−0.349, P=0.040)。

2.3 NPM1的表达水平与预后的相关性

在157例鼻咽癌病例中,统计结果(表2)显示,鼻咽癌患者的预后与临床分期(χ^2=9.000, P=0.029)和淋巴结分期(χ^2=9.742, P=0.021)有相关性,与NPM1和Ki67的表达水平无相关性。

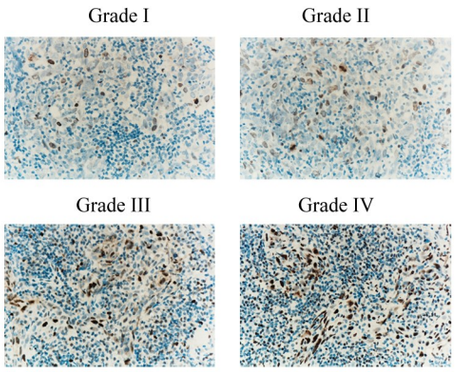

图2 Ki67在鼻咽癌组织中表达于细胞核(×200)

Fig. 2 Ki67 localed in cell nucleus of nasopharyngeal carcinoma tissues(×200)

3 讨 论

本研究发现,NPM1在鼻咽癌组织中高表达并与Ki67的表达水平呈正相关,再次证明NPM1有促进细胞增殖的作用。在其他器官肿瘤中检测到相似的结果。在人胃癌组织中,NPM1蛋白表达水平明显高于癌旁组织,且在临床分期较高及远处转移的患者中表达水平更高[3]。人结直肠癌组织中NPM1表达水平明显高于癌旁组织、绒毛状腺瘤、管状腺瘤及正常粘膜组织;NPM1的表达与癌栓、淋巴结转移、肿瘤分化程度及肿瘤复发相关,且是结直肠癌独立的预后因素[4]。在人原发性肝细胞肝癌组织中,NPM1无论在mRNA还是蛋白水平的表达明显高于相应癌旁组织[6]。在脑星形细胞瘤中,NPM1高表达与高肿瘤分期、年老、低卡氏评分和肿瘤复发有关[12]。这些结果说明,NPM1在包括鼻咽癌在内的恶性肿瘤的发生、发展中可能起着一定作用。

NPM1表达水平与有淋巴结转移组的治疗后淋巴结的情况呈负相关,与无淋巴结转移组治疗后的原发灶情况亦呈负相关,这说明NPM1的表达水平越高,个体化治疗的效果越好。这可能与NPM1表达水平越高肿瘤增殖越活跃,对放射线更敏感有关。

NPM1与淋巴结分期呈负相关,且NPM1在N1组与N3组,N2组与N3组中表达水平的差异有统计学意义。根据WHO TNM分期,N1(N2)定义为单侧(双侧)锁骨上窝之上的转移淋巴结直径小于6 cm,N3定义为转移淋巴结直径大于6 cm和/或已转移到锁骨上窝。

本研究结果显示，NPM1 的表达水平越高，转移的淋巴结直径反而越小。NPM1 在肿瘤发生发展上，既有癌基因的一面又有抑癌基因的一面性，因此NPM1 可能在淋巴结转移后的某些机制上抑制了转移癌的生长。

表 1　NPM1 的表达强度与临床病理参数的关系（*n*）

Tab. 1　NPM1 expression level in nasopharyngeal carcinomas with clinical parameters (*n*)

Item	NPM1			Total	Statistic value	*P*
	Weakly Positive	Positive	Strong Positive			
Age (*t*/a)				157	*r*=0.086	0.284
＜50	41	38	20	99		
≥50	18	27	13	58		
Ki67				157	*r*=0.445	0.000
GradeI	53	38	10	101		
GradeII	2	9	11	22		
GradeIII	1	10	3	14		
GradeIV	3	8	9	20		
Nodes				157	*r*=−0.235	0.003
N0	11	12	13	36	N1 *vs* N3	N1 vs N3 *P*=0.003
N1	17	30	10	57	*Z*=−2.994	N2 vs N3 *P*=0.018
N2	19	20	9	48	N2 vs N3	
N3	12	3	1	16	*Z*=−2.365	
Tumor				157	*r*=0.006	*P*=0.940
T1	4	2	2	8		
T2	17	14	10	41		
T3	23	31	14	68		
T4	15	18	7	40		
Clinical staging				157	*r*=−0.74	*P*=0.358
I	3	1	2	6		
II	9	9	6	24		
III	23	35	15	73		
IV	24	20	10	54		
Lymph node(s) after therapy				119	*r*=−0.196	*P*=0.033
					Z=−2.192	*P*=0.028
Palpable	18	15	2	35		
Not palpable	29	37	18	84		
Primary lesion status after therapy				35	*r*=−0.349	*P*=0.040
					Z=−2.036	*P*=0.042
Remained	3	1	0	4		
Disappeared	8	10	13	31		

r: Correlation index of Spearman's rank correlation; Z: Test value of Mann-Whitney

