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REVIEW

The role of *Streptococcus intermedius* in brain abscess

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Abstract Brain abscess represents a significant medical problem, despite recent advances made in detection and therapy. *Streptococcus intermedius*, a commensal organism, has the potential to cause significant morbidity. *S. intermedius* expresses one or more members of a family of structurally and antigenically related surface proteins termed antigen I/II, which plays a potential role in its pathogenesis. It is involved in binding to human fibronectin and laminin and in inducing IL-8 release from monocytes, which promotes neutrophil chemotaxis and activation. There are few published data on the role of this organism in brain abscess. This review focuses on the clinical evidence, pathogenic role, mechanism of predisposition, and currently employed strategies to fight against *S. intermedius* associated to brain abscess.

Introduction

Brain abscess is an increasingly common condition that affects people of all ages. Despite improvements in detection and treatment strategies, brain abscesