REVIEW

THE BLOOD-SALIVARY BARRIER AS A MULTIFACETED SYSTEM: A REVIEW

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The purpose of this review is to provide a comprehensive description of the blood-salivary barrier and systematize the result of recent studies on its structure and function in healthy and diseased states. The blood-salivary barrier (BSB) is considered a multifaceted system, which includes following key components: the salivary glands, oral epithelium, intercellular junction proteins that maintain barrier strength, and also saliva and mucus. The barrier's blood supply, neural connections, local immune responses, and the oral microbiome create the microenviroment, in which BSB operates. The BSB requires consideration of a number of additional variables, including innervation, blood supply, the presence of circulating metabolites in the vessels supplying the oral epithelium and salivary glands, as well as the volume of secreted saliva and its rheological properties, the composition of the oral microbiome, and the state of the immune system.

Key words: BSB; salivary glands; oral mucosa; microbiome; immune system; intercellular connections

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Abbreviations: AJ – adherens junction; ALRs – AIM2-like receptors; aPKC – atypical protein kinase C; AQP5 – aquaporin 5; Clnd – claudin; CLRs – C-type lectin receptors; Cx – connexin; DAMPs – damage-associated molecules; ED – excretory duct; FNB6 – TERT2 immortalized cell line of oral keratinocytes derived from the buccal mucosa; HCO_3^- – bicarbonate; ID – intercalated duct; IFN-γ – interferon-gamma; IL – interleukin; JAK – janus kinase; JAM – junctional adhesion molecule; KRS – Krebs ringer bicarbonate solution; LSR – lipolysis-stimulated lipoprotein receptor; MALT – mucosa-associated lymphoid tissue; miR-145 – tumor-suppressing microRNA; Mist1 (Bhlha15) – a basic helix-loop-helix transcription factor found primarily in exocrine secretory cells such as pancreatic acinar cells, zymogenic cells of the stomach, and Paneth cells, regulates downstream genes that control se-cretory vesicle maintenance and trafficking; MUC – gene coding a family if proteins mucine; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRs – nucleotide oligomerization domain-like receptors; NOD – non-obese diabetes; NOF – normal oral fibroblasts; NOK – normal oral keratinocytes; Ocln – occludin; PAMPs – pathogen-associated molecular patterns; PG – parotid salivary gland; PI3K – Phosphoinositide 3-kinase; Plg – plasminogen; Pm – plasmin; PRRs – pattern recognition receptors; RLRs – retinoic acid-inducible gene I-like receptors; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; SD – striated duct; SLCs – solute carrier transporters; SLG – sublingual salivary gland; SMG – submandibular salivary gland; STAT – signal transducer and activator of transcription; TJ – tight junctions; TLRs – toll-like receptors; TNF-α – tumor necrosis factor-α; ZO – ZONULA occludens

INTRODUCTION

The constancy of the body's internal environment is maintained by numerous physiological mechanisms, in which various histohematic barriers play an important role. Histohematic barriers include the blood-brain barrier, the blood-placental barrier, the blood-ocular barrier, and the blood-salivary barrier (BSB) [1-3]. The functional properties of the BSB are still require deeper studies and better understanding [4-6]. To date, a fully adequate model of the BSB, capable of accurately describing the causes and mechanisms of dynamic changes in its functional properties, has not been developed yet [7-10]. Furthermore, an interesting area of research is the study of the migration of molecules from blood to saliva and from saliva to blood depending on the integrity of the BSB, its physicochemical properties, and humoral and neural regulation in both physiological and pathological conditions [11-12]. Understanding the functional properties of the BSB in various pathologies, including cancer, will enable the use of saliva as an adequate and reliable biological material for diagnostics [13-15].

This work aims to provide a comprehensive analisys of the components associated with the BSB as well as known and completely new approaches used to study the BSB *in vitro*.

In this review, we consider the BSB as a complex system comprising both its core components and its microenvironmental components. The core components include the salivary glands and oral epithelium, the intercellular junction proteins responsible for barrier integrity and strength, saliva, and mucus. The microenvironmental components include the blood supply and innervation of the BSB, local immunity, and the oral microbiome. The microenvironment of the BSB directly influences its integrity and functional properties. In many ways, the structural components and the microenvironment are inseparable components of a single whole—the BSB (Fig. 1).

