The importance of Veillonella in the oral microbiome and its impact on dental and periodontal pathology: a literature review

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ABSTRACT

Relevance. *Veillonella* is associated with diseases of the oral cavity. Representatives of this genus occupy a significant share in the composition of the plaque microbiota and are involved in the formation of food chains and regulating the pH of the oral microbiome.
The aim of this article is to provide an overview of scientific studies on the *Veillonella* taxonomic group's position in the oral microbiome and their possible impact on the development of infectious diseases of the oral cavity.
Materials and methods. A scientific search was conducted in the databases MEDLINE, EMBASE, NCBI, Web of Science, PubMed, Scopus, and eLibrary.RU for the last 40 years. 88 sources in English and 1 in Russian were analyzed and included in this review.
Results. Various species of *Veillonella* promote the adhesion of *Streptococcus mutans* and metabolize the lactate produced by streptococci. They also play an essential role in forming the periodontium microbial biofilm, entering into co-aggregation with primary, intermediate and late colonizers, including such periodontal pathogens as *Fusobacterium nucleatum* and *Porphyromonas gingivalis*. *Veilonella* is involved in the formation of lipopolysaccharides and hydrogen sulfide in pulpitis, periapical periodontitis and halitosis.
Conclusion. *Veillonella spp.* is a significant component of the oral microbiome and can be viewed as a stabilizing component and as an indicator of a violation of the ecosystem's metabolic situation.
Key words: *Veillonella*, oral microbiome, biofilm, dental caries, periodontitis, periodontopathogens.
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Значение Veillonella в микробиоме полости рта и ее влияние на патологию зубов и пародонта. Обзор литературы

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АННОТАЦИЯ

Актуальность. Вейлонеллы связаны с заболеваниями полости рта. Представители этого рода занимают значительную долю в составе микробиоты зубного налета (бляшки) и участвуют в формировании пищевых цепей и регуляции pH микробиома полости рта.
Целью данной статьи является предоставление обзора научных исследований, посвященных положению таксономической группы вейлонелл в микробиоме полости рта и их возможном влиянии на развитие инфекционных заболеваний полости рта.
Материалы и методы. Был проведен научный поиск в базах данных MEDLINE, EMBASE, NCBI, Web of Science, PubMed, Scopus и eLibrary.RU за последние 40 лет. Были проанализированы 88 источников на английском языке, 1 на русском языке.

Результаты. Различные виды *Veillonella* способствуют адгезии Streptococcus mutans и метаболизируют лактат, вырабатываемом стрептококками. Они также играют важную роль в формировании микробной биопленки пародонта, вступая в коагрегацию с первичными, промежуточными и поздними колонизаторами, в том числе с такими пародонтопатогенами, как *Fusobacterium nucleatum* и *Porphyromonas gingivalis*. Вейлонеллы участвуют в образовании липополисахаридов и сероводорода при пульпите, периапикальном периодонтите и галитозе.
Заключение: *Veillonella spp*. является важным компонентом микробиома полости рта и может рассматриваться как стабилизирующий компонент и как индикатор нарушений метаболической ситуации в экосистеме ниши.
Ключевые слова: *Veillonella*, микробиом полости рта, биопленка, кариес зубов, пародонтит, пародонтопатогены.
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INTRODUCTION

Microaerophilic streptococci and *Veilonella* are early colonizers of the oral mucosa and dental surface. Some authors consider *Veilonella* as dependent on acid-producing streptococci since they utilize organic acids, in particular, lactate [1, 2]. Hence, *Veillonella spp*. are the most important symbiont that primarily colonizes the enamel's surface, cement of the tooth and the oral mucosa.

Due to the continuous clearance of the oral cavity (saliva flow, swallowing, chewing, oral hygiene), the attachment of primary colonizers to the tooth surface and subsequent cellular co-adhesion/co-aggregation of microorganisms are necessary for the formation of oral biofilm [1-6].

The aim of this article is to provide an overview of scientific studies on the *Veillonella* taxonomic group's position in the oral microbiome and their possible impact on the development of infectious diseases of the oral cavity. In particular, the materials on the type strain of *Veillonella parvula* and other representatives of this genus were analyzed.

MATERIALS AND METHODS

Using the PRISMA criteria, a scientific search was conducted in the databases MEDLINE (n = 47), EMBASE (n = 3), NCBI, Web of Science (n = 2), PubMed (n = 2,011), Scopus (n = 98), and eLibrary.RU (n = 3,190) for the last 40 years. 5,262 records were removed before screening. 88 sources in English and 1 in Russian were analyzed and included in this review.

The main keywords for which the search was conducted were: "Veillonella", "oral microbiota", "perodontal disease", "periodontal pathogens". There were no restrictions on the source's language, the duration of the study, or the demographics of the patients; the publications were dated 1980-2020.

RESULTS

Features of Veillonella metabolism a nd its co-aggregation properties

Representatives of the family *Veillonellaceae*, the genus *Veillonella* are gram-negative anaerobic micrococci belonging to the type Firmicutes [6]. There are currently 12 species in the genus *Veillonella* [6, 7], five of them *(V. parvula, V. atypica, V. dispar, V. rogosae, V. denticariosi*) are usually isolated from the human oral cavity [6, 8, 9]. *Veillonella* species are among the most common and dominant oral bacteria [10-12]. Oral *Veillonella* colonises the tongue's surface, the mucous membrane of the cheeks, and the supra-and subgingival plaque.

Veillonella has the property of using lactate, pyruvate, and oxaloacetate as the primary energy sources [13, 14]. The ATP formed in this way is used in the ATP-dependent transport of amino acids, the so-called "ATP-binding cassette transporters", found in a wide range of bacteria [15]. It is known that the concentration of lactic acid on the surface of the tongue reaches 6.7-7.8 mmol/l after rinsing with sucrose [16, 17] due to the dominance of lactate-producing bacteria [15]. Under these conditions, the specific association of *Veillonella spp*. is facilitated with lactate-producing bacteria in dental plaque, which allows us to consider them as an indicator of a high risk of developing dental caries [18].

Another characteristic of *Veillonella* species is its ability to proliferate co-aggregately with colonizers at different stages. *Veillonella* is categorized under the "purple complex" in the microbiological color scheme of periodontal diseases, and serves as a major antagonist to acid-producing streptococci and periodontopathogenic species within the "red complex". [19-23, 85]. However, this does not exclude the possible antagonistic role of *Veillonella* against periodontal pathogenic and aggressive species, particularly enterococci and staphylococci [23].

It is proved that the majority of *Veillonella spp*. isolates isolated from the cheeks and tongue's mucous membrane (42 out of 55) have co-aggregation properties. Of the 24 *Veillonella spp*. isolates isolated from subgingival dental plaque samples, 20 were represented by *Veillonella parvula* and were co-aggregated with *Actinomyces viscosus, Actinomyces naeslundii, Actinomyces israelii, S. sanguis, Fusobacterium nucleatum* and other bacteria present in the periodontal flora. Simultaneously, all *Veillonella* species were co-aggregated with *S. salivarius* on the surface of the tongue, but not in the subgingival plaque [24].

Previous studies by Distler W et al. and Mix et al. showed a symbiosis between *Veillonella spp*. and streptococci in dental plaque, and streptococci, producing lactate, acts as a nutrient source for *Veillonella* [25, 26]. Moreover, co-existence with *Veillonella* induced A-amylase expression in *Streptococcus gordonii*, which allows *Streptococcus* to decompose starch into oligosaccha-

rides and, consequently, metabolize them into lactate, which can then be used by *Veillonella* [27].

In vivo and in vitro studies (Kolenbrander, 2011, Valm et al., 2011) showed that *Veillonella* also co-aggregates with middle and late colonizers, including the periodontal pathogen *Porphyromonas gingivalis* [28, 29].

These results indicate that the three species of *Veillonella* are evenly distributed on the oral mucosa and the partners in the co-aggregation and form the oral cavity's bacterial ecology.

The ability of Veillonella to produce hydrogen sulfide

Bad breath – halitosis is caused by the products of oral bacteria's metabolism that live on the back of the tongue [30, 31]. First of all, halitosis is associated with inflammatory periodontal diseases caused by periodontal pathogens [32-35]. Periodontal pathogens produce hydrogen sulfide (H_2S), which causes bad breath [36, 37]. *Veillonella* were also identified as producers of hydrogen sulfide, although this ability is less pronounced in them [14, 30, 33, 37-39].

In a study by Jumpei Washio et al. (2005), on the contrary, it was found that the predominant hydrogen sulfide-producing bacteria were not periodontopathogens but were resident oral bacteria, such as *Veillonella* and *Actinomyces* [9].

Jumpei Washio et al. in 2014 studied the metabolic activity of the typical strains of *Veillonella atypica*, *Veillonella dispar*, and *Veillonella parvula* and their symbiosis with other bacteria [40]. *Veillonella* was found to produce hydrogen sulfide from L-cysteine (keratin, as the main protein in desquamation, contains cystine molecules), with the participation of cystathionine synthase and cystathionine lyase. The authors noted that the production of hydrogen sulfide is regulated by oral factors (pH and lactate levels). In addition to hydrogen sulfide, *V. atypica* and *V. parvula* secrete ammonia and serine, suggesting the involvement of cystathionine synthase lyase (EC 4.2.1.22).

The role of Veillonella parvula in the formation of the microbiome in infancy and early childhood

The formation of the oral microbiome begins in the prenatal period and is closely related to the development of the dentoalveolar system. Studies by Caroline Bearfield et al. (2002) and Kjersti Aagaard et al. (2014) found that the colonization of microorganisms in the fetus begins before birth. Almost 70% of pregnant women have several oral microorganisms present in their amniotic fluid, such as *Streptococcus spp., Fusobacterium nucleatum, Porphyromonas, Neisseria spp.*, and *Prevotella tannerae*. A type of Firmicutes has also been found in the human placenta and amniotic fluid [41-43]. Microbial colonization of the oral cavity continues after birth by passing through the maternal birth canal [44-47]. Apparently, the set of earlier colonizers determines the subsequent colonization, which may vary depending on the chosen obstetric reception (natural birth or C-section) and the conditions of maintenance after birth (premature babies, children with various pathologies and healthy infants) [48, 49], which leads to more complex and stable ecosystems in the adult period [50]. In a study by Eimear Hurley et al. (2019), it was noted that over time, the bacterial communities of natural born infants resemble the bacterial communities of mothers' birth canal, while the bacterial profile of babies after C-section resembles the bacteriome present in the cutaneous tissue, mainly *Veillonella spp.* and others [14]. Although, this effect disappears after the first week after birth [51].

The oral microbiome gradually evolves with the eruption of the first baby teeth in infancy [52]. It is noteworthy that the oral ecosystem begins to reform with the first tooth's eruption, which provides new places of adhesion and shows significantly greater diversity compared to that in young children. A lower level of representatives of Gram-positive facultative anaerobic species and a higher level of gram-negative facultative anaerobic species are observed during the eruption of baby teeth [44].

The oral microbiome is also involved in the formation of innate and acquired immune functions that affect the child's future health. Following birth, colonization and the formation of microbial pioneers in the oral cavity commence through contact with the outside world through breathing, feeding, and contact with attending physicians and relatives [14]. The core of the oral microbiome in young children was determined by Mason et al. and included *Streptococcus, Gemella, Granulicatella* and *Veillonella genera* [16]. Interestingly, these main species accounted for 45% (23% - 61%) of each child's total oral microbiota. Of the 178 identified species, only 33 were common in more than 75% of infants [14, 44].

