



唾液肿瘤标志物的研究进展*

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【摘要】 唾液是由口腔唾液腺分泌的混合生物体液, 蕴含丰富的物质信息。随着唾液组学的不断发展, 唾液不仅作为巨大的生物标志物储存库, 唾液诊断也成为一种新型诊断技术, 具有无侵袭性、易于获取、成本低等优势。但口腔环境复杂多变, 标志物含量等易受影响, 找到“真正的”唾液生物标志物仍然是一个挑战。本文主要关注常见肿瘤的潜在唾液标志物, 包括DNA、RNA、蛋白质、代谢物和微生物等, 针对目前已鉴定的或关联性标志物进行系统性总结, 并指出建立多学科交叉体系开发唾液诊断技术, 逐步构建唾液诊断平台, 寻找更加精准的肿瘤预警标志物是未来发展方向。

【关键词】 唾液 肿瘤标志物 早期诊断

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【Abstract】 Saliva, a complex mixed biological fluid secreted by the salivary glands in the oral cavity, contains a wide variety of substances and information. With the development of saliva omics, studies have shown that saliva not only serves as a huge reservoir of biomarker, but saliva diagnostics has also become a new diagnostic technology with the advantages of non-invasiveness, easy access, and low cost. However, finding "true" saliva biomarkers is still a challenge due to the complex and changeable nature of the oral environment and the high susceptibility of biomarker content to influences. Herein, mainly focusing on potential salivary biomarkers of common tumors, including DNA, RNA, proteins, metabolites and microorganisms, we gave a systematic overview of the biomarkers that had been identified so far or the associated biomarkers. We suggested that the future development direction should be the establishment of a multidisciplinary system for developing saliva diagnosis technology, the gradual construction of a saliva diagnosis platform, and the search for more precise pre-warning tumor biomarkers.

【Key words】 Saliva Salivary tumor biomarkers Early diagnosis

人类唾液是一种口腔内自然分泌的混合性生物体液, 主要由三大唾液腺分泌, 包括腮腺、颌下腺和舌下腺^[1]。健康成年人每天产生唾液量约为0.5~1.5 L(流速约0.5 mL/min), 唾液的流量受各种因素的刺激而发生变化, 如性别、年龄、情绪、食物和昼夜节律等^[2]。唾液是无色无味偏微酸性的低渗胶体(pH6.0~7.0), 水分占99%, 固体成分仅占1%, 其主要包括食物残渣、有机物、矿物质和蛋白质等^[1-3]。研究发现, 唾液含有大量血浆物质, 但它们在唾液中的含量很低, 如有机物、电解质(钠、钾、磷酸盐、微量元素等)、免疫球蛋白、蛋白质和酶等^[2, 4]。这些发现提示从唾液中寻找全身疾病的重要标志物, 在疾病早期预测、诊断和治疗方面具有重要科学意义。

1 唾液肿瘤标志物在肿瘤诊断中的优势

肿瘤是人类重大疾病, 更是主要的全球公共卫生问

题, 2020年全世界约有1 000万人死于癌症^[5]。它是全球第二大死因, 每六人中就有一人死亡, 约50%的癌症在确诊时处于晚期^[6]。癌症或癌前病变的早期检测有利于早期干预, 以减缓或预防癌症的发展。除了借助特殊设备进行筛查, 血清肿瘤标志物筛查也是一种常见的单癌种或多癌种筛查方式, 通常是以侵入性方式采集血液, 并分析血清的肿瘤标志物。唾液被喻为“身体的镜子”, 蕴含丰富的物质资源, 包含血清中的大部分物质, 其主要是通过细胞间隙或跨细胞途径从血液进入唾液^[7]。

唾液肿瘤标志物筛查作为一种潜在的血清筛查替代方法, 其优势在于: ①非侵入性, 如无须采血; ②采样操作简便; ③安全无痛; ④成本低; ⑤方便储存和运输; ⑥易于获取大量样本, 可长时间跟踪检测^[2, 7]。基于上述优势, 唾液筛查成为检测肿瘤标志物较为理想的方式, 尤其在肿瘤的阶段性监测和筛查方面具有潜在应用价值。本文主要对常见肿瘤唾液生物标志物的最新研究进展进行系统性总结, 以期对全身肿瘤的早期筛查、预防、诊断和治疗提供新的理论依据和技术策略。

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2 唾液肿瘤标志物

肿瘤标志物可能是肿瘤细胞特定的基因或其产物,也可能是正常细胞和肿瘤细胞共有的基因或其产物,但在特定的环境刺激下它们在肿瘤细胞中异常表达^[8]。唾液包含丰富的物质信息,既有来源于唾液近端接触部位所分泌的,也有来自远端疾病组织循环而来的,包括DNA、RNA和蛋白质等。

2.1 口腔癌

头颈部肿瘤是全球范围内第六大常见的恶性肿瘤,其中主要以口腔鳞状细胞癌(oral squamous cell carcinomas, OSCC)为主,近20年来OSCC患者5年生存率不超过50%^[9]。口腔视诊是当前口腔癌筛查的主要方式,该方式既不能区分正常黏膜组织是否发生癌前病变,也不能分辨癌前病变是良性还是恶性^[10]。传统切取活检仍然是口腔癌诊断的金标准,但也具有创伤性和潜在的并发症^[10]。唾液与口腔癌病灶直接接触,唾液可能含有大量口腔癌的物质信息,这为口腔癌筛查和诊断提供重要线索。通过现代鉴定技术分析口腔癌患者和正常人的唾液组成,研究发现两者之间唾液组成存在巨大差异,主要包括DNA、RNA、蛋白质和微生物(表1),如前者DNA表

