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內文：

Abstract

Saliva as a diagnostic tool provides a noninvasive, simple and low-cost method for disease detection and screening. Saliva collection is more practical and comfortable compared with other invasive methods, and saliva can be a desirable body fluid for biomarker detection in clinical applications

Introduction

The earlier a disease is detected and diagnosed, the more likely appropriate treatment will be administered to reduce the severity. Early detection is therefore urgent for clinical treatment

Three limitation:

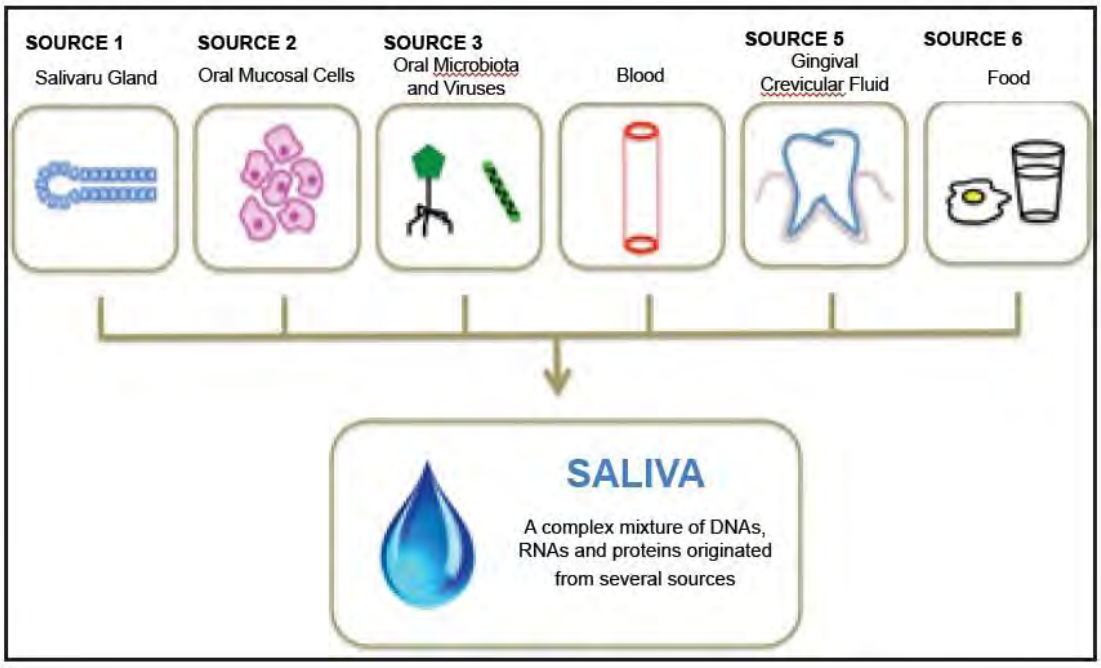
1. Definitive biomarkers associated with disease
2. Simple and inexpensive methods that are minimally invasive; and
3. An accurate, portable, and easy-to use diagnostic platform

Saliva is low-cost, noninvasive, simple, and does not cause discomfort for the patient

The aim of this review is to provide a status review of salivary “omics” constituents, salivary diagnostics, and their translational and clinical applications

Salivaomics

we can detect changes in their salivary concentration to develop dysregulated biomarkers to detect early oral and systemic diseases, evaluate disease prognosis and risk, and monitor the response to treatment



The salivary genome and epigenome(DNA)

DNA methylation is an epigenetic process that can change in response to the passage of time. Aberrant methylation of genes is common in cancers. Viet et al. found significant differences in methylation patterns between the preoperative and postoperative saliva of cancer patients, and between preoperative saliva from OSCC patients and saliva from healthy controls

Transcriptomes(mRNA and miRNA)

The mRNA and miRNA, which are secreted from cells and enter the oral cavity The transcription of specific mRNA and miRNA is altered in disease states.

Zhang et al. identified four mRNA biomarkers (KRAS, MBD3L2, ACRV1, and DPM1) that can differentiate early stage resectable pancreatic cancer patients from non-cancer subjects

Hu et al. reported that three mRNA biomarkers (MNDA, GBP-2, and FCGR3B) were significantly elevated in patients with primary Sjögren's syndrome

miRNA is a group of small noncoding RNAs, which were centrally involved in various biological processes, including cell differentiation, proliferation, and survival Compared with salivary mRNA, salivary miRNA are more stable.