1. THE MAIN COMPONENTS OF THE BSB

The oral mucosa epithelium is a biological barrier that serves as a boundary between the underlying tissues and the environment. In the context BSB, the oral mucosa epithelium acts as a barrier between the blood (internal environment) and saliva and the microbiome (external environment). The epithelium consists of a superficial stratified squamous epithelium and a dermis, which is represented by a loose papillary layer and a dense reticular layer [16]. The oral mucosa epithelium can be of two types: keratinizing and nonkeratinizing [17]. The oral

mucosa epithelium performs a number of biologically important functions, such as: protective, plastic, sensory, and absorptive [18]. The BSB Permeability for drugs occurs mainly through the epithelium of the oral mucosa. Removal of lipids from the buccal mucosa leads to increased permeability for drugs [19]. There are significant differences in permeability between different areas of the oral cavity due to the different structures and functions of the different oral mucosa. In general, the permeability of the oral mucosa decreases in the following order: the sublingual mucosa is greater than the buccal mucosa, and the buccal mucosa is greater than the palatine mucosa [18].

The salivary glands are among the most complex and multifunctional components of the BSB. This is due to the fact that the salivary glands, like oral mucosa epithelium, perform separation functions between blood, saliva, and the microbiome, and also produce saliva and oral mucus [20-21]. Saliva and oral mucus themselves, in turn, perform barrier functions. There are the parotid, submandibular, sublingual, buccal, labial, and lingual glands in the oral cavity, and the parotid salivary gland (PG), the sublingual salivary gland (SLG), and the submandibular salivary gland (SMG) are three paired major salivary glands. The salivary glands have a branched structure with complex and numerous ducts. The terminal unit of the salivary glands is the acinus, which can be serous (producing more of the protein component), mucous (producing mainly mucins), or mixed serous-mucous. Serous acinar cells produce more protein; the cells are characterized by abundant eosinophilic zymogen granules and a spherical nucleus [22]. Mucous acinar cells have a transparent cytoplasm rich in mucins; the nuclei are polarized toward the cell basement membrane [23]. Acinar cells produce and secrete saliva, which is further modified and transported by a sequential duct system: intercalated duct (ID) cells, striated duct (SD) cells, and excretory duct (ED) cells, which connect the gland to the oral cavity [24]. The acini themselves are formed by 8–12 pyramidal acinar cells, which are laterally connected to each other by adhesive and tight junctions. Such lateral connections maintain the apical-basolateral polarity of the cells and prevent free lateral transport of ions between acinar cells. For ion transport, acinar cells contain specialized water channels and ion pumps, which regulate the secretion and concentration of salivary ions [25]. Identification of acinar cells occurs through the expression of markers such as aquaporin 5 (AQP5) and Mist1 (Bhlha15). Saliva is also secreted into the oral cavity by minor salivary glands located in the lips, cheeks, palate, tongue and respiratory tract [26-29].

Although the salivary glands have been well studied, a breakthrough was made in this area in 2020. Valstar et al. described the tubarial salivary glands [30], which are located between the nasal cavity and throat, deep in the nasopharynx, behind the tubal ridge (torus tubarius) [31-33]. Alisha Ebrahim et al. demonstrated that there are sex differences in the tubarial salivary glands, which explains gender differences in salivation. Thus, comprehensive criteria and approaches to the classification of salivary glands were revised to better describe histological features [34].

Within the BSB, such discoveries are important because they provide a more complete understanding of the properties of each component. This is useful for creating more adequate *in vitro* models, bioengineered oral mucosal equivalents, drug delivery, and the development of more gentle therapies for head and neck cancer and other diseases, all aimed at reducing alterations to

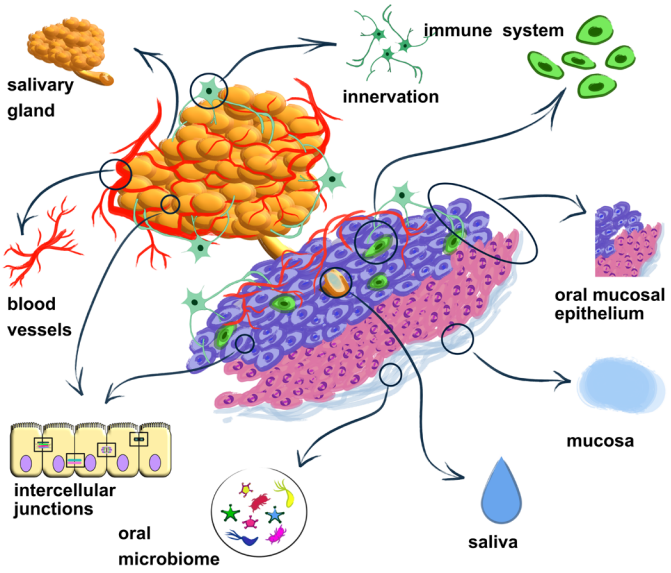

Figure. 1. A comprehensive representation of the blood-salivary barrier.