现为肿瘤抑制基因突变(*p53*),微卫星改变,启动子甲基化异常,线粒体DNA突变,含肿瘤相关病毒DNA^[11]。由于唾液多肽或蛋白在口腔癌诊断中具有较高的敏感性和特异性,因此常作为口腔癌检测的生物标志物。通过收集台湾地区唾液样本(包括健康组96例、低危组103例、高危组130例和OSCC组131例),YU等^[12]利用质谱和分类回归树鉴定出一组蛋白肿瘤标志物:基质金属蛋白酶1(matrix metalloproteinase 1, MMP1),激肽原1(kininogen 1, KNG1),膜联蛋白A2(annexin A2, ANXA2)和热休克蛋白家族A5(heat shock protein family A member 5, HSPA5),且在另一组检测样本(106例)中用它们区分OSCC患者和健康人群的灵敏度和特异度分别高达87.5%和80.5%,因此在OSCC早期诊断、风险评估和治疗监测方面具有较高的临床应用价值。其次,CD59、防御素-1和过氧化氢酶的灵敏度和特异度分别均为90%和80%^[2];虽然癌胚抗原(carcinoembryonic antigen, CEA)在OSCC诊断中的灵敏度和特异度分别为76.4%和80.4%^[13],但在其他很多恶性肿瘤中CEA也会升高,因此CEA和上述其他标志物联合应用对OSCC的预测较有意义。通过对口腔癌患者唾液转录组分析发现,OSCC患者唾液中部分小RNA显著上调,如白细胞介素(interleukin, IL)-8和组

表 1 潜在的口腔癌唾液标志物
Table 1 Potential salivary biomarkers for oral cancer

Category	Salivary tumor biomarkers	Sensitivity	Specificity	Expression	References
DNA	3p, 9q, 13q, and 17p	—	—	—	[8, 16]
	<i>p53</i> , <i>p16</i> , <i>p27</i> , <i>p63</i> , and <i>p73</i>	—	—	—	[8]
	<i>p16</i> , <i>MGMT</i> , <i>DAP-K</i> , <i>NID2</i> , and <i>HOXA9</i>	—	—	—	[8]
	Cyclin D1 and Ki67	—	—	↑	[8, 17]
	<i>OGG1</i> , <i>P-Src</i> , and <i>Maspin</i>	—	—	↓	[8, 18]
mRNA	<i>IL-8</i> , <i>H3F3A</i> , <i>IL-1-β</i> , <i>S100P</i> , <i>DUSP1</i> , <i>OAZ1</i> , and <i>SAT</i>	—	—	↑	[8, 14]
	miR-708, miR-10b, miR-19a, miR-30e, miR-26a, and miR-660	—	—	↑	[2, 19-20]
	miR-99, miR-15a, miR-197, miR-145, and miR-150	—	—	↓	[2, 19-20]
Protein	CD59, defensin-1, and catalase	90%	80%	↑	[2]
	CEA	76.4%	80.4%	↑	[13]
	MMP1, KNG1, ANXA2, and HSPA5	87.5%	80.5%	↑	[12]
	CD44, IL-8, and telomerase	—	—	↑	[8, 21-22]
	IPA, SCC-Ag 2, CA19-9, CA128, CA125, Cyfra 21-1, TPS, 8-OHdG, LDH, IgG, s-IgA, IGF, MMP-2, MMP-11, calcyclin, and RhoGDI	—	—	—	[8, 23]
	Clusterin	—	—	↓	[8, 24]
	ROS, RNS, and NO	—	—	↑	[2, 15, 20]
Microorganism	<i>Porphyromonas gingivalis</i> , <i>Tannerella forsythia</i> , <i>Candida albicans</i> , <i>Prevotella melaninogenica</i> , <i>Streptococcus mitis</i> , <i>Pseudomonas aeruginosa</i> , and <i>Human papilloma virus</i>	—	—	↑	[15, 25-26]

MGMT: O6-methylguanine-DNA methyltransferase; *DAP-K*: death-associated protein kinase; *NID2*: nidogen-2; *HOXA9*: homeobox A9; *OGG1*: 8-oxoquinine DNA glycosylase; *IL*: interleukin; *H3F3A*: H3 histone, family 3A; *S100P*: S100 calcium binding protein P; *DUSP1*: dual specificity phosphatase 1; *OAZ1*: ornithine decarboxylase antizyme 1; *SAT*: spermidine/spermine N1-acetyltransferase; CD: cluster of differentiation; CEA: carcinoembryonic antigen; MMP1: matrix metalloproteinase 1; KNG1: kininogen 1; ANXA2: annexin A2; HSPA5: heat shock protein family A member 5; IPA: inhibitors of apoptosis; SCC-Ag 2: squamous cell carcinoma antigen 2; CA: cancer antigen; Cyfra 21-1: cytokeratin 19 fragment; TPS: tissue polypeptide specific antigen; 8-OHdG: 8-hydroxydeoxyguanosine; LDH: lactate dehydrogenase; Ig: immunoglobulin; IGF: insulin growth factor; RhoGDI: Rho GDP dissociation inhibitor; ROS: reactive oxygen species; RNS: reactive nitrogen species; NO: nitrogen monoxide. ↑: Upregulated genes or proteins; ↓: Downregulated genes or proteins; —: None.

