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SARS-CoV-2: A Promising Path in Salivary Diagnosis

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Since March 2020, the World Health Organization (WHO) established the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously provisionally named 2019 novel coronavirus or 2019-nCoV) disease (COVID-19) as a pandemic, with nearly 239.604 deaths and with a range of confirmed diagnosis that presently exceeded 3.435.894 people worldwide [1]. Coronavirus is a large family of respiratory viruses ranging from relatively mild (similar to the common cold) to severe (bronchitis, pneumonia, and renal involvement) respiratory syndromes [2].

Accurate and rapid diagnosis of COVID-19 is essential to manage the outbreak in this pandemic. Reverse transcription-polymerase chain reaction (RT-PCR) analysis of respiratory tract swabs is currently recognized as the gold standard for the diagnosis of SARS-CoV-2 infection [3]. However, studies demonstrated issues regarding the persistence of the virus in the body after the pharyngeal swab conversion or false-negative outcomes [4]. Moreover, oropharyngeal nasopharyngeal tests cause discomfort to patients and require trained professionals to be carried out and close contact between health professionals and patients, which represents a high risk of transmission of the virus to professionals [5, 6]. Therefore, the purpose of salivary fluids in the detection of SARS-CoV-2 is a subject that has gained attention from current literature [6].

Approximately 99% of saliva is water and 1% includes a wide group of elements for the function of taste, digesting, the balance of mineralization, and anti-microorganisms [7]. This oral fluid is one of the simplest ways to collect body fluids and represents an important source for the analysis of biomarkers with multiple functions. The benefits of saliva over conventional fluids are that collection is relatively easy to perform and almost noninvasive [7]. Additionally, saliva spe-

cimen collection has the advantage of being more secure for healthcare workers during the diagnosis of coronavirus [8].

In patients with COVID-19, studies suggest saliva as a promising sample type for diagnosis, monitoring, and infection control [8, 9]. This oral fluid has a great concordance rate higher than 90% with nasopharyngeal specimens in the identification of respiratory viruses, including coronaviruses [5]. Moreover, in two studies on coughed out saliva, a total of 91.67% (11 cases out of 12) [6] and 86.96% (20 cases out of 23) [10] COVID-19 patients were SARS-CoV-2 RNA affirmative in saliva, respectively. While regarding the use of saliva directly from the salivary gland duct, Chen *et al.* showed that four cases out of 13 COVID-19 patients were SARS-CoV-2 RNA affirmative in saliva [11].

Detection of Immunoglobulin M (IgM) antibodies tends to suggest recent exposure to infection, whereas the identification of IgG antibodies suggests virus exposure in the past [12]. The rapid recognition of both IgG and IgM antibodies could give additional immunological information for physicians in the diagnosis along with others assays and to begin COVID-19 patient treatment. In this sense, posterior oropharyngeal saliva specimens could be useful in assays involving Enzyme-linked Immunosorbent Assay (EIA) of IgG and IgM against internal viral nucleoprotein [10]. It is important to mention that mucosal immune responses seem to be characterized first by the production of secretory IgA, while systemic antibodies occur posteriorly. For instance, Guo *et al.* demonstrated that 92.7% of the participants tested presented with anti-SARS-CoV-2 nuclear capsid IgA, whilst only 85.4% obtained IgM and 77.9% IgG [13]. Therefore, it is suggested that IgA in saliva could be a promising path to salivary research in the diagnosis of COVID-19 and that the monitoring of anti-viral secretory IgA (associated with specific T cells and immune complexes) [14] could supply mechanistic insights in the pathophysiology of SARS-CoV-2 infection. However, further

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saliva studies on its role in immunopathology or antiviral therapy and the possible cross-reactivity with other coronaviruses and flu viruses are warranted.

Since there is the expression of angiotensin-converting enzyme II (ACE2) receptor on the mucosa of the oral cavity [15], theoretically, ACE2-positive cells in salivary glands could be the target cells of SARS-CoV-2 and produce saliva containing this virus [11]. Another speculation involves the fact that the tongue has an increased risk of coronavirus infection and that furin is greatly expressed in lung tissue, probably inducing a gain-of-function to the infectivity of COVID-19 [16]. Nevertheless, while it indicates that cells expressing furin have reduced restriction for virus entry speculatively, it should still be prudent whether the furin-like cleavage site implies a significant function in COVID-19 infection [16]. Moreover, the molecular mechanism of SARS-CoV-2 infection is not completely known and we should not overstate the present virus-invade-host hypothesis.

The diagnostic importance of saliva specimens for the COVID-19 assessment is auspicious, and much desired in a time that many populations require extensive testing in order to return to work and their daily routines. More research is needed to assess the potential diagnostic of SARS-CoV-2 in saliva, studies with a large number of participants, possibly including saliva biobanks and preferably comparing the different stages of SARS-CoV-2 infection and during the infection (viral charge) and after the infection (immune signature of the patient). In this way, our group leads an international salivary research initiative in order to establish a universal collection, processing, and storage protocols for saliva of COVID-19 patients. It is also important to emphasize that a complete diagnosis should be reinforced with full information regarding epidemiological history, symptoms, and analysis of multiple clinical evaluations [8, 9].

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