Ki67 是一种细胞增殖核抗原，与有丝分裂密切相关并能反应恶性肿瘤的增殖状态[13]。Ki67 广泛应用于临床，在多种肿瘤的亚分类、预后判断、治疗方案选择等方面起重要作用，如乳腺癌[14]、肺癌[15]、宫颈癌[16]、神经内分泌肿瘤[17]、前列腺癌[18-19]。由于Ki67 在恶性肿瘤细胞中高表达而正常细胞几乎不表达，因此可能成为有前途的肿瘤治疗新靶点[20]。Ki67 存在于细胞周期的G1、S、G2 期，至分裂晚期迅速消失，G0 期无 Ki67 的表达，半衰期仅 1 h 或更短，是反映细胞增殖状态的理想标记物。而 NPM 的半衰期大于 6 h，在细胞周期中容易积累因此不能很好地反映细胞的增殖状态。另外，NPM1 在鼻咽癌组织中几乎全部是阳性表达，因此只能用染色深度而不能用阳性细胞比例来进行评分。假如不是同一批实验条件下完成的切片就很难对其强度进行量化。但随着免疫组化流程进一步标准化，减少了不同批次之间实验条件的误差。为了更好地进行染色强度分级，可将NPM1 强阳性、阳性及弱阳性的标准组织作为阳性对照捞在同一张片子上，便于判读鼻咽癌临床病例的染色强度。NPM1 与淋巴结分期呈负相关，可帮助临床预测鼻咽癌患者的淋巴结转移情况。因临床上淋巴结有无转移主要靠影像学判定，但影像学不能作为淋

巴结转移的金标准,有时候会存在判定困难,此时可以利用NPM1的表达强度协助判断淋巴结的转移情况,从而帮助临床分期及预后的判断。综上所述,NPM可以作为研究鼻咽癌方面的补充标记物。

表**2 NPM1**的表达强度与预后的关系 **(*n*)**

Tab. 2 NPM1 expression level in nasopharyngeal carcinomas with prognosis parameters (*n*)

Item	Survival time (*t*/month)		Log-rank test	*P*
	＜60	≥60		
NPM1			χ^2=1.025	*P*=0.599
Weak	21	26		
Intermediate	22	26		
Enhanced	20	8		
Ki67			χ^2=1.077	*P*=0.783
GradeI	35	42		
GradeII	11	7		
GradeIII	6	5		
GradeIV	11	6		
Nodes			χ^2=9.742	*P*=0.021
N0	15	19	N0 *vs* N3:	N0 *vs* N3:
N1	19	27	χ^2=4.716	*P*=0.030
N2	21	10	N1 *vs* N3:	N1 *vs* N3:
N3	8	4	χ^2=9.107	*P*=0.003
Clinical staging			χ^2=9.000	*P*=0.029
I	3	3	II *vs* III:	II *vs* III:
II	6	16	χ^2=4.087	*P*=0.043
III	30	23	II *vs* IV:	II *vs* IV:
IV	24	18	χ^2=7.995	*P*=0.005

[参 考 文 献]

[1] BOX J K, NICOLAS P, ADAMS M N, et al. Nucleophosmin: from structure and function to disease development[J/OL]. BMC Mol Biol, 2016, 17(1): 19[2017-10-20]. https://bmcmolbiol.biomedcentral.com/articles/10.1186/s12867- 016- 0073- 9. DOI:10.1186/s12867-016-0073-9.

[2] SHAHAB S, SHAMSI T S, AHMED N. Prognostic involvement of nucleophosmin mutations in acute myeloid leukemia[J]. Asian Pac J Cancer Prev, 2013, 14(10): 5615- 5620. DOI: 10.7314/APJCP.2013.14.10.5615

[3] ZHOU F, CHEN E, YOU D, et al. Both high expression of nucleophosmin/B23 and CRM1 predicts poorer prognosis in human gastric cancer [J]. APMIS, 2016, 124(12):1046- 1053. DOI: 10.1111/apm.12604.

[4] YANG Y F, ZHANG X Y, YANG M, et al. Prognostic role of nucleophosmin in colorectal carcinomas[J]. Asian Pac J Cancer Prev, 2014, 15(5): 2021-2026.