Park et al. found that two miRNAs (miR-125a, miR-200a) in the saliva of OSCC patients were significantly reduced compared with healthy controls

Matse et al. found a combination of four miRNAs (hsa-miR-132, hsa-miR-15b, mmu-miR-140, and hsa-miR-223) is valuable in the detection of parotid gland malignancy

The proteome

Esser et al. reported that salivary protein degradation happens rapidly, and even happens during saliva collection and handling. Our laboratory has developed methods to stabilize the salivary proteome with protease inhibitors

Using 2D-DIGE, Hu et al. reported 16 peptides in saliva that were found at significantly different levels in patients with primary Sjögren's syndrome

Xiao et al. reported three proteins (HP, AZGP1, and human calprotectin) that had good discriminatory power in Lung Cancer patients and healthy control subjects, with high sensitivity (89%) and high specificity (92%).

The metabolome

Based on the different metabolomic technology, studies have reported salivary metabolites cannot only identify health status, but can also discriminate diseased patients from healthy control subjects

Sugimoto et al. investigate discriminatory metabolites from patients with oral cancer, pancreatic cancer, breast cancer, periodontal disease, and healthy controls

The result is relatively high concentrations in all three cancer patient groups

three metabolites (taurine, piperidine, and a peak at 120.0801 m/z) were oral cancer-specific markers, and eight metabolites (leucine, isoleucine, tryptophan, valine, glutamic acid, phenylalanine, glutamine, and aspartic acid) were pancreatic cancer-specific markers

Wei et al. found that a combination of three salivary metabolites (phenylalanine, valine, and lactic acid) could distinguish OSCC patients from healthy controls with high sensitivity and high specificity

The microbiome

A series of evidence shows that oral dysbiosis can lead to Oral Diseases such as periodontal diseases and caries , as well as cancer and other systemic diseases.

Mager et al. used checkerboard DNA-DNA hybridization to evaluate the oral microbiota in saliva from patients with OSCC and healthy subjects found a combination of three microbiotas (*Capnocytophaga gingivalis, Prevotella*

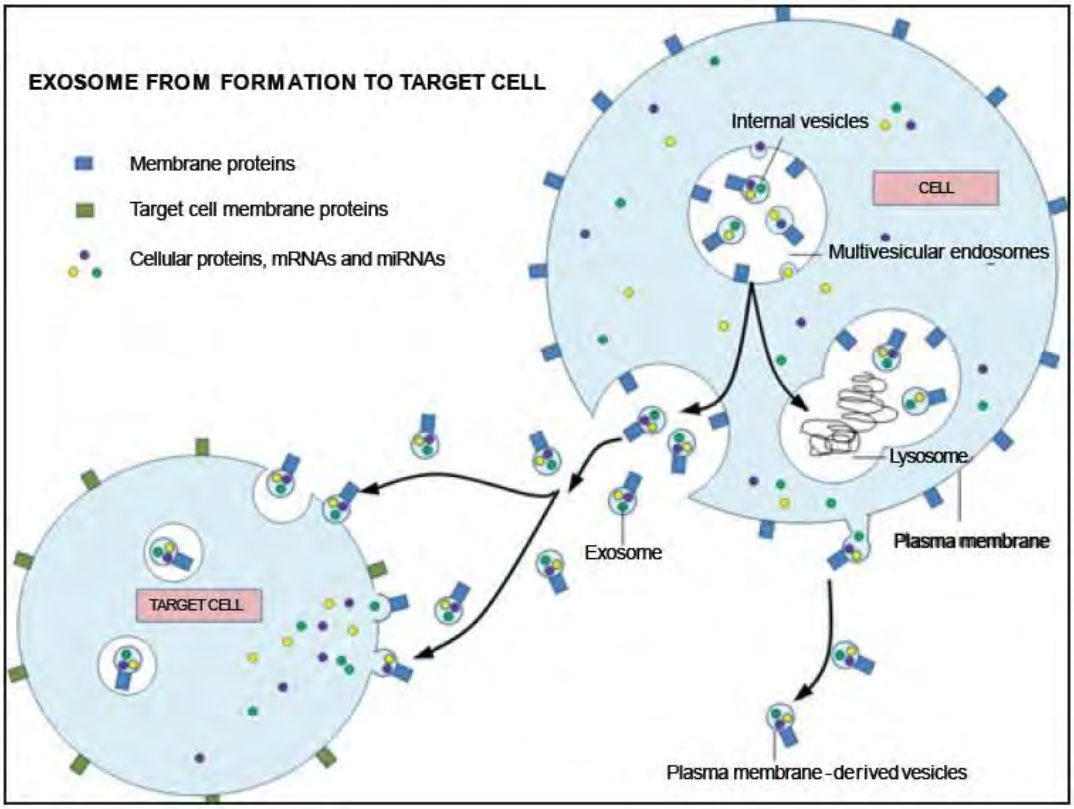
melaninogenica, and *Streptococcus mitis*) that could be used as diagnostic biomarkers with 80% sensitivity and 82% specificity

Farrell et al. profiled the salivary microbiota from patients with pancreatic cancer and healthy subjects; the results showed that 31 bacterial species were increased and 25 were decreased in pancreatic cancer, and two bacterial candidates (*Neisseria elongate* and *Streptococcus mitis*) were able to distinguish patients

The mechanism of salivary diagnostics

Signals transmitted through such networks might induce related signaling pathways that result in altered gene expression and protein translation, and thereby produce disease-induced salivary biomarker profiles

Exosome: from formation to target



Biological function of exosomes

Lässer et al. recently discovered substantial amounts of RNA in exosomes derived from mast cells, which have the capacity to donate their RNA to other cells and can subsequently affect the protein production of a recipient cell. This finding suggests that RNA can be transferred between mammalian cells by an extracellular exosome-based transport mechanism.

Because a single miRNA can regulate hundreds of genes and may act as a master regulator of processes. Another feature that makes miRNAs excellent candidates for biomarker studies is their remarkable stability and resistance to degradation

Skog et al. suggested that glioblastoma tumor-derived exosomes in patient serum carry a distinctive miRNA payload that can be used diagnostically.

The diagnostic and therapeutic potential of exosomes

The result of Lau et al. study supported the hypothesis that tumor-derived exosomes provide a mechanism for the development of discriminatory salivary biomarkers that are applicable to distal systemic diseases

Translational and clinical applications of saliva biomarkers

Table 1. Discovered salivary biomarkers using epigenomics, transcriptomics, proteomics and Metabolomics for detecting oral disease, oral cancer, pancreas cancer, Lung Cancer, and breast cancer.

Disease	Approach		Markers
Periodontal disease	proteomic	ELISA [91]	IL-6
	Proteomic and microbial studies	ELISA [88,89]	IL-1 and *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, and Treponema denticola*
		Multiplex protein array discovery [90]	IL-6, IL-8
Oral cancer	Epigenomics	Candidate from previous study, Q-MSP discovery and validation [93]	KIF1A, EDNRB
	Transcriptomics	Microarray discovery and qPCR validation [20]	IL-8, SAT, IL-1B, OAZ1, H3F3A, DUSP, S100P
		Microarray discovery and qPCR validation [49]	IL8, IL1B, OAZ1, SAT
		Discovery and validation by RT-preamp-qPCR or andidate gene selection based on previous study, qRT-PCR quantification [16,94]	miR-200a, miR-125a and miR-31
		ELISA assessment and qPCR confirmation [95]	IL-8
Pancreatic cancer	Transcriptomics	Affymetrix array discovery and qRT-PCR validation [19]	KRAS, MBD3L2, ACRV1, DPM1
	Metabolomics	Discovery by CE-TOF-MS-based *Metabolomics* [56]	Leucine with isoleucine, tryptophan, valine, glutamic acid, phenylalanine, glutamine, aspartic acid
	Microbiome	microbial profiling using the Human Oral Microbe Identification Microarray [69]	*Neisseria elongata* and *Streptococcus mitis*
Lung Cancer	Transcriptomics	Microarray discovery and qRT-PCR verification and pre-validation [21]	CCNI, EGFR, FGF19, FRS2, GREB1
	Proteomics	Two-dimensional gel *Electrophoresis* and LCMS-MS [47]	Calprotectin, AZGP1, haptoglobin hp2
	Metabolomics	Discovery by SERS [105]	Unidentified peak wavelengths; 822, 884, 909, 925, 1009, 1,077, 1,369, 1,393, 1,721 cm-1
Breast cancer	Combination proteomic/ transcriptomic approaches	Discovery by 2D-DIGE and RT-PCR/Affymetrix, validation by qRT-PCR[22]	mRNAs: CSTA, TPT1, IGF2BP1, GRM1, GRIK1, H6PD, MDM4, S100A8 Protein: CA6

Conclusion

The development of high-throughput technology has revealed advanced insights toward an understanding of saliva as a reflection of the condition of the whole body. The interpretation and utilization of this information will bolster the applicability of saliva to diagnosing disease, evaluating therapies, and designing personalized medicine.

題號	題目
1	根據上文，哪個敘述為非? (A) Saliva as a diagnostic tool provides a noninvasive, simple and low-cost method for disease detection (B) Compared with salivary mRNA, salivary miRNA are more stable. (C) DNA methylation is common in patients with systemic disease (D) salivary protein degradation happens rapidly, and even happens during saliva collection and handling
答案( )	出處：OHDM (Oral Health and Dental Management)- Vol. 13 - No. 2 - June, 2014
題號	題目
2	唾液腺發生惡性腫瘤比率最高的位置在哪?
	(A) Parotid gland (B) Submandibular gland (C) Sublngual gland (D) Minor salivary gland
答案( )	出處：p.474, Oral and Maxillofacial Pathology ,third edition