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Salivary Biomarker Potential for Early Detection of Oral Squamous Cell Carcinoma by Surface Acoustic Wave Technology: A Narrative Review

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most frequent oral cancer that occurs with a prevalence of about 90%. OSCC ranked as the sixth most common oral cancer in the world with morbidity and mortality rates of more than 50%. Southeast Asia has the highest prevalence compared to other countries, which is 6.4/100.000, 20-40% of new OSCC cases are detected after experiencing metastasis to the lymph nodes that cause further complications. Therefore, OSCC early detection is needed for better patient management. Surface Acoustic Wave (SAW) is the latest technology that can detect OSCC using salivary biomarkers. Analysis of the potential of saliva-containing biomarkers for early detection of OSCC using Surface Acoustic Wave technology. Salivary biomarkers such as IL-1β, IL-8, and Galectin-3-binding protein (LGALS3BP) increased significantly even in the early stages of OSCC. SAW technology provides accurate label-free detection of various analytes, from molecular to cellular levels through the inverse piezoelectric effect of interactions between specific biomarkers as good as gold standards ELISA. SAW electromechanical between the piezoelectric crystal and the single input electric crystal that combines sends a surface wave to the SAW substrate then binds to OSCC biomarkers and changes SAW frequency. SAW velocity is sensitive to changes in mass loading, causing shifts in latitude and design phases that allow high sensitivity detection. The concentration of IL-1β, IL-8, and LGALS3BP can be defined by this frequency shift measurement, then OSCC can be detected earlier. Salivary biomarkers potentially utilized for early detection of OSCC disease using Surface Acoustic Wave technology.

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1. INTRODUCTION

Oral Squamous Cell Carcinoma or OSCC has the highest prevalence of malignancy cases that occur in the oral cavity, which is approximately 80-90% from all malignant neoplasms in the oral cavity. The incidence increased by more than 50% within a decade [1]. OSCC originates from pre-existing and de novo potentially malignant lesions and it's frequently found on the dorsal of the tongue, alveolar mucosa, palate, lower labial mucosa, buccal mucosa, and ground of the mouth [2], [3]. The survival rate of OSCC patients after 5 years is only 50% [4]. According to WHO, the highest prevalence of OSCC is found in Southeast Asia with a figure of 6.4/100.000, where the percentage of morbidity and mortality in men is 8.7/100.000 and 7.3/100.000, while in women, it is 3.6/100.000 and 3.7/100.000 [5].

One of the main reasons for the low survival rate in patients with OSCC is that the disease usually is diagnosed at an advanced stage [6]. Detection of OSCC depends on clinical examination of the patient's oral cavity and biopsy for histological analysis. Despite having easy access for visual inspection, the early-stage OSCC is generally asymptomatic so misdiagnosis can occur and a correct diagnosis can only be made at an advanced stage when treatment must include surgical procedures, radiation, and sometimes chemotherapy. The combination of these procedures can impair the normal function of the oral cavity, thus affecting the appearance and reducing the quality of life of the patient. In addition, the patient's recovery rate can decrease up to 40% [7]. Furthermore, about 20-40% of new OSCC cases can be detected after having metastases to lymph nodes through the lymphatic channels where recent studies have shown that if OSCC patients are diagnosed with cervical lymph node metastases, it can worsen the prognosis and reduce life expectancy significantly [8].

Nowadays, there are several biomarkers that have been identified from human body fluids. Saliva is one of the most widely studied body fluids that can contain trusted biomarkers for detecting malignancy. Several researchers are investigating the clinical importance of salivary biomarkers in oral malignancies, such as OSCC [9]. The current research also leads to an early diagnosis of OSCC, where an early diagnosis can make the treatment required is simpler and the cure rate reaches above 80% [7]. Therefore, the latest technology is needed to detect OSCC early to monitor the disease activity that affects patient management. In the field of genetics, biomarkers are currently very promising for the early detection of OSCC. One of them is biosensor technology in the form of Surface Acoustic Wave (SAW) using a combination of early-stage salivary OSCC biomarkers, namely and Galectin-3-binding protein (LGALS3BP), Interleukin (IL) IL-1β, and IL-8. The objective of this article is to explain the potential of salivary biomarkers as early detection of oral squamous cell carcinoma using Surface Acoustic Wave technology.