the salivary glands and oral mucosa. For example, hypofunction of the salivary glands, which may be due to systemic disease (autoimmune diseases [35–36], diabetes mellitus [37–39], and thyroid diseases [40–41], neurological/psychiatric disorders [42–45], infectious [46–47], and genetic diseases [48–51], hypertension [52], and sarcoidosis [53]), medications [54], aging [55], and radiation therapy for head and neck cancer, can cause dry mouth, which increases the risk of diseases such as periodontitis, taste disturbances, pain and burning in the mouth, and dental caries [56]. A detailed description of the dysfunction of the salivary gland system in the above-mentioned diseases is the subject of a separate review; however, the general principles underlying these disorders include damage to the parenchyma of the salivary gland due to activation of the immune system and an increase in the level of reactive oxygen species, disruption of the innervation of the salivary glands, which directly affects its secretory activity, etc.

The principles of saliva secretion are well described in the literature. Furthermore, SLC transporters are known to play an important role in salivary gland secretion. These transporters are responsible for the transport of ions such as nitrites, chlorides, bicarbonates, and water. The functional activity of SLCs results in the formation of nitric oxide [57-58]. Currently known SLC transporters expressed by the salivary glands are presented in Table 1.

The most studied to date are SLC17A5, SLC4A2, SLC2A4, and SLC26A6 transporters. Involved in nitrate (NO_3^-) entry SLC17A5 is located in the plasma membrane of salivary gland cells. It is important for the nitrate-nitrite-nitric oxide pathway, which facilitates nitric oxide signaling in mammals [59-60]. SLC4A2 is an electroneutral transporter. It is involved in the exchange of chlorides (Cl^-) and bicarbonates (HCO_3^-), thereby facilitating the regulation of intracellular pH and chloride concentration in salivary gland cells [60]. SLC2A4 and SLC26A6 are involved in the secretion of iodide (I^-) and bicarbonate (HCO_3^-); they also regulate the transmembrane conductance in cystic fibrosis in the parotid gland duct [60]. In the salivary glands SLC15A2, SLCO1A2, SLC22A1, SLC22A3, SLC22A4, SLC22A5, SLC22A6 and SLC22A7 transporter are expressed [60]. In the human salivary gland the SLC5A5 gene

Table 1. Salivary gland SLC transporters [57-60]

Transporters	Functions
SLC17A5	It participates in nitrate (NO_3^-) uptake. This is important for the nitrate-nitrite-nitric oxide pathway, which facilitates nitric oxide signaling in mammals.
SLC4A2	It is an electroneutral transporter. It participates in the exchange of chlorides (Cl^-) and bicarbonates (HCO_3^-), thereby regulating intracellular pH and chloride concentration in salivary gland cells.
SLC2A4 and SLC26A6	It is involved in the secretion of iodide (I^-) and bicarbonate (HCO_3^-), and also regulates the transmembrane conductance regulator in cystic fibrosis in the parotid duct.
SLC5A5	Belongs to the sodium/iodide symporter. Expressed at higher levels than SLC17A5.
SLC15A2	Absorption of peptides and some drugs.
SLCO1A2	Transfer of organic anions and regulation of the influx and outflow of their substrates, regulation of salivary secretion.
SLC22A1	Transport of organic cations, absorption and excretion of drugs and toxins.
SLC22A3	Absorbs and secretes organic cations from the blood into the acinar cells of the salivary glands. It is responsible for the accumulation of drugs, such as metformin, in the salivary glands, which can lead to drug-induced taste disturbances.
SLC22A4	Transporter of carnitine and other organic cations.
SLC22A5	A transporter of carnitine into cells. It is crucial for fatty acid metabolism and energy production in the mitochondria.
SLC22A6	A transporter of organic anions, involved in the regulation of the secretion of endogenous and exogenous molecules, including drugs and other metabolites, into saliva.
SLC22A7	Organic anion transporter. Other functions of the transporter are little studied.

