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Salivary Biomarkers in the Diagnosis of Sjogren's Syndrome: A Review of Current Research Progress

Siting Li[1], Haotian Zheng[1] & Jing Guan[2]

[1] North China University of Science and Technology

[2] Hebei General Hospital

Correspondence: Jing Guan, Hebei General Hospital.

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Abstract

Saliva contains a variety of biomarkers, which are closely related to the occurrence, progression, diagnosis and treatment of oral and systemic diseases. Currently, the diagnosis of Sjögren's syndrome (SS) still relies on invasive salivary gland biopsy procedures and serum Ro-52/SSA and La/SSB testing, which often makes early diagnosis extremely difficult, so screening for specific saliva biomarkers is extremely beneficial in the diagnosis and individualized treatment of Sjögren's syndrome. This article elaborates the research progress of Sjogren's syndrome-related biomarkers in saliva, in order to provide new methods and ideas for the early diagnosis of Sjogren's syndrome.

Keywords: Sjogren's syndrome, biomarkers, saliva

1. Introduction

Salivary is a complex, dynamic biological fluid secreted by the salivary glands and gingival sulcus and is an important component of the oral system (Kaczor-Urbanowicz K E, Martin Carreras-Presas C, Aro K, et al., 2017). It plays an important role in many biological functions, such as buffering, lubrication, chewing, swallowing, and digestion. In addition, saliva protects the oral mucosa from biological, mechanical and chemical stimuli, prevents bacterial, viral and fungal infections, and maintains the balance of the oral ecosystem. When diagnosing diseases in the oral cavity, the lesion is in direct contact with saliva, and detection of saliva has a natural advantage. Studies have shown that microorganisms, nucleic acids, proteins and other biomarkers in saliva can be used not only for the early detection of dental caries (Gao X, Jiang S, Koh D, et al., 2016), periodontal disease (Inonu E, Hakki S S, Kayis S A, et al., 2020), oral cancer (Proctor G B., 2016), but also for the diagnosis of Sjogren's syndrome (Jung J Y, Kim J W, Kim H A, et al., 2021).

Sjögren's syndrome (SS) is a lymphocyte-mediated systemic autoimmune disease (Fox R I., 2005), the clinical manifestations are mainly damage to exocrine glands (such as salivary glands and lacrimal glands), and its systemic damage mainly affects the lungs, kidneys and nervous system. Symptoms such as dry mouth and dry eyes have a negative impact on the patient's daily life; Systemic diseases involving the whole body, such as peripheral neuropathy, pulmonary interstitial fibrosis, and secondary lymphoma, reduce the quality of life of patients and even threaten their lives (Jaskólska M, Chylińska M, Masiak A, et al., 2020).

Currently, SS is diagnosed primarily according to criteria proposed by the 2002 US-EU Consensus Group (Zhao Yan, Jia Ning & Wei Li, 2003) or the 2012 American College of Rheumatology (Shiboski S C, Shiboski C H, Criswell L A, et al., 2012), but in trials evaluating salivary gland involvement, salivary gland imaging and lip gland biopsy are invasive tests that are unacceptable to some patients. With the continuous development of accurate and non-invasive concepts, more and more diagnostic techniques with non-invasive properties are used in the diagnosis of Sjogren's syndrome. Among them, saliva detection, as a cheap, accessible, radiation-free and

safe examination method, has unique clinical value. Therefore, the academic community has carried out in-depth research on SS-related saliva biomarkers and published a large number of literature. This article will review the progress of saliva biomarkers in the diagnosis of Sjogren's syndrome.