2. ORAL SQUAMOUS CELL CARCINOMA

Oral Squamous Cell Carcinoma or OSCC is a cancerous neoplasm originating from the stratified squamous epithelium of the oral mucosa, with a multifactorial pathogenesis [10]. In general, OSCC affects the tongue and ground of the mouth with a prevalence of 20-40% and 15-20% of all cases. In addition, OSCC can also attack the gingiva, palate, retromolar area, and buccal and labial mucosa [4].

The OSCC recurrence rate reaches 32.7%, with 40%-50% of recurrences can be advanced OSCC [11]. One of the predictive factors for OSCC patient recovery is the level of recurrence that is observed in all age groups without association with age, sex, and tumor location. Despite upgrades in treatment modalities in targeted therapy, radiotherapy, surgery, and chemotherapy, the prognosis of OSCC is still low because of the characteristics that it invades, can metastasize, and cause recurrence [12], [13].

The main etiology of the development of oral cancer is the changes in DNA bases, breaks in strands, damage to tumor suppressor genes, and increased expression of protooncogenes due to the overproduction of reactive

oxygen species (ROS) [14]. In OSCC patients, levels of their antioxidants are significantly lower than in healthy individuals. Antioxidants can prevent cell damage and cell death by stopping the chain reactions caused by free radicals and oxidative stress. It is shown from their uric acid and bilirubin levels. Because of low levels of antioxidants, ROS cannot be neutralized and the progression of oral cancer cannot be prevented [15- 17].

OSCC also arises as a consequence of a series of molecular events that develop from the combination of genetic factors and exposure to environmental carcinogens such as cigarettes, alcohol, ionizing radiation or ultraviolet, chemical carcinogens, and microorganisms. It can cause chromosome damage if it's experiencing chronic exposure to carcinogens. Genetic damage causes increased cell proliferation and survival through activating mutations or amplification of oncogenes. Unfortunately, genetic damage can also inactivate tumor suppressor genes involved in inhibiting cell proliferation. This can cause cell dysregulation that makes the growth turn into an autonomic mechanism and develops into an invasive one. When OSCC grows and invades, angiogenesis occurs as a vital step in tumor formation [1], [10].

3. INTERLEUKIN-1β

Interleukin-1β (IL-1β) is one of the chemical mediators that plays part in cell proliferation, differentiation, apoptosis, and inflammation. Despite representing its presence in other pathological and physiological aspects, it shows a significant increase in serum levels of patients with oral squamous cell carcinoma. IL-1β is quickly produced and released by various types of immune and non-immune cells in response to inflammatory signals. IL-1β acts as an immune response enhancer. IL-1 exerts strong pyrogenic activity. IL-1 has been widely recognized as a prerequisite for the efficient initiation of innate and forming adaptive immune responses to overcome the acute inflammation process, which is the levels of IL-1β related to diseases' onset, severity, and progress [18], [19].

In an early study by IL-1β has been identified as an important node gene for OSCC development, and increased IL-1β expression is parallel to oral carcinogenesis. In particular, IL-1β expression in the epithelium gradually increases as oral malignancies progress [20]. It has been investigated that both the expression and secretion of IL-1β are regulated in OSCC cell lines (SCC25, UM1, and CAL27). In a co-culture system, the expression of IL-1β in OSCC cells stimulates fibroblast activation. Because the co-culture system mimics epithelial-mesenchymal interactions in vivo, it was concluded that activated fibroblasts are involved in promoting IL-1β production in premalignant and malignant oral epithelial, and this is essential tumor-derived IL-1β is It is an important signal that mediates epithelial-mesenchymal transition [21].

High levels of IL-1β are closely associated with an oral malignant transformation of OSCC. IL-1β stimulates the secretion of carcinogenic cytokines and induces epithelial-mesenchymal transition (EMT). This is in line with increased angiogenesis and migration, as well as morphological changes in OSCC cells. At the tumor site, IL-1β secreted by OSCC cells and infiltrated immune cells can create an inflammatory microenvironment that induces angiogenesis and EMT and also contributes to metastasis by inducing the release of carcinogenic cytokines [22- 24].