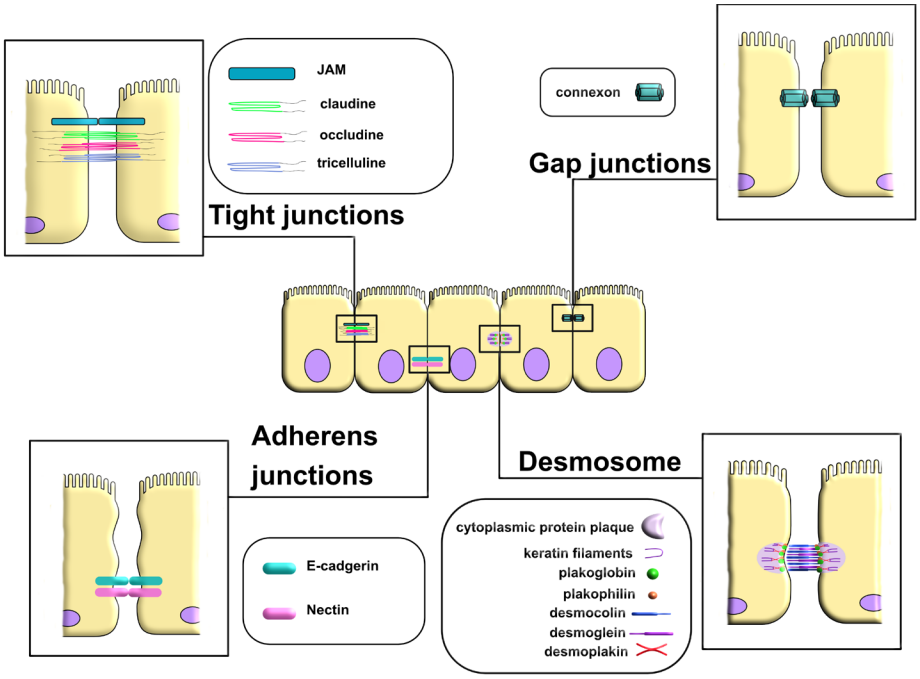

Figure. 2. Intercellular contacts (tight junctions, gap junctions, adherents' junctions and desmosomes).

expression and the level of its protein product NIS (sodium/iodide symporter) are higher than that SLC17A5 NIS mediates the absorption of nitrate by the salivary glands and the concentration of nitrate in saliva [61]. Nitrate, through conversion to nitrite, forms nitric oxide, which is involved in signaling. Exposure to potassium iodide reduced the level of SLC5A5 in ductal salivary gland cancer cells, as well as their proliferation due to increased levels of reactive oxygen species and the triggering of caspase-dependent apoptosis [62].

The intercellular junction proteins, which include tight junctions, gap junctions, adherens junctions, and desmosomes are other important structural component of the BSB [63-65] (Fig. 2).

Many pathogens and somatic diseases lead to disruption of the structure and, consequently, dysfunction of tight and adherens junctions. This, in turn, further aggravates the condition of the area affected by the pathogenic change, leading to the progression of pathological processes [66]. A detailed description of the functions and structure of individual proteins of intercellular junctions is provided in Table 2.

Disruption of contacts is observed in a number of pathologies. For example, in Sjogren's syndrome, the expression of epithelial

Table 2. Intercellular junction proteins

Protein	Functions	Reference
Tight junctions		
Junctional adhesion molecule (JAM)	JAMs play a minor role in regulating junctional structure. Their main function is to promote adhesion and transmit intercellular signals [67].	JAM structure [68-70]
Claudine	Generation of TJ filaments, the structural and functional core of TJ in the plasma membrane [71].	Claudine structure [72-74]
Occludine	Auxiliary function in TJ formation [75]. Barrier function of TJ and intercellular adhesive interactions [76-78]. Transmissive properties due to binding to tyrosine kinase c-Yes, atypical protein kinase C (aPKC) and phosphoinositide 3-kinase (PI3K), protein phosphatase 2A [79-80].	Occludine structure [81-82]
Tricelluline	Regulation of macromolecular flux and TJ organization. Maintenance of the structure of three-cell and two-cell contacts [83-84].	Tricelluline structure [85-86]
Zonula occludens (ZO)	Formation of TJs in epithelial cells [87]. They participate in the sequential stages of AJ and TJ assembly, as well as in their physical segregation in the membrane [88-90].	ZO structure [91-93]
Gap junctions		
Connexon	Providing direct communication between cells, whereby small molecules are able to penetrate into the cytoplasm of neighboring cells [94].	Connexon structure [95-102]
Desmosome		
Cytoplasmic protein plaque	They influence signaling pathways and potentially contribute to disease progression through mechanisms such as stimulating protein aggregation in conditions such as microglial activation. They perform functions of structural support and intercellular interaction [103].	Cytoplasmic protein plaque structure [104]
Keratine filaments	Mechanical support and tissue integrity of epithelial cells. Coordination of tissue spreading by balancing forces within the tissue. Cell migration, differentiation, and resistance to chemical stress and apoptosis [105].	Keratine filaments structure [106]
Plakophilin	Regulation of cell adhesion, signaling pathways, metabolism, ciliary function, and intercellular junction dynamics. Plakophilin-2 coordinates energy metabolism and cardiomyocyte contractility, as well as modulates intestinal barrier function. Plakophilin-3 is involved in basal body docking in multiciliated cells, while plakophilin-4 and p120 catenin promote the formation of lateral adhesive junctions [107]	Plakophilin structure [108-109]
Desmocolin	Functions of cellular adhesion, forming desmosomes to maintain tissue integrity and strength, especially in the epithelium and cardiac muscle. Linking the cell membrane to intracellular intermediate filaments, providing structural support during mechanical stress. Restoration of the intestinal mucosa and influence on cell migration [110].	Desmocolin structure [111]
Desmoglein	Cohesion and functioning of cardiomyocytes (cardiac muscle cells), epithelial differentiation and maintenance of tissue barrier integrity [112].	Desmoglein structure [112]
Desmoplakin	Maintains tissue integrity, regulates cell differentiation and migration, and participates in myocardial development. It regulates the expression of genes responsible for electrical conductivity in the heart and is involved in processes such as wound healing and neurogenesis [113].	Desmoplakin structure [114]
Adherens junctions		
E-cadgerin	Maintenance of epithelial hemostasis. Participation in immune reactions [115].	E-cadgerin structure [116]
Nectine	Establishment of cellular polarity and connections, control of cell proliferation and movement, regulation of immune responses and participation in the development and maintenance of tissues [117].	Nectine structure [118]