As the child get older, the versatility of the oral microbiome continue to expand. Regardless of the caries index, there was a significant difference in the microbial composition of saliva and plaque samples [14]. In the saliva samples of children, *Streptococcus vestibularis/salivarius* and *Veillonella parvula/atypica/dispar* were the dominant taxa, accounting for 60% of the total volume [14]. In plaque, the most common genera were *Veillonella, Streptococcus, Actinomyces, Selenomonas* and *Leptotrichia*, which constituted 30-50% of the bacterial plaque community [14, 50].

The saliva microbiome

When the oral mucosa's epithelium is desquamated and the biofilms are separated as they mature, the associated bacteria are released into the saliva from different oral biotopes. The saliva microbiome also contains microorganisms from the biofilm of the tongue surface. The tongue's papillary surfaces contain microbiota biased towards anaerobic genera such as *Prevotella* and *Veillonella*, while the ventral surface of the tongue carries microbiota rich in streptococci and gemellae [53].

Veillonella parvula and the pathogenesis of dental caries

Features of oral hygiene, the level of fluoride in water, dietary characteristics, as well as the incidence of dental caries and the availability of dental care vary significantly in different countries of the world (www.who.int). In the Nordic countries, long-term population-based and individual caries prevention measures have resulted in a low average incidence of caries, while in developing

countries, there is an increase or continuation of a high incidence of caries. However, even in communities with a low incidence of caries, despite preventive efforts, caries is detected in about 15-20% of the population [54].

The prevailing ecological hypothesis of microbial plaque / biofilm [55, 56] describes an ecological shift towards enrichment with acidogenic and acid-resistant species under low pH conditions, such as after sugar consumption [57-59]. In the study of Esberg et al. [60], diverse strains of *Actinomyces, Bifidobacterium*, and *Veillonella*, as well as *S. wiggsiae, S. mutans,* and *S. sobrinus,* were found in groups of patients consuming high doses of sucrose, which were associated with the presence of dental caries in children and adults in other studies [59, 61, 62]. The shift of the oral cavity's pH level to the acidic side activates enzymes and regulates the transcription and translation of bacterial proteins/enzymes [56]. According to the authors, in children who do not suffer from caries, the detection of *Veillonella*, and not *S. mutans*, is considered as a predictor of a high risk of developing caries in the future. However, in our opinion, this statement needs more serious arguments.

S. mutans is associated only with the initiation of caries (white spot stage) but not with caries' progression. Other potential acid-producing bacteria, including strains of *Selenomonas, Neisseria*, and *S. mitis*, are observed at high levels in white spots indicating primary demineralized enamel. *Propionibacterium spp*. are associated with the progression of caries but are not detected at high levels.

Initially, the diverse community in caries-free areas of enamel or in white spots shifts to a progressive loss of microbial diversity in caries-active areas. Species minimized in caries-active foci include *Lachnospiraceae spp., S. mitis group, Corynebacterium matruchotii, S. gordonii, S. cristatus, Capnocytophaga gingivalis, Eubacterium IR009*, and *Campylobacter rectus* [63].

Streptococci of the *S. mitis group*, such as *S. gordonii,* produce hydrogen peroxide in abundance in several ways [1, 64-66]. Kreth et al. have reported that the H_2O_2 concentrations generated by *S. sanguinis* and *S. gordonii* are sufficient to inhibit the growth of cariogenic *Streptococcus mutans* [67].