蛋白3.3(H3 histonefamily 3A, H3F3A),提示存在口腔癌发生的潜在风险^[14]。微生物感染是肿瘤发生发展的重要环境致病因素之一,某些疾病的发生常伴有微生物菌群的紊乱,如口腔癌组织中牙龈卟啉单胞菌、福赛斯坦纳菌和白色念珠菌等微生物丰度显著高于正常组织^[8,15],提示某些微生物的聚集可能是口腔癌发生发展的重要标志。由于唾液具有易于收集、非侵入性、成本低等优势,唾液肿瘤标志物检测可能是初筛OSCC危险因素最好的方式。当前具有较高灵敏度和特异度的标志物还需要通过大量临床样本进行验证,以便寻找更为精确的标志物预测口腔癌的发生。

2.2 肺癌

肺癌是起源于肺部支气管黏膜或腺体的恶性肿瘤,全球发病率及死亡率排名第一,5年生存率约4%~17%,约占全球肿瘤死亡人数的三分之一,是对人群健康和生命威胁最大的恶性肿瘤之一^[27]。通过对肺癌患者(42例)和正常人(74例)唾液进行转录组分析,研究发现细胞周期蛋白 I(cyclin I, CCNI)、表皮生长因子受体(epidermal growth factor receptor, EGFR)、成纤维细胞生长因子

19(fibroblast growth factor 19, FGF 19)、成纤维细胞生长因子受体底物2(fibroblast growth factor receptor substrate 2, FRS2)和乳腺癌雌激素调控蛋白(growth regulation by estrogen in breast cancer 1, GREB1)的mRNA表达水平显著上升,其灵敏度和特异度分别为93.75%和82.81%^[28]。当前肺癌血清检测标志物主要有CA125、CA19-9、CEA等,其缺点是灵敏度(22%~76%)和特异度(40.5%~85.3%)均较低^[28],肺癌唾液标志物诊断将有望弥补血清标志物诊断的不足。基于唾液蛋白组分析发现肺癌患者(26例)比健康人群(26例)的触珠蛋白(haptoglobin)、锌 α 2糖蛋白(zinc-alpha-2-glycoprotein, ZAG)和钙网蛋白(calreticulin)的表达水平上升,其灵敏度和特异度分别为88.5%和92.3%^[1](表2),期望这些异常表达的分子可作为筛查或诊断的潜在标志物。利用表面增强拉曼光谱(surface enhanced Raman spectroscopy, SERS)对肺癌组 and 对照组的唾液进行检测和分析,结果显示肺癌患者在多处波数位的峰强较正常人有所下降,而这些峰主要为蛋白质和核酸,表明肺癌患者唾液中这些成分的含量较正常人偏少^[29-30],揭示了唾液SERS用于诊断肺癌的潜力。

表 2 潜在的肺癌唾液标志物

Table 2 Potential salivary biomarkers for lung cancer

Category	Salivary tumor biomarkers	Sensitivity	Specificity	Expression	References
mRNA	CCNI, EGFR, FGF19, FRS2, and GREB1	93.75%	82.81%	↑	[1, 28]
Protein	Haptoglobin, ZAG, and calreticulin	88.5%	92.3%	↑	[1]

CCNI: cyclin I; EGFR: epidermal growth factor receptor; FGF19: fibroblast growth factor 19; FRS2: fibroblast growth factor receptor substrate 2; GREB1: growth regulation by estrogen in breast cancer 1; ZAG: zinc-alpha-2-glycoprotein.

2.3 胰腺癌

胰腺癌是消化道常见恶性肿瘤之一,在肿瘤领域素有“癌症之王”的称号,全球癌症致死率排名第四,5年生存率仅为3%~5%^[31]。由于缺乏有效的治疗方案、生物标志物和早期检测工具,几乎所有胰腺癌患者都会发生肿瘤转移或死亡。因此,亟须在胰腺癌早期作出筛查、诊断和分类,以便患者获得最佳治疗时机,降低死亡率。研究表明CEA和CA125不仅在胰腺癌患者唾液中的含量较正常人显著升高,而且它们在唾液中的平均浓度也显著高于血清中的浓度^[32]。此外,二者除了具有较高的灵敏度(92.31%)和特异度(84.62%),还发现预后生存期较短的患者中二者的浓度也相对较高,这也体现出CEA和CA125具有较好的诊断和预后评估价值^[32]。通过对胰腺癌患者唾液转录组学分析,相比正常人群(42例),胰腺癌患者(42例)唾液中Kirsten 大鼠肉瘤病毒癌基因同源物(Kirsten rat sarcoma viral oncogene homolog, KRAS)、甲基-CpG 结合域蛋白3样2(methyl-CpG binding domain