tricellulin is suppressed by IFN-γ via the JAK/STAT1/miR-145 signaling pathway. It was shown that restoration of TJ integrity and re-expression of tricellulin resulted in normalization of salivation in patients [119]. Results of another study showed that increased IL-17 activity led to damage of tricellulin via the NF-κB signaling pathway in the submandibular salivary glands of mice with Sjogren's syndrome. In addition, the expression of claudin-1 and -3 increased, especially on the basolateral membranes, whereas claudin-4, occludin, and zonula occludens-1 (ZO-1) were decreased in the submandibular salivary glands of mice

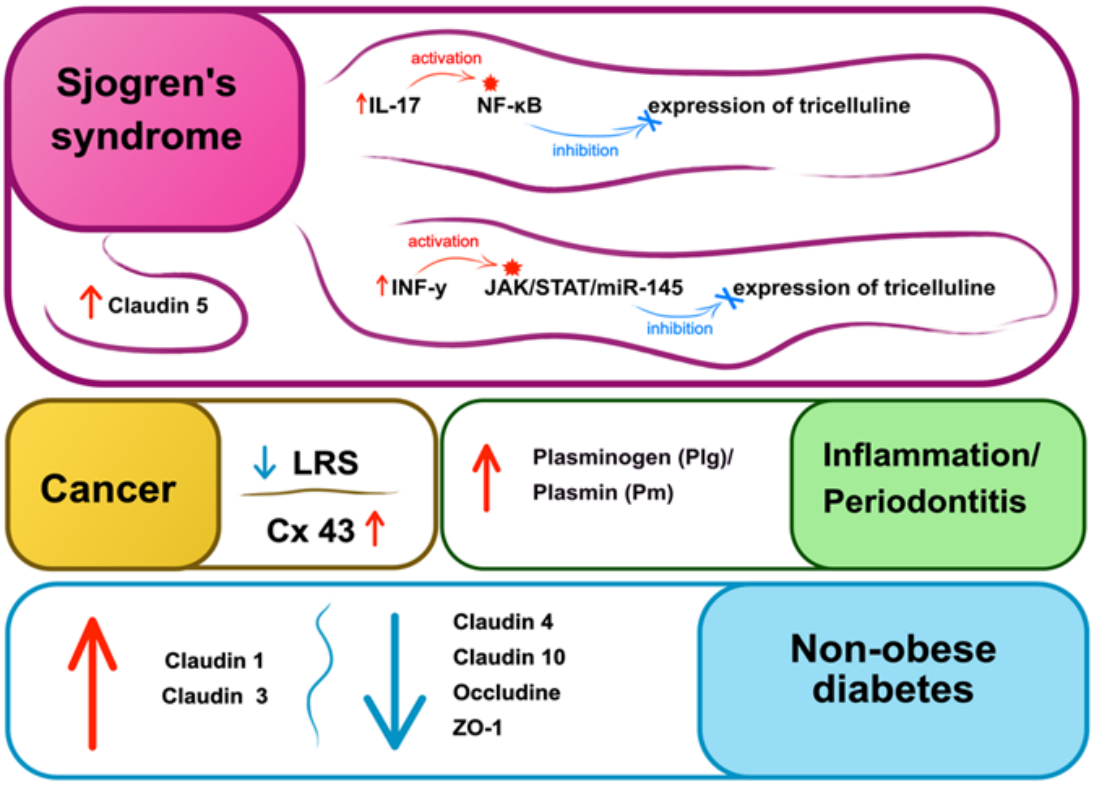

Figure. 3. Pathologies associated with damage to intercellular junctions of the salivary glands and the oral cavity epithelium. Cx-43 – connexin 43, LSR – lipolysis-stimulated lipoprotein receptor, ZO-1 – zonula occludens, NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells, INF-y – interferon gamma, JAK – Janus kinases, STAT – signal transducer and activator of transcription, miR-145 – microRNA-145.

with non-obese diabetes (NOD) [120]. Certain evidence exist that the BSB was disrupted. In the disease this resulted in dilation of blood vessels and infiltration of lymphocytes, involved in the pathogenesis of Sjogren's syndrome [121]. The inflammatory environment resulted in disrupted localization and increased levels of claudin-5. Furthermore, a large accumulation of blood vessels was observed surrounding infiltrated lymphocytes [122-123]. Nishida et al. have demonstrated that lipolysis-stimulated lipoprotein receptor (LSR), localized in tight tricellular junctions and associated with lipid metabolism, also plays an important role in maintaining epithelial homeostasis. This receptor is highly expressed in normal cells and well-differentiated tumors and its expression decreases during tumor malignancy [124] (Fig. 3).

Morphological changes of salivary glands and their intercellular contacts have been demonstrated in diabetes mellitus [125]. Ultrastructural damage, such as swollen mitochondria of the acini of the submandibular and parotid glands, as well as expansive endoplasmic reticulum and autophagosomes, were reported. Levels of claudin-1 (Cldn1) and claudin-3 (Cldn3) were increased, while levels of claudin-4 (Cldn4), occludin (Ocln), and ZO-1 were decreased in the submandibular salivary gland. High levels of Cldn1 and Cldn3 and lower levels of claudin-10 (Cldn10) and Ocln were demonstrated in the parotid gland. Such structural abnormalities of the submandibular and parotid salivary glands may contribute to hyposalivation [125]. Another study demonstrated that connexins 43 (Cx43) and connexins 26 (Cx26)were expressed in normal cells, whereas only Cx43 expression was observed in patients with early stage oral squamous cell carcinoma [126].