4. INTERLEUKIN-8 (IL-8)

IL-8 is a mediator that acts an essential part in supporting angiogenesis and tumor development [25], [26]. IL-8 is a chemotactic factor for basophils, neutrophils, and T lymphocyte subsets because it activates basophils and releases lysosomal enzymes, thereby increasing the attachment of neutrophils to endothelial cells [6]. Stimulation in neutrophils and macrophages will activate the nuclear factor kappa B (NF-κB) signaling pathway, which in turn will activate the IL-8 production. IL-8 acts on two receptors that look

structurally similar but antigenically different, CRCX-1 and CRCX-2. These receptors can be found on tumor-related macrophages, neutrophils, and cancer cells. The presence of these receptors on cancer cells strongly suggests that IL-8 levels are important for the cancer cell microenvironment [26].

Patients with cancer had higher salivary IL-8 levels than stated cutoff values, including in ovarian cancer and OSCC patients. OSCC patients' IL-8 levels can be increased by various inflammatory conditions in the oral cavity and are involved in angiogenesis and tumor development. However, the contribution of OSCC to IL-8 elevation is greater than any other potential background contribution, by host inflammatory conditions [26-28].

5. GALECTIN-3-BINDING PROTEIN (LGALS3BP)

LGALS3BP is involved in the regulation of cell-cell and cellular matrix interactions and is a protein member from a family of human beta galactoside binding proteins. The original protein specifically binds to galectin 1 also to human macrophage-related lectins known as Mac2. The enhancement of LGALS3BP has been shown in the sera of cancer patients and patients infected with the human immunodeficiency virus (HIV). It seems to be involved in the cytotoxic immune response of natural killer cells (NK) and lymphokine-activated killer cells (LAK) [29].

It has been observed that in the OSCC patient at early-stage and high-risk PMOD there are elevated LGALS3BP levels, but it has shown relatively reduced levels in patients undergoing late-stage OSCC and chemotherapy or in postoperative cases with recurrence. LGALS3BP has also proven to become an essential indicator in stage III of patients with OSCC and high-risk PMOD. However, it does not discriminate against the latest OSCC. LGALS3BP is able to be utilized as a favorable indicator for early detection of OSCC [30].

6. SURFACE ACOUSTIC WAVES

Surface Acoustic Wave (SAW) is a biosensing technique that can be used to detect malicious markers. The protein content in the sample is known by measuring the delay in signal input when using a SAW-based biosensor. This allows the protein content in the sample to be measured by phase change. The increased complexity and cost of reading electrons in SAW is due to the high-frequency electronics used because SAW has a narrow frequency band and high-frequency characteristics [31]. The advantages of the SAW biosensor are its real-time measurement properties, and a modified protocol for chip preparation and cleaning allows measurement of analysis times of up to 15 minutes. Moreover, unlike most other types of side-flow sensors that rely solely on color indicators and bands, this biosensor has a scaled reading sensor system [32].

SAW consists of two components of particle displacement. The two components are different, one of which is in the direction the wave propagates and the other is perpendicular to the surface like a Rayleigh wave. Rayleigh waves that generate compressed waves are affected and attenuated by the load of the liquid and the dissipation of wave energy to the liquid. Shear Horizontal Surface Acoustic Waves (SH-SAW), with polarized substrates that are perpendicular to wave propagation, are most frequently used in sensor applications, including fluid engineering [33]. Due to this characteristic, less energy is released by SH-SAW into the liquid, making it suitable for immunosensors. On the other hand, Rayleigh Surface Acoustic Waves (R-SAW) are waves that are polarized elliptically with a displacement component consisting of the second displacement component of the substrate plane on which the wave propagates and the surface plane. Longitudinal waves will be emitted into the liquid when the liquid is applied to the surface. Nonlinear dynamics will appear in liquids when SAW amplitude increases, such as agitation or vibrating, streaming, small droplets flying, atomization, and heating [34].

7. DISCUSSION

Saliva is one of the important fluids in the human body, composed of various compounds (organic and inorganic) that are useful for most physical functions such as lubrication, mucous membrane maintenance, cleaning, antibacterial effect, and decomposition of foods swallowed. As an examination medium, saliva is the most suitable for identifying OSCC biomarkers because non-professional personnel can collect them by non-invasive methods easily and offers easier patient monitoring. In addition, cancer cells directly interact with saliva so that the material has a higher advantage [1], [19]. The use of saliva as a diagnostic test has been researched for HPV infection and it shows the level of it's specificity 90% and sensitivity 89% [35].