protein 3 like 2, MBD3L2)、顶体小泡蛋白1(acrosomal vesicle protein 1, ACRV1)和多萜醇磷酸甘露糖基转移酶亚基1(dolichol-phosphate mannosyltransferase subunit 1, DPM1)的 mRNA灵敏度和特异度均分别为90.0%和95.0%^[33]。通过qRT-PCR和芯片技术分析发现,多个miRNA在胰腺癌患者唾液中表达上调,灵敏度和特异度普遍较高^[34](表3)。口腔微生物与胰腺癌发生密切相关,相对于健康人群,胰腺癌患者唾液有31种细菌数量增加,25种减少,其中长奈瑟菌和缓症链球菌在胰腺癌诊断中具有较高的灵敏度和特异度,分别为96.4%和82.1%^[35]。此外,胰腺癌患者唾液中存在低丰度长奈瑟氏菌以及纤毛菌属与卟啉单胞菌属比例较高的现象,进一步表明菌群变化可能是胰腺癌发生发展的前兆或结果^[36]。研究发现胰腺癌小鼠唾液中7种基因转录产物(*Apbb1ip*, *Aspn*, *BCO31781*, *Daf2*, *Foxp1*, *Gng2*和*Incenp*)表达显著上升,同时它们存在于唾液、血清和Panc02细胞系来源的外泌体中且其表达几乎均显著上调^[37]。相反,抑制胰腺癌

表 3 潜在的胰腺癌唾液标志物
Table 3 Potential salivary biomarkers for pancreatic cancer

Category	Salivary tumor biomarkers	Sensitivity	Specificity	Expression	References
mRNA	KRAS, MBD3L2, and ACRV1	90.0%	95.0%	↑	[33]
	DPM1	90.0%	95.0%	↓	[33]
miRNA	miR-17, miR-21, miR-181a, miR-181b, and miR-196a	—	—	↑	[38]
	hsa-miR-21	71.4%	100%	↑	[34]
	hsa-miR-23a	85.7%	100%	↑	[34]
	hsa-miR-23b	85.7%	100%	↑	[34]
	miR-29c	57%	100%	↑	[34]
Protein	CEA and CA125	92.31%	84.62%	↑	[32]
Microorganism	<i>Neisseria elongata</i> and <i>Streptococcus mitis</i>	96.4%	82.1%	↓	[35]

KRAS: Kirsten rat sarcoma viral oncogene homolog; MBD3L2: methyl-CpG binding domain protein 3 like 2; ACRV1: acrosomal vesicle protein 1; DPM1: dolichol-phosphate mannosyltransferase subunit 1; CEA: carcinoembryonic antigen; CA: cancer antigen.

外泌体合成可破坏唾液中胰腺癌标志物形成^[37],这或许解释了唾液中胰腺癌标志物存在的原因并暗示外泌体在标志物远端运输过程中具有重要作用。

2.4 胃癌

胃癌是起源于胃黏膜上皮的恶性肿瘤,多发生于胃窦部,胃大弯、胃小弯及前后壁均可受累,是全球第五大常见恶性肿瘤,癌症相关死亡人数中排名第三^[5]。绝大多数胃癌属于腺癌,早期无明显症状,而胃癌患者就诊时已是中期或晚期,因此早期的筛查显得尤为重要。通过采用串联质谱标签系统的定量蛋白质组学技术,研究人员在鉴定胃癌患者唾液生物标志物时发现48个蛋白在健康组(40例)和胃癌患者组(40例)之间具有显著差异表达,其中半胱氨酸蛋白酶抑制剂B(cystatin B, CSTB)、磷酸丙糖异构酶(triosephosphate isomerase, TPI1)和恶性脑肿瘤1(deleted in malignant brain tumors 1 protein, DMBT1)通过酶联免疫吸附法也进一步得到验证,同时这3种生物标志物联合使用时,其灵敏度和特异度高达85%和80%^[39]。此外,研究发现胃癌患者(61例)唾液中丝氨酸肽酶抑制因子Kazal 7型(serine peptidase inhibitor Kazal type 7, SPINK7)、周膜蛋白(periplakin, PPL)和信号素4B(semaphorin 4B, SEMA4B)的mRNA和2个miRNA(miR140-5p和miR301a)的表达量相比健康人群

(31例)明显下降,而且唾液中5个RNA联合检测极大地提高了胃癌预测的准确度^[40]。以上标志物不同于当前胃癌常见的血清肿瘤标志物(如CEA、CA72-4、CA19-9等)^[41],体现了唾液检测的独特性,暗示在唾液中检测胃癌相关标志物有望作为一种辅助验证手段。近年临床研究发现微生物(尤其是幽门螺杆菌, *Helicobacter pylori*, Hp)与胃癌发生关系密切。在我国临床研究中发现Hp的感染率大约在60%~80%,Hp的感染率与胃癌死亡率呈正相关^[42]。研究表明,口腔Hp感染不仅与胃Hp感染呈正相关,而且口腔Hp感染患者的胃中Hp难以清除^[43]。因此,唾液Hp检测很大程度上能够预警胃癌的发生。