There are a number of contradictory studies regarding TJ expression and cancer progression [127]. Martin et al showed that loss of TJ could to tumor recurrence and carcinogenesis [128]. A number of other studies show that overexpression of TJ, namely JAM and claudins, were associated with tumor growth [129-131]. It can be assumed that depending on the stage of the disease and the type of cancer, increased or decreased expression of intercellular contact proteins contributes differently to the progression of carcinogenesis and tumor growth. Recently, a new observation showing that components of the plasminogen (Plg)/plasmin (Pm) system expressed in oral tissues, namely in the salivary gland tissues has been made. These components can contribute to microbial infection and inflammation, such as periodontitis [132].

Another structural component of the BSB is saliva. Saliva is a multifunctional fluid that lubricates the oral mucosa and contains electrolytes, antibacterial compounds, and a wide variety of enzymes involved in protecting the oral mucosa [133]. An interesting fact is that, despite its fluidity, saliva is not a Newtonian fluid, meaning that its viscosity changes with changes in the flow rate. This means that with changes in shear (flow rate), the viscosity of saliva changes; that is, with high shear, saliva is more fluid, while with low shear, saliva is more viscous. In other words, saliva is a viscoelastic material that exhibits both elastic (solid-like) and viscous (liquid-like) properties and reactions [134-135]. Saliva also exhibits thixotropic properties when structural changes in saliva occur under shear and are restored at rest [136-137]. In addition to time and shear, the rheological properties of saliva are also influenced by biochemical parameters such as Ca^{2+} concentration, total protein, and glycoproteins (mucins). Mucins have been shown to consist of 50-80% carbohydrates and are essential for the viscous properties of saliva. In one experiment, removal of mucins resulted in a decrease in saliva viscosity to the level of water. Thus, large, highly glycosylated glycoproteins with viscoelastic and protective properties play a crucial role in the viscous lubrication of the oral mucosa and are among the main factors that determine the rheological properties of saliva [138-139].