A study by Peng Zhou et al. has shown that the association of the *Veillonella parvula* PK1910 strain (formerly *Veillonella atypica* PK1910 [68]) in a mixed culture of *S. gordonii-S. mutans prevents* the inhibition of *S. mutans* from *S. gordonii* [69]. It is assumed that the anaerobic *V. parvula* PK1910 has a high resistance to oxygen stress and actively counteracts the effect of H_2O_2 due to the catalase encoded by the catagene in *V. parvula* PK1910 [70]. *Veillonella* levels correlate with the total number of acid-forming species. The main explanation for this phenomenon may be the ability of *Veillonella* to participate in lactate metabolism.

Thus, the microbial community's cariogenic potential is primarily associated with the metabolic activity of bacteria that acidify the oral cavity, and representatives of the genus *Veillonella* act as metabolic antagonists and neutralize the acidogenic effect of streptococci and other cariogenic species. Their presence in significant numbers is most likely due to the availability of an available food source, which creates the possibility of rapid reproduction and colonization of this biotope.

Protective role of Veillonella parvula in the pathogenesis of inflammatory periodontal diseases

The oral cavity pioneer colonizers' metabolic activity creates an environment favourable for colonization by intermediate species, all of which are *Veillonella species*. *Veillonella spp.* actively co-aggregate with many bacteria, including the initial colonizer *Streptococcus gordonii* and the periodontal pathogen *Fusobacterium nucleatum*, at various oral biofilm formation stages [19, 20-22]. *F. nucleatum*, which is a strict anaerobe and an early intermediate colonizer [11], plays an essential role in protecting anaerobic microorganisms from atmospheric oxygen and hydrogen peroxide in the oral biofilm and is able to support the growth of *Porphyromonas gingivalis* under aerated conditions [71, 72]. Unlike fusobacteria, *Veillonella spp.* more tolerant to oxygen stress. Peng Zhou et al. hypothesized that the catalase activity of *Veillonella spp.* can play a crucial role in protecting obligate anaerobes, particularly *F. nucleatum*, from oxygen stress and contribute to its persistence in the early microbiome [70]. A similar phenomenon was also found in the study of Periasamy and Kolenbrander [21]: the strain *Veillonella spp.* PK1910 increased the biomass of *F. nucleatum* in the biofilm using the flow cell system. The growth of intermediate species causes a change in the local environment and generates nutrients, such as heme / hemin, that promote the growth of later colonizers, many of which are periodontopathogens [73]. A study by Peng Zhou et al. has also been shown that *Veillonella* produces nutrients for the survival and growth of periodontal pathogens [70]; however, in our opinion, this cannot be considered as an argument for their pathogenic role in the development of gingivitis and periodontitis.

Usually, the biofilm community maintains homeostasis, but when the periodontal immune response is impaired, periodontal tissue pathology occurs due to the release of matrix metalloproteinases from neutrophils. At the same time, T cells contribute to the resorption of the alveolar bone through the activation of the cytokine cascade [74-76].

The bacteria that dominate the polymicrobial communities associated with various forms of periodontitis can also be found in a healthy state but with a markedly reduced relative abundance compared to healthy tooth surfaces' plaques [77]. According to the ecological hypothesis, changes in environmental conditions may contribute to pathogens' growth (currently defined as pathobionts) with the development of periodontitis [78]. In periodontal diseases, the appearance of new types of exogenous pathogens that are absent in a healthy state is not observed. The reason may be that the decrease in the number of *Streptococcus mutans, Veillonella parvula, Streptococcus sobrinus, Scardovia wiggsiae* and *Actinomyces spp.* compensates for the increase in the number of putative periodontopathogens of the “red” and “orange” groups [79-81].

Lingyang Tian et al. (2015) differentiated the microflora in dental plaque from healthy coronal surfaces and periodontal pockets using PCR-dipstick DNA chromatography. In this study, *V. parvula* was observed mainly subgingival (93.8%) together with *S. mutans* (100%) (since *Veillonella* shows a coactive relationship with acidogenic bacteria), against supragingival parts, where the concentration of *V. parvula* was 18.8% [77]. While *V. parvula* was ubiquitous in all intraoral niches [79, 82], this species lost its dominant role in plaques in patients suffering from inflammatory periodontal diseases. This result is in good agreement with previous studies by Kumar et al. (2005, 2006) and Stingu et al. (2012), who suggested that *V. parvula* is a species demonstrating periodontal health [62, 83, 84].