2.5 乳腺癌

乳腺癌是发生在乳腺上皮组织的恶性肿瘤,同时经常转移至远端器官,如肝、肺、脑^[44]。据WHO资料统计,乳腺癌全球新增病例数及发病率正逐年上升,预计在2040年增至3 020万^[45]。因此,乳腺癌的早期筛查、诊断、治疗及预后成为当下研究的热点。传统的X射线扫描灵敏度并不理想,因此乳腺癌标志物的鉴定工作也在逐渐增加。通过对乳腺癌患者(10例)和正常人(10例)唾液转录组和蛋白组分析,8个mRNA和1个CA6蛋白标志物被鉴定(表4),利用qPCR和定量蛋白质免疫印迹在30例乳腺癌患者和63例正常人群中再次验证了它们的灵敏度和特

表 4 潜在的乳腺癌唾液标志物
Table 4 Potential salivary biomarkers for breast cancer

Category	Salivary tumor biomarkers	Sensitivity	Specificity	Expression	References
mRNA	CSTA, TPT1, IGF2BP1, GRM1, GRIK1, H6PD, MDM4, and S100A8	83%	97%	↑	[46]
Protein	CA6	—	—	↑	[1]
	CA15-3	95.87%	88.66%	↑	[48]
	ER-α, VEGF, EGF, CEA, HER2, CA15-3, P53, and CA125	—	—	↑	[4]
Small molecule	Choline, isethionate, cadavarine, N1-acetylspermidine, and spermine	—	—	↑	[1]

CSTA: cysteine protease inhibitor A; TPT1: translationally-controlled tumor protein 1; IGF2BP1: insulin-like growth factor 2 mRNA-binding protein 1; GRM1: metabotropic glutamate receptor 1; GRIK1: glutamate receptor, ionotropic, kainate 1; H6PD: hexose-6-phosphate dehydrogenase; MDM4: murine double minute 4; S100A8: S100 calcium-binding protein A8; CA: cancer antigen; ER-α: estrogen receptor-alpha; VEGF: vascular endothelial growth factor; EGF: epidermal growth factor; CEA: carcinoembryonic antigen; HER2: human epidermal receptor 2.

异度,分别高达83%和97%^[1,46]。此外,研究显示乳腺癌患者血清和唾液中CA15-3含量呈正相关,目前主要用于监测乳腺癌转移^[1,47]。基于SERS技术检测乳腺癌患者(33例乳腺癌前病变和31例纤维化乳腺癌)和正常人(33例)的唾液标志物,研究发现CA15-3作为标志物诊断的灵敏度和特异度分别为95.87%和88.66%^[48]。通过对乳腺癌患者和正常人唾液进行代谢物质谱分析,研究发现相比正常人,乳腺癌患者唾液中5种小分子浓度明显偏高^[1],这些小分子可能作为潜在的乳腺癌标记物,但其具体机制还需进一步研究。

2.6 其他肿瘤

卵巢癌是妇科三大恶性肿瘤之一,发病率位居妇科恶性肿瘤第3位,其致死率居女性生殖系统恶性肿瘤之首,严重威胁女性的生命健康^[49]。CA125作为卵巢癌的首选标志物,研究发现血清中CA125含量与唾液中的含量呈正相关^[50]。16例子宫内膜癌患者的唾液和血清CA125检测的灵敏度分别为81.3%和93.8%,但患者血清CA125检测的假阳性率高于唾液,推测唾液CA125含量分析更能准确预测卵巢癌发生^[50]。唾液腺肿瘤作为口腔癌的分支,研究发现唾液腺肿瘤组织中瘦素表达量高于健康的腮腺组织,暗示唾液瘦素可能作为唾液腺肿瘤的潜在标志物^[51]。

结直肠癌是世界范围内最常见的恶性肿瘤之一,是仅次于乳腺癌和肺癌的第3大常见癌症,是癌症死亡的第三大诱因^[52]。研究显示,相比健康人群,结直肠癌患者血浆和唾液中miR-21表达水平均有显著差异,血浆中miR-21诊断灵敏度和特异度分别为65%和85%,而在唾液中分别为97%和91%^[53],暗示唾液miR-21含量分析更能准确预测结直肠癌的发生。此外,多项研究表明口腔来源的具核梭杆菌可定植于结直肠的癌组织部位,并促进癌症的发生发展^[52],暗示检测唾液中具核梭杆菌含量可预测结直肠癌发生的可能性。

3 应用前景和展望

唾液组学是一种用于研究唾液成分的技术,主要借助现代组学手段进行物质鉴定,包括基因组和表观基因组、转录组、蛋白质组、代谢组和微生物组等,对寻找疾病分子标志物和药物靶标具有重要意义,对疾病的早期筛查具有广阔的应用前景。肿瘤防治的关键是早期预测和早期干预,迫切需要具有高灵敏度和特异度的筛选方法。唾液作为早期癌症检测器,蕴含丰富的物质信息,相较于血液检测,唾液有明显优势,如操作简单、非侵入性等,在疾病诊断中具有很高的应用潜力和价值。尽管某

些疾病的发生与某些唾液标志物关系密切,但口腔环境复杂多变,标志物含量等易受影响,找到“真正的”唾液生物标志物仍然是一个挑战,还需要在大量样本中进行验证与评估。因此,我们将继续拓展唾液相关知识,建立多学科交叉体系开发唾液诊断技术,逐步构建唾液诊断平台,寻找更加精准的肿瘤预警标志物,为实现口腔和全身疾病的精准医疗提供新策略。