The combination of various salivary biomarkers has improved the diagnosis of oral cancer, including OSCC. These combinations have high sensitivity and specificity that collectively have discriminatory power within detecting OSCC. Most of the potent salivary biomarkers of OSCC in the early stages are salivary proteins, including LGALS3BP, IL-1β, and IL-8 [9], [30]. Research has shown that the combination of these salivary proteins can predict precancerous patients with a probability of up to 80% of OSCC patients. Therefore, this combination can be considered to be used as the new screening tool to improve detection of pre-oral cancer, also early detection, and accurate diagnosis of cancer [36].

However, to be able to differentiate OSCC from other common oral inflammatory diseases requires standardization which requires a high level of specificity and sensitivity in salivary diagnosis. The levels of potential salivary biomarkers in OSCC can be affected by the presence of oral trauma, plaque, gingival inflammation, periodontal disease, fungal infections, and other inflammatory mucosal disorders [4].

This standardization of salivary diagnostics is in line with the advantages of the SAW biosensor which fulfills the characteristics of very high sensitivity, unlabeled detection, and also excellent reproducibility characteristics. SAW has also been developed to use in other fields as a suitable and promising biosensor system [37]. In its development, the effects of temperature and viscosity fluctuations that give non-specific effects on the sample are reduced in SAW prototype technology that uses a sensitive 2-channel biochip with in-situ reference [38].

The performance of biosensors can be affected by several major factors in detecting biological changes. Such as the selectivity of the sensor is determined by the material of the sensor. The medium for the transducer to be able to contact the sensor material is provided by the material interface through facilitating direct contact and strong coupling. This is because it is a major component that absorbs the interactions of chemical-biological and transforms them into electrical signals, similar to converters that determine the operating quality of the entire system. These factors recognize target species in the form of liquids or solids with the help of massive exposure to surface acoustic waves. Gold (Au) has a high degree of bonding to the piezoelectric material, so it is used to coat the surface of the SAW device that is made by ZnO. The thin layer of Au on top of the piezoelectric layer encourages effective isolation of the ZnO layer by reducing its reactive nature and essentially supplies a highly potent waveguide. It occurs because gold and ZnO have different acoustic shear velocities and density, which is gold is relatively lower in velocity and higher for density. That condition also presents the waveguiding mechanism that is extremely effective which can be used for liquid phase sensing. Piezoelectric Immunosensor applications detect cancer biomarkers through antigen-antibody binding and are also used for medical applications such as bacterial, virus, and toxin detection, clinical diagnosis and analysis, the food industry, and environmental analysis for compound detection [32], [39].

SAW's biosensor concept lies in the sensor area, which consists of a thin Au film, where the titanium adhesive layer on the quartz is manipulated by a single layer of capture ligand using alkanethiol linking chemistry. In

this case, the focused proteins are LGALS3BP, IL-1β, and IL-8. The biomarker of the OSCC antibody was shown in a solution that binds to the capture ligand in a sample. The enhancement amount of surface-bound capture protein and biomarker bound to the biochip results in wave phase shift increases. This structure facilitates the excitation of SAW with a specified wavelength and frequency [32]. Therefore, when using antigens containing body fluids such as LGALS3BP, IL-1β, and IL-8, the antigen-antibody binding occurs due to the phase difference of the waves between input and output electrodes causing mass and viscosity perturbations. This made the biomarker detectable.

Body fluids are considered capable of initial diagnostic material for OSCC because biomarkers have been identified in them. Saliva is considered a medium that is simpler, non-invasive, and less expensive than other body fluids such as blood. Previous study mentioned that there are increasing levels of IL-1β, IL-8, and LGALS3BP significantly in OSCC patients even in the early stage so that the combination of these three biomarkers can provide an early diagnosis with a high probability [30]. This component is then detected using prototype technology, namely SAW which has high sensitivity with components that are more up-to-date compared to other prototypes so that the time required for measurement is faster and the method performed is simpler.

8. CONCLUSION

Salivary biomarkers have the potential for early detection of OSCC disease using Surface Acoustic Wave technology because they have high sensitivity and specificity.

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CONFLICT OF INTEREST:
The authors declare no conflict of interest.

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