In an experimental model for the treatment of ligature periodontitis, Tsarev and Ippolitov (2013) used eubiotic strains of *Veillonella parvula* and *Streptococcus salivarius* [23, 85]. After 10 days of the experiment, the frequency of isolation of pathogenic microorganisms decreased sharply, S. salivarius was isolated in 80% of laboratory rats, *V. parvula* – in 20% (in the amount of 4.5-4.0 lg CFU). After the end of the course, the control study showed the preservation of *S. salivarius* in 40% and *V. parvula* – in 60% of the animals. Cytomorphological manifestations of reparative changes in bone tissue and a decrease in periodontal inflammation intensity were observed in the experimental group.

Inflammation is an important environmental change that can stimulate the growth of periodontal pathogenic microorganisms, by destroying tissues, with the release of nutrients (for example, degraded collagen, heme-containing compounds, sources of amino acids and iron, respectively) [86, 87]. These nutrients can be transferred through the inflammatory exudate into the gingival fissure, stimulating the growth of subgingival proteolytic and saccharolytic bacteria that have the ability to absorb iron [88].

Thus, many pathobionts can actively colonize the supragingival and subgingival zones and selectively expand their habitat at the expense of those species that cannot adapt to new environmental conditions, thereby creating dysbiosis of the periodontal complex tissues. The dominance of representatives of the genus *Veillonella*, which exhibit antagonistic activity in relation to periodontopathogenic species of the red complex, should probably be considered an essential factor in stabilizing the periodontal microbiome.

In a study by Samir Shah et al. saprophytic biofilms (consisting of *Streptococcus oralis, Streptococcus sanguis, Streptococcus mitis, Actinomyces naeslundii, Neisseria mucosa and Veillonella parvula*) under the influence of cigarette smoke showed early and widespread cell death, the main metabolic functions of bacteria in the microbiome were significantly reduced; however, in biofilms (including *S. oralis, S. sanguis, S. mitis, A. naeslundii, N. mucosa, and V. parvula, Fusobacterium nucleatum, Porphyromonas gingivalis, Filifactor alocis, Dialister pneumosintes, Selenonomas sputigena, Selenominas noxia, Catonella morbi, Parvimonas micra, and Tannerella forsythia*) in response to smoke exposure, several metabolic pathways were over-expressed. A cytokine-rich, pro-oxidant anaerobic environment supports inflammatory pathobionts and, in the absence of commensal antagonism, can promote the creation of pathogen-rich biofilms in smokers [89].

CONCLUSION

An analysis of the results of the studies presented in this review revealed the critical role of *Veillonella spp.* in the oral microbiome at all stages of human life, starting from perinatal age. The role of the human microbiome in immune, inflammatory, and degenerative diseases is increasing with the development of technologies that link oral and intestinal dysbiosis with a high risk of inflammatory, autoimmune, and systemic degenerative diseases.

In our opinion, the taxonomic group (genus) *Veillonella spp*. is a significant component of the oral microbiome in terms of quantity and functional activity, it can be considered in two main aspects:

1. As a stabilizing component in the numerous microbial associations of this ecological niche – the oral cavity, which supports the most important metabolic pathways and regulates the pH of the ecosystem.

2. As an indicator of a violation of the ecosystem's metabolic situation, indicating the excessive development of caries-causing microbiota (mainly streptococci and actinomycetes), which is an indicator, but not a predictor of a high risk of dental caries.

Considering the above, the therapeutic effect depends on the degree of colonization of *Veillonella spp.*, including with the help of various oral hygiene products that may contain probiotic strains of *Veillonella spp.*, which seems to be an urgent task of dentistry.

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