* * *

利益冲突 所有作者均声明不存在利益冲突

参 考 文 献

- [1] WANG X, KACZOR-URBANOWICZ K E, WONG D T. Salivary biomarkers in cancer detection. *Med Oncol*, 2017, 34(1): 7. doi: 10.1007/s12032-016-0863-4.
- [2] GOPAL S K, RAVI P. Salivary biomarkers--a modern approach to diagnosis. *J Pharm Sci Res*, 2021, 13(11): 677-680.
- [3] DEVARAJ S D. Salivary biomarkers--a review. *J Pharm Sci Res*, 2013, 5(10): 210.
- [4] LAIDI F, ZAOUI F. Saliva diagnostic and cancer monitoring: overview. *J Intern Dent Med Res*, 2015, 8(2): 94-97.
- [5] SUNG H, FERLAY J, SIEGEL R L, *et al*. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 2021, 71(3): 209-249. doi: 10.3322/caac.21660.
- [6] CROSBY D, BHATIA S, BRINDLE K M, *et al*. Early detection of cancer. *Science*, 2022, 375(6586): eaay9040. doi: 10.1126/science.aay9040.
- [7] ZHANG A, SUN H, WANG X. Saliva metabolomics opens door to biomarker discovery, disease diagnosis, and treatment. *Appl Biochem Biotechnol*, 2012, 168(6): 1718-1727. doi: 10.1007/s12010-012-9891-5.
- [8] SAXENA S, SANKHLA B, SUNDARAGIRI K S, *et al*. A review of salivary biomarker: a tool for early oral cancer diagnosis. *Adv Biomed Res*, 2017, 6: 90. doi: 10.4103/2277-9175.211801.
- [9] FAN T, WANG X, ZHANG S, *et al*. NUPR1 promotes the proliferation and metastasis of oral squamous cell carcinoma cells by activating TFE3-dependent autophagy. *Signal Transduct Target Ther*, 2022, 7(1): 1-11. doi: 10.1038/s41392-022-00939-7.
- [10] WARNAKULASURIYA S, KERR A R. Oral cancer screening: past, present, and future. *J Dent Res*, 2021, 100(12): 1313-1320. doi: 10.1177/00220345211014795.
- [11] LIAO P H, CHANG Y C, HUANG M F, *et al*. Mutation of p53 gene codon 63 in saliva as a molecular marker for oral squamous cell carcinomas. *Oral Oncol*, 2000, 36(3): 272-276. doi: 10.1016/S1368-8375(00)00005-1.
- [12] YAO Z, AN W, TUERDI M, *et al*. Identification of novel prognostic indicators for oral squamous cell carcinoma based on proteomics and metabolomics. *Transl Oncol*, 2016, 33: 101672. doi: 10.1016/j.tranon.2023.101672.