[5] WANG H, YUAN G, ZHAO B, et al. High expression of B23 is associated with tumorigenesis and poor prognosis in bladder urothelial carcinoma[J]. Mol Med Rep, 2017, 15(2): 743- 749. DOI: 10.3892/mmr.2016.6033.

[6] YUN J P, MIAO J, CHEN G G, et al. Increased expression of nucleophosmin/B23 in hepatocellular carcinoma and correlation with clinicopathological parameters[J]. Br J Cancer, 2007, 96(3): 477- 484. DOI:10.1038/sj.bjc.6603574.

[7] PIANTA A, PUPPIN C, FRANZONI A, et al. Nucleophosmin is overexpressed in thyroid tumors[J]. Biochem Biophys Res Commun, 2010, 397(3):499-504. DOI: 10.1016/j.bbrc.2010.05.142.

[8] KAMRAN S C, RIAZ N, LEE N. Nasopharyngeal carcinoma[J]. Surg Oncol Clin N Am, 2015, 24(3): 547- 561. DOI: 10.1016/j.soc.2015.03.008.

[9] PETERSSON F. Nasopharyngeal carcinoma: a review[J]. Semin Diagn Pathol, 2015, 32(1): 54-73. DOI: 10.1053/j.semdp.2015.02.021.

[10] ZHANG L,CHEN Q Y,LIU H, et al. Emerging treatment options for nasopharyngeal carcinoma[J/OL]. Drug Des Devel Ther, 2013, 7: 37- 52[2017- 10- 21]. https://www.dovepress.com/emerging- treatment-options-for-nasopharyngeal-carcinoma-peer-reviewed-article-DDDT. DOI: 10.2147/DDDT.S30753.

[11] LEE A W, MA B B, NG W T. Management of nasopharyngeal carcinoma: current practice and future[J]. J Clin Oncol, 2015, 33(29): 3356-3364. DOI: 10.1200/JCO.2015.60.9347.

[12] KUO Y H, CHEN Y T, TSAI H P, et al. Nucleophosmin overexpression is associated with poor survival in astrocytoma[J]. APMIS, 2015,123(6): 515-522. DOI: 10.1111/apm.12381.

[13] HALL P A, LEVISON D A, WOODS A L, et al. Proliferating cell nuclear antigen (PCNA) immunolocalization in paraffin sections: an index of cell proliferation with evidence of deregulated expression in some neoplasms[J]. J Pathol, 1990, 162(4): 285-294. DOI: 10.1002/path.1711620403.

[14] DOWSETT M, NIELSEN T O, A'HERN R, et al. Assessment of Ki67 in breast cancer: recommendations from the international Ki67 in breast cancer working group[J]. J Natl Cancer Inst, 2011, 103(22): 1656-1664. DOI:10.1093/jnci/djr393.

[15] MARTIN B, PAESMANS M, MASCAUX C, et al. Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta- analysis[J]. Br J Cancer, 2004, 91(12): 2018-2025. DOI: 10.1038/sj.bjc.6602233.

[16] PIRI R, GHAFFARI A, AZAMI-AGHDASH S, et al. Ki-67/MIB-1 as a prognostic marker in cervical cancer - a systematic review with meta- analysis[J]. Asian Pac J Cancer Prev, 2015, 16(16): 6997-7002. DOI: 10.7314/APJCP.2015.16.16.6997.

[17] KLÖPPEL G. Neuroendocrine neoplasms: dichotomy, origin and classifications[J]. Visc Med, 2017, 33(5): 324- 330. DOI: 10.1159/000481390.

[18] PASCALE M, AVERSA C, BARBAZZA R, et al. The proliferation marker Ki67, but not neuroendocrine expression, is an independent factor in the prediction of prognosis of primary prostate cancer patients[J]. Radiol Oncol, 2016, 50(3): 313- 320. DOI:10.1515/raon-2016-0033.

[19] LOBO J, RODRIGUES Â, ANTUNES L, et al. High immunoexpression of Ki67, EZH2, and SMYD3 in diagnostic prostate biopsies independently predicts outcome in patients with prostate cancer [J/OL]. Urol Oncol, 2017, [Epub ahead of print] [2017-10-21]. http://www.urologiconcology.org/article/S1078- 1439(17)30565- 3/fulltext. DOI: 10.1016/j.urolonc.2017.10.028.

[20] YANG C, ZHANG J, DING M, et al. Ki67 targeted strategies for cancer therapy[J]. Clin Transl Oncol, 2017, (3): 1-6. DOI: 10.1007/s12094-017-1774-3.

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