2. Saliva

Saliva is an acidic (pH = 6-7) biological fluid, composed of 94%~99% water, 0.2% inorganic substances, 0.5% organic substances and a variety of other cellular elements (Li Y, Ren B, Peng X, et al., 2020). There are abundant capillaries and acinar around the salivary glands, and enzymes, hormones, antibodies, antibacterial molecules, and growth factors rich in blood can enter the saliva. The composition of saliva is similar to that of serum and reflects the pathophysiology of the body (Lee Y H & Wong D T., 2009). Currently, anti-Ro/SS-A and La/SS-B antibodies may be the two most characteristic autoantibodies for detecting SS, but these antibodies are not completely specific to SS, and they can also be found in the serum of patients with systemic lupus erythematosus and rheumatoid arthritis (Ma W T, Chang C, Gershwin M E, et al., 2017), with relatively low sensitivity and specificity, with certain limitations. These autoantibodies are also present in the saliva of patients with SS and can increase their specificity to more than 95 percent (Wei P, Li C, Qiang L, et al., 2015). Some autoantibodies may appear before symptoms appear and are valuable for early diagnosis (Zhu Hui & Yu Guangyan, 2021).

There are two types of saliva specimens: unstimulated whole saliva (UWS) and stimulated whole saliva (SWS). Efficient saliva collection from SS patients is difficult due to significantly reduced saliva velocity (Lacombe V, Lacout C, Lozac'h P, et al., 2020), and longer collection times may affect sample quality. C Alvariño found that SWS is more suitable than UWS for measuring saliva flow and performing qualitative analysis of saliva in SS patients (Alvariño C, Bagan L, Murillo-Cortes J, et al., 2021). Therefore, many studies have used SWS as a sample to meet saliva sample requirements by inducing patients to chew to increase saliva flow by using paraffin wax or chewing gum as irritants.

3. Salivary Proteomic Analysis

At present, protein experimental analysis shows that salivary protein is closely related to the physiological function of saliva. The use of proteins in saliva as biomarkers to evaluate health status and early diagnosis of diseases has increasingly become a hot spot in clinical research and has broad application prospects. In addition, single protein markers are used to diagnose clinical diseases with many affected factors, poor sensitivity and specificity, and have certain limitations. Saliva proteomics can conduct multivariate research and analysis on multiple saliva proteins at the same time, improve the sensitivity and specificity of disease diagnosis, and facilitate early detection and early diagnosis of diseases.

In recent years, liquid chromatography tandem mass spectrometry (LC-MS/MS) has become the technique of choice for high-throughput characterization of proteins (Aebersold R & Mann M., 2016), and for SS saliva biomarkers for diagnosis (Aqrawi L A, Galtung H K, Vestad B, et al., 2017). Aqrawi L.A. using liquid chromatography (LC)-MS analysis showed that the levels of salivary neutrophil gelatinase-associated lipid carrier protein (NGAL), granulin, and calmodulin in SS patients were significantly higher than in normal healthy people (Aqrawi L A, Galtung H K, Vestad B, et al., 2017). Their study further clarified the association between changes in saliva and extracellular vesicle proteins in saliva and histopathological features in patients with SS (Aqrawi L A, Galtung H K, Guerreiro E M, et al., 2019). Levels of peptidyl-prolyl cis- trans- isomerase FK506-binding protein 1A, CD44, β2m, Ly-6/uPAR-associated protein 1 and cluster proteins were elevated in SWS patients. Sembler-Møller et al. used LC-MS to perform proteomic analysis of saliva, plasma, and salivary gland tissue in patients with SS (Sembler-Møller M L, Belstrøm D, Locht H, et al., 2020). The results showed elevated levels of neutrophil elastase, calreticulin, and triplet-containing 29 (TRIM 29) in the saliva of SS patients. In addition, Sembler-Møller et al. found that the use of saliva TRIM 29 could distinguish between SS and non-SS patients (AUC 0.8), while serum anti-SSA/Ro and saliva TRIM 29 combined diagnostic SS had higher accuracy (AUC 0.995) (Sembler-Møller M L, Belstrøm D, Locht H, et al., 2021).

4. SS Biomarkers in Saliva

Associated lipid carrying protein, salivary cytokines, saliva autoantibodies.