- [13] KAUR J, JACOBS R, HUANG Y, *et al.* Salivary biomarkers for oral cancer and pre-cancer screening: a review. *Clin Oral Investig*, 2018, 22(2): 633–640. doi: [10.1007/s00784-018-2337-x](https://doi.org/10.1007/s00784-018-2337-x).
- [14] LI Y, JOHN M A S, ZHOU X, *et al.* Salivary transcriptome diagnostics for oral cancer detection. *Clin Cancer Res*, 2004, 10(24): 8442–8450. doi: [10.1158/1078-0432.ccr-04-1167](https://doi.org/10.1158/1078-0432.ccr-04-1167).
- [15] KAKABADZE M Z, PARESISHVILI T, KARALASHVILI L, *et al.* Oral microbiota and oral cancer: review. *Oncol Rev*, 2020, 14(2): 476. doi: [10.4081/oncol.2020.476](https://doi.org/10.4081/oncol.2020.476).
- [16] CALIFANO J, Van Der RIET P, WESTRA W, *et al.* Genetic progression model for head and neck cancer: implications for field cancerization. *Cancer Res*, 1996, 56(11): 2488–2492. doi: [10.1016/S0194-5998\(96\)80631-0](https://doi.org/10.1016/S0194-5998(96)80631-0).
- [17] VIELBA R, BILBAO J, ISPIZUA A, *et al.* p53 and cyclin D1 as prognostic factors in squamous cell carcinoma of the larynx. *Laryngoscope*, 2003, 113(1): 167–172. doi: [10.1097/00005537-200301000-00031](https://doi.org/10.1097/00005537-200301000-00031).
- [18] SHPITZER T, HAMZANY Y, BAHAR G, *et al.* Salivary analysis of oral cancer biomarkers. *Br J Cancer*, 2009, 101(7): 1194–1198. doi: [10.1038/sj.bjc.6605290](https://doi.org/10.1038/sj.bjc.6605290).
- [19] POORNIMA G, KUMAR T S M. Genomic alphabets of saliva as a biomarker in oral cancer. *J Indian Acad Oral Med Radiol*, 2017, 29(4): 300. doi: [10.4103/jiaomr.JIAOMR_90_16](https://doi.org/10.4103/jiaomr.JIAOMR_90_16).
- [20] YANG Y, LI Y X, YANG X, *et al.* Progress risk assessment of oral premalignant lesions with saliva miRNA analysis. *BMC Cancer*, 2013, 13(1): 1–8. doi: [10.1186/1471-2407-13-129](https://doi.org/10.1186/1471-2407-13-129).
- [21] FRANZMANN E J, REATEGUI E P, PEDROSO F, *et al.* Soluble CD44 is a potential marker for the early detection of head and neck cancer. *Cancer Epidemiol Biomarkers Prev*, 2007, 16(7): 1348–1355. doi: [10.1158/1055-9965.EPI-06-0011](https://doi.org/10.1158/1055-9965.EPI-06-0011).
- [22] JOHN M A S, LI Y, ZHOU X, *et al.* Interleukin 6 and interleukin 8 as potential biomarkers for oral cavity and oropharyngeal squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*, 2004, 130(8): 929–935. doi: [10.1001/archotol.130.8.929](https://doi.org/10.1001/archotol.130.8.929).
- [23] MARKOPOULOS A K, MICHAILIDOU E Z, TZIMAGIORGIS G. Salivary markers for oral cancer detection. *Open Dent J*, 2010, 4: 172–178. doi: [10.2174/1874210601004010172](https://doi.org/10.2174/1874210601004010172).
- [24] HU S, ARELLANO M, BOONTHEUNG P, *et al.* Salivary proteomics for oral cancer biomarker discovery. *Clin Cancer Res*, 2008, 14(19): 6246–6252. doi: [10.1158/1078-0432.CCR-07-5037](https://doi.org/10.1158/1078-0432.CCR-07-5037).
- [25] KANG M S, OH J S, KIM H J, *et al.* Prevalence of oral microbes in the saliva of oncological patients. *J Bacteriol Virol*, 2009, 39(4): 277–285. doi: [10.4167/jbv.2009.39.4.277](https://doi.org/10.4167/jbv.2009.39.4.277).
- [26] MAGER D, HAFFAJEE A, DEVLIN P, *et al.* The salivary microbiota as a diagnostic indicator of oral cancer: a descriptive, non-randomized study of cancer-free and oral squamous cell carcinoma subjects. *J Transl Med*, 2005, 3: 27. doi: [10.1186/1479-5876-3-27](https://doi.org/10.1186/1479-5876-3-27).
- [27] HIRSCH F R, SCAGLIOTTI G V, MULSHINE J L, *et al.* Lung cancer: current therapies and new targeted treatments. *Lancet*, 2017, 389(10066): 299–311. doi: [10.1016/S0140-6736\(16\)30958-8](https://doi.org/10.1016/S0140-6736(16)30958-8).
- [28] ZHANG L, XIAO H, ZHOU H, *et al.* Development of transcriptomic biomarker signature in human saliva to detect lung cancer. *Cell Mol Life Sci*, 2012, 69(19): 3341–3350. doi: [10.1007/s00018-012-1027-0](https://doi.org/10.1007/s00018-012-1027-0).
- [29] QIAN K, WANG Y, HUA L, *et al.* New method of lung cancer detection by saliva test using surface-enhanced Raman spectroscopy. *Thoracic Cancer*, 2018, 9(11): 1556–1561. doi: [10.1111/1759-7714.12837](https://doi.org/10.1111/1759-7714.12837).
- [30] 李晓舟, 杨天月, 丁建华. 唾液表面增强拉曼光谱用于肺癌的诊断. *光谱学与光谱分析*, 2012, 32(2): 391–393. doi: [10.3964/j.issn.1000-0593\(2012\)02-0391-03](https://doi.org/10.3964/j.issn.1000-0593(2012)02-0391-03).
- [31] 高明, 徐钧, 杨文慧. 胰腺癌早期诊断的肿瘤标志物研究进展. *肿瘤研究与临床*, 2020, 32(12): 881–884. doi: [10.3760/cma.j.cn115355-20191021-00482](https://doi.org/10.3760/cma.j.cn115355-20191021-00482).
- [32] 赵治锋, 谢荣理, 沈东杰, 等. 唾液肿瘤标志物诊断胰腺癌的研究. *外科理论与实践*, 2019, 24(2): 149–154. doi: [10.16139/j.1007-9610.2019.02.013](https://doi.org/10.16139/j.1007-9610.2019.02.013).
- [33] ZHANG L, FARRELL J J, ZHOU H, *et al.* Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer. *Gastroenterology*, 2010, 138(3): 949–957.e947. doi: [10.1053/j.gastro.2009.11.010](https://doi.org/10.1053/j.gastro.2009.11.010).
- [34] HUMEAU M, VIGNOLLE-VIDONI A, SICARD F, *et al.* Salivary microRNA in pancreatic cancer patients. *PLoS One*, 2015, 10(6): e0130996. doi: [10.1371/journal.pone.0130996](https://doi.org/10.1371/journal.pone.0130996).
- [35] FARRELL J J, ZHANG L, ZHOU H, *et al.* Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer. *Gut*, 2012, 61(4): 582–588. doi: [10.1136/gutjnl-2011-300784](https://doi.org/10.1136/gutjnl-2011-300784).
- [36] TORRES P J, FLETCHER E M, GIBBONS S M, *et al.* Characterization of the salivary microbiome in patients with pancreatic cancer. *PeerJ*, 2015, 3: e1373. doi: [10.7717/peerj.1373](https://doi.org/10.7717/peerj.1373).
- [37] LAU C, KIM Y, CHIA D, *et al.* Role of pancreatic cancer-derived exosomes in salivary biomarker development. *J Biol Chem*, 2013, 288(37): 26888–26897. doi: [10.1074/jbc.M113.452458](https://doi.org/10.1074/jbc.M113.452458).
- [38] GAO S, CHEN L Y, WANG P, *et al.* MicroRNA expression in salivary supernatant of patients with pancreatic cancer and its relationship with ZHENG. *Biomed Res Int*, 2014, 2014: 756347. doi: [10.1155/2014/756347](https://doi.org/10.1155/2014/756347).
- [39] XIAO H, ZHANG Y, KIM Y, *et al.* Differential proteomic analysis of human saliva using tandem mass tags quantification for gastric cancer detection. *Sci Rep*, 2016, 6: 22165. doi: [10.1038/srep22165](https://doi.org/10.1038/srep22165).
- [40] LI F, YOSHIZAWA J M, KIM K M, *et al.* Discovery and validation of salivary extracellular RNA biomarkers for noninvasive detection of gastric cancer. *Clin Chem*, 2018, 64(10): 1513–1521. doi: [10.1373/clinchem.2018.290569](https://doi.org/10.1373/clinchem.2018.290569).
- [41] RÖCKEN C. Predictive biomarkers in gastric cancer. *J Cancer Res Clin Oncol*, 2023, 149(1): 467–481. doi: [10.1007/s00432-022-04408-0](https://doi.org/10.1007/s00432-022-04408-0).
- [42] USUI Y, TANIYAMA Y, ENDO M, *et al.* *Helicobacter pylori*, homologous-recombination genes, and gastric cancer. *N Engl J Med*, 2023, 388(13): 1181–1190. doi: [10.1056/NEJMoa2211807](https://doi.org/10.1056/NEJMoa2211807).
- [43] 杨皓毓, 李雨庆, 周学东. 口腔幽门螺杆菌与胃幽门螺杆菌感染关系的研究进展. *华西口腔医学杂志*, 2014, 32(3): 314–318. doi: [10.7518/hxkq.2014.03.025](https://doi.org/10.7518/hxkq.2014.03.025).