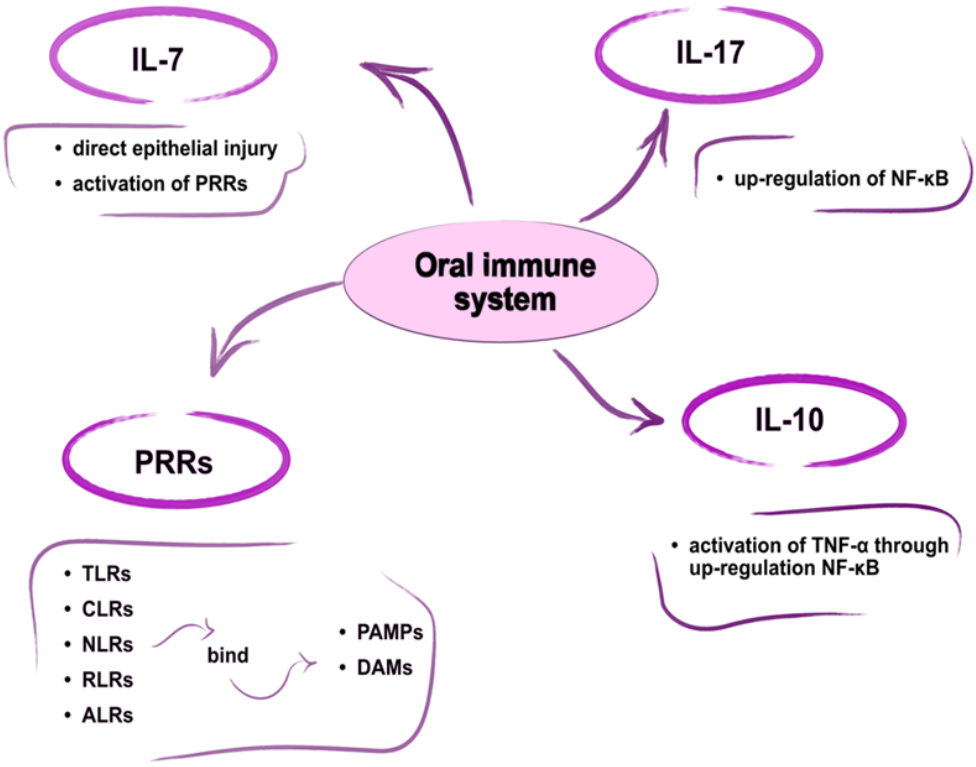

Figure 4. Oral immune system. PRRs - pattern recognition receptors, PAMPs - pathogen-associated molecular patterns, DAMPs - damage-associated molecules, TNF-α - tumor necrosis factor-alpha, NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells, TLRs - Toll-like receptors, CLRs - C-type lectin receptors, NLRs - nucleotide oligomerization domain-like receptors, RLRs - retinoic acid-inducible gene I-like receptors, ALRs - AIM2 (Absent in melanoma 2)-like receptors.

2. COMPONENTS OF THE BSB MICROENVIRONMENT

From a BSB perspective, blood supply and innervation are important for understanding the causes of changes in the composition of secreted saliva.

The vasculature of the salivary glands and the epithelium of the oral mucosa are represented by numerous arteries and veins and have a complex structure. It is worth noting that the volume of saliva produced per day is 1–2 liters, which is equal to the amount of urine produced in a physiologically normal human being and is directly dependent on arterial blood flow and vascular pressure [24]. The volume of the vascular network, the caliber of the vessels, and the pressure within them are of particular interest, as these characteristics will largely determine the rate of secretion, the volume of saliva secreted the condition of the salivary glands, and the epithelium of the oral mucosa [24].

The type of innervation directly influences the composition of secreted saliva. Thus, parasympathetic secretory innervation affects vasodilation of blood vessels, thereby increasing blood supply and, through acetylcholine and substance P, stimulates the secretion of serous saliva. Sympathetic nerves respond to norepinephrine, which causes the secretion of mucous saliva [140-141]. Nerve endings of nerve fibers are localized near the acinar cells of the salivary glands, duct cells and myoepithelial cells, and can be either naked or surrounded by Schwann cells. Parasympathetic and sympathetic innervation can have a direct effect on secretory cells, leading to an increase in intracellular Ca^{2+} levels, changes in cell membrane permeability, and the secretion of organic molecules, electrolytes, water and mucus in saliva [142]. In addition, nerve stimuli act on myoepithelial cells surrounding the acini and duct cells, which are regulated by both cholinergic and adrenergic neurotransmitters. This facilitates degranulation and fluid movement into the lumens of the salivary glands [143]. It has been shown that blockade of adrenergic receptors on myoepithelial cells leads to a slowdown in the fluid movement in the salivary glands without changing its secretion [144-146]. Steroidal and nonsteroidal hormones can be allosteric regulators of muscarinic receptors. Membrane cholesterol is able to bind and modulate the function of several G-protein-coupled receptors, including muscarinic acetylcholine receptors. This represents a new pharmacological approach to treatment of diseases associated with altered cholinergic signaling [147].

The oral immune system consists of three main compartments: the epithelial layer, the lamina propria, and the mucosa-associated lymphoid tissue (MALT) [148]. Pattern recognition receptors (PRRs) are immune cell proteins that detect and bind conserved pathogen-associated molecular patterns (PAMPs) and damage-associated molecules (DAMPs), thereby triggering the innate immune response. Currently identified PRR families include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene I-like receptors (RLRs), and AIM2-like receptors (ALRs) [148]. Furthermore, innate defense plays a key role in the activation and regulation of adaptive immunity (Fig. 4).

The interleukin-7 cytokine-mediated immune pathway is induced within hours of epithelial cell injury or PRR activation [149]. Although IL-17 has been described as a T-cell-secreted cytokine, it has been shown that a significant portion of the IL-17 released during the inflammatory response is produced by innate immune cells [150]. Innate immune cell populations, which are an early source of IL-17 in response to stress, injury, or pathogens, are thought to reside in barrier tissues at the host-environment interface [150]. Epithelial cells are thought to perform a variety of sentinel functions, recognizing and mounting defenses against pathogens, in addition to their

role as a physical barrier [150]. This region is also thought to be dominated by very strong immune tolerance, which allows for the monitoring and control of the interaction between the host's innate defenses and the microbiota [151]. IL-10 may play a protective role in head and neck squamous cell carcinoma. IL-10 has been shown to increase tumor necrosis factor-α (TNF-α) and lead to upregulation of NF-κB, which mediated the antitumor effect [152].

Due to their fundamental symbiotic lifestyle, the microbiota and innate immunity are ivolved in extensive two-way communication [153]. While the immune system influences and maintains the microbiota's microenvironment, the host microbiota restructures and promotes the immune system's tolerance of commensal and beneficial microbiota members [153]. Both the microbiota and the immune system also interact to mount necessary responses against pathogenic and harmful microorganisms. Achieving both local and systemic homeostasis while maintaining the host's biological integrity requires a highly regulated and coordinated interaction between the immune system and the microbiota. In this context, symbiosis and dysbiosis represent two extremes of the complex relationship between the oral microbial community and the immune responses to its presence. Many multifactorial disorders are thought to be dependent on and/or caused by alterations in the close interaction between the immune system and the microbiota [154].

In recent years, studies of microbiota metabolites and their interactions with the immune system have also opened a new dimension in understanding host-microbiota interactions. It is believed that host perception of bacterial metabolites is much more informative in determining the state of microbial colonization than recognition of microbial surface molecules, as metabolites provide information about the activity and functions of microorganisms, rather than their presence or absence [155-156].

CONCLUSIONS

The scientific community is presently engaged in rigorous research on the BSB, developing models that accurately replicate *in vivo* conditions. This review aims to enhance our understanding of the BSB by categorizing its components into core elements and those pertaining to the microenvironment. The core components consist of the salivary glands, oral epithelium, intercellular junction proteins responsible for barrier integrity and strength, saliva, and mucus. Microenvironmental components include innervation and blood vessels, local oral immunity, and the microbiome. Thus, the BSB is a broader concept, and its study should go beyond considering only the tissues located at the border between blood and saliva.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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ГЕМАТОСАЛИВАРНЫЙ БАРЬЕР КАК МНОГОГРАННАЯ СИСТЕМА: ЛИТЕРАТУРНЫЙ ОБЗОР

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Цель данного обзора — дать всестороннее описание гематосаливарного барьера, систематизировать результаты последних исследований его структуры и функции в норме и при патологии. Гематосаливарный (ГСБ) барьер – многогранная система, ключевыми компонентами которой являются слюнные железы, эпителий полости рта, белки межклеточных соединений, поддерживающие прочность барьера, а также слюна и слизь. Кровоснабжение барьера, нервные связи, местные иммунные реакции и микробиом полости рта создают среду, в которой функционирует ГСБ. При оценке ГСБ необходимо учитывать ряд дополнительных факторов, включая иннервацию, кровоснабжение, наличие циркулирующих метаболитов в сосудах, снабжающих эпителий полости рта и слюнные железы, а также объем выделяемой слюны и ее реологические свойства, состав микробиома полости рта и состояние иммунной системы.

Ключевые слова: гематосаливарный барьер; слюнные железы; слизистая оболочка полости рта; микробиом; иммунная система; межклеточные связи

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