4.1 Salivary Beta2-Microglobulin (β2-m)

β2-m is a non-glycosylated low molecular weight protein that is part of the major histocompatibility complex-I, produced primarily by lymphocytes, expressed on antigen-presenting cells (including T and B lymphocytes), and regulated by interferon (Berko D, Carmi Y, Cafri G, et al., 2005). Salivary beta2-m has been associated with disease progression in SS (Garza-García F, Delgado-García G, Garza-Elizondo M, et al., 2017). There was a significant positive correlation between patient salivary β2-m levels as determined by enzyme-linked immunosorbent and patient-reported index (ESSPRI) and histopathological changes in patients with EURAR Sjogren's syndrome. Wang Ping found that patients with SS with higher pathological grade had less saliva

secretion and higher levels of β2-m in serum and saliva (Wang Ping, 2010). This experiment proves that the level of β2-m expression in saliva is related to the pathological grade of SS. Experiments by Asashima determined an optimal critical level of 2.3 mg/L for β2-m to distinguish SS patients from healthy individuals (Asashima H, Inokuma S, Onoda M, et al., 2013). Saliva β2-m may be an ideal biomarker for diagnosing SS and reflecting SS disease activity.

4.2 Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipid carrier protein is a member of the lipid carrier family and plays an important role in physiological processes such as cell differentiation, apoptosis, and inflammatory immune response. Aqrawi LA found that patients with SS had elevated levels of NGAL in the salivary glands and saliva (Aqrawi L A, Galtung H K, Vestad B, et al., 2017). Their subsequent study found that patients with SS had higher levels of NGAL in the salivary acinar and ductal epithelium and were positively correlated with the degree of inflammation of the SS target organ, consistent with their previous findings of significantly higher levels of NGAL in saliva in SS patients (Aqrawi L A, Jensen J L, Fromreide S, et al., 2020). Therefore, saliva NGAL can be used for the detection of SS to determine the degree of inflammation of target organs in SS patients, which has certain diagnostic value.

4.3 Saliva Cytokines

Cytokines have a broad immunomodulatory role and are closely related to the pathogenesis of SS (Yu Xiaowen, Huang Lu, Wang Miao & Wu Bin, 2022). Chronic inflammation in patients with SS reflects an imbalance in cytokine expression in the local and systemic blood of the gland. Kang found expression of multiple cytokines in whole saliva samples from SS patients, including elevated levels γ interferon (IFN-γ), tumor necrosis factor-α (TNF-α), interleukins IL-1, IL-4, IL-10, IL-12p40, and IL-17 (Kang E H, Lee Y J, Hyon J Y, et al., 2011). Benchabane tested 17 patients with SS and found that saliva and serum IL-6A, IL-10, TNF-α, and IL-44 levels were higher than those in 15 healthy patients (Benchabane S, Boudjelida A, Toumi R, et al., 2016), where saliva IL-6 levels were associated with glandular cell infiltration. Cytokines play an important role in immune defense mechanisms, and they are also involved in other physiological and pathological responses in the body. Stadler's meta-analysis found that patients with periodontitis had significantly elevated IL-6 levels of gingival sulcus compared with healthy controls (Stadler A F, Angst P D M, Arce R M, et al., 2016). Inönü measured the concentration of IL-17 in saliva in patients with periodontitis, gingivitis, and periodontal health patients of varying severity, and found that the concentration of IL-17 was significantly increased in both the gingivitis group and the periodontitis group. (Inönü E, Kayis S A, Eskan M A, et al., 2020) Use these markers alone to detect reduced specificity for SS. However, SS inflammation is an imbalance in the expression of multiple cytokines, so the combination of multiple cytokines still has the potential to become an indicator of the diagnosis of SS.

4.4 Saliva Autoantibodies

Currently, serum Ro/SSA and La/SSB are necessary indicators for the diagnosis of SS. Hu et al. identified potential autoantibodies (e.g., anti-SSA, anti-SSB, anti-glutamic aminotransferase, and anti-histones) in the saliva of SS patients that can distinguish SS patients from patients with systemic lupus erythematosus (SLE) and healthy individuals. (Hu S, Vissink A, Arellano M, et al., 2011) However, anti-Ro/SSA and La/SSB are also expressed in other autoimmune diseases (such as rheumatoid arthritis), so they cannot be used as specific indicators for the diagnosis of SS.

Muscarinic type 3 receptor (M3R) is highly expressed in exocrine glands and regulates the secretion of salivary acinar cells (Sumida T, Iizuka M, Asashima H, et al., 2012). Jayakanthan found that saliva anti-M3R IgG antibodies have high specificity for the detection of SS and are more easily detectable in younger patients and hyperglobulinemia (Jayakanthan K, Ramya J, Mandal S K, et al., 2016). The results of Mona showed that saliva anti-M3R levels in SS patients were 3.59 times higher than in healthy people (Mona M, Mondello S, Hyon J Y, et al., 2021).

4.5 Salivary Soluble Sialic Acid-Binding Immunoglobulin-Like Lectin (Siglec)-5

Siglecs family molecules are involved in several important physiological processes such as immune cell activation, proliferation, and apoptosis, and play a role in defense against infections and autoimmune diseases (Gianchecchi E, Arena A & Fierabracci A., 2021). Lee J found that the level of (Siglec)-5 in the saliva of SS patients was significantly elevated (Lee J, Lee J, Kwok S K, et al., 2018). They also found that saliva-5 levels were negatively correlated with saliva flow velocity and positively correlated with ocular surface scores (Lee J, Lee J, Baek S, et al., 2019). Siglec-5 not only shows saliva secretion function, but also reflects the severity of ocular surface damage. However, the mechanism of high-concentration (Siglec)-5 expression in the saliva of patients with SS and its pathological role in SS are not clear, and the use of SS in the diagnosis of SS remains to be determined.

4.6 Salivary Calprotectin

Calprotectin belongs to the S100 protein family, and an elevated level of S100A8/A9 indicates the presence of a large number of activated dendritic cells and macrophages in the salivary glands, which is related to the number of lymphocyte infiltration foci in the salivary glands and indirectly reflects the degree of damage to the glands. In multiple studies, elevated serum calprotectin levels in patients with SS (Balarini G M, Zandonade E, Tanure L, et al., 2016; Nicaise C, Weichselbaum L, Schandene L, et al., 2017), were positively correlated with lesion scores (Nicaise C, Weichselbaum L, Schandene L, et al., 2017). Jazzar (Jazzar A A, Shirlaw P J, Carpenter G H, et al., 2018) found that there was no significant difference between S100A8/A9 levels in parotid saliva and full-mouth saliva levels in SS patients (P=0.001 and 0.031, respectively). The median concentration of S100A8/A9 in parotid saliva in SS patients was 743.1 (91-3526) ng/mL, which was significantly higher than that in the healthy group (31.9; 0-273.2 ng/mL) and the lymphoma disease control group (208.9; 0-265.3 ng/mL). Saliva S100A8/A9 levels help diagnose SS and distinguish between SS lymphoma or patients at higher risk of lymphoma.

4.7 Adiponectin

Adiponectin is a protein belonging to the soluble defensive collagen superfamily that is synthesized and secreted primarily by adipose tissue. Adiponectin levels in saliva are elevated in SS (Tvarijonaviciute A, Zamora C, Martinez-Subiela S, et al., 2019). Studies have shown that the level of adiponectin in the saliva of patients is positively correlated with the levels of saliva IL-1, IL-8, TNF-α.

5. Summary

Saliva has the advantages of non-invasive acquisition and low cost. Many biomarkers in saliva are highly correlated with blood levels, making them ideal as tools for early diagnosis, process monitoring, and efficacy assessment. Because SS is a slow-progressing and often incubating disease, patients need to undergo a number of years of pathological changes before they meet the classification criteria when the chronic functional organ disorder may be irreversible. Therefore, saliva markers are of great clinical significance as an early diagnostic tool for SS.

In summary, β2-m and NGAL present in saliva have the potential to become biomarkers for early diagnosis of SS and applied clinically. Some experiments have proved that interleukin (IL-6, IL-17, etc.), M3R and (Siglec)-5 in saliva are biomarkers for early diagnosis of SS, but specific experimental data are lacking, and their clinical application needs further verification. In addition, patients with SS are often accompanied by xerostomia, which brings certain difficulties to saliva collection. Therefore, it is necessary to establish a saliva sample bank as soon as possible, and further improve the collection, storage, component separation and detection technology of saliva and standardize it.

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