- [44] SUN Y S, ZHAO Z, YANG Z N, *et al.* Risk factors and preventions of breast cancer. *Int J Biol Sci*, 2017, 13(11): 1387–1397. doi: [10.7150/ijbs.21635](https://doi.org/10.7150/ijbs.21635).
- [45] YARDIM-AKAYDIN S, KARAHALIL B, BAYTAS S N. New therapy strategies in the management of breast cancer. *Drug Discov Today*, 2022, 27(6): 1755–1762. doi: [10.1016/j.drudis.2022.03.014](https://doi.org/10.1016/j.drudis.2022.03.014).
- [46] ZHANG L, XIAO H, KARLAN S, *et al.* Discovery and preclinical validation of salivary transcriptomic and proteomic biomarkers for the non-invasive detection of breast cancer. *PLoS One*, 2010, 5(12): e15573. doi: [10.1371/journal.pone.0015573](https://doi.org/10.1371/journal.pone.0015573).
- [47] FÜZÉRY A K, LEVIN J, CHAN M M, *et al.* Translation of proteomic biomarkers into FDA approved cancer diagnostics: issues and challenges. *Clin Proteomics*, 2013, 10(1): 1–14. doi: [10.1186/1559-0275-10-13](https://doi.org/10.1186/1559-0275-10-13).
- [48] WU W, GONG H, LIU M, *et al.* Noninvasive breast tumors detection based on saliva protein surface enhanced Raman spectroscopy and regularized multinomial regression//Proceedings of the 2015 8th International Conference on Biomedical Engineering and Informatics (BMEI). Shenyang: IEEE, 2015: 214–218. doi: [10.1109/BMEI.2015.7401503](https://doi.org/10.1109/BMEI.2015.7401503).
- [49] 李艺, 祝洪澜, 昌晓红, 等. 初诊晚期上皮性卵巢癌的规范化治疗. *现代妇产科进展*, 2020, 29(10): 778–782. doi: [10.13283/j.cnki.xdfckjz.2020.10.011](https://doi.org/10.13283/j.cnki.xdfckjz.2020.10.011).
- [50] CHEN D X, SCHWARTZ P E, LI F Q. Saliva and serum CA 125 assays for detecting malignant ovarian tumors. *Obstet Gynecol*, 1990, 75(4): 701–704.
- [51] SCHAPHER M, WENDLER O, GRÖSCHL M, *et al.* Salivary leptin as a candidate diagnostic marker in salivary gland tumors. *Clin Chem*, 2009, 55(5): 914–922. doi: [10.1373/clinchem.2008.116939](https://doi.org/10.1373/clinchem.2008.116939).
- [52] WANG N, FANG J Y. *Fusobacterium nucleatum*, a key pathogenic factor and microbial biomarker for colorectal cancer. *Trends Microbiol*, 2023, 31(2): 159–172. doi: [10.1016/j.tim.2022.08.010](https://doi.org/10.1016/j.tim.2022.08.010).
- [53] SAZANOV A A, KISELYOVA E V, ZAKHARENKO A A, *et al.* Plasma and saliva miR-21 expression in colorectal cancer patients. *J Appl Genet*, 2017, 58(2): 231–237. doi: [10.1007/s13353-016-0379-9](https://doi.org/10.1007/s13353-016-0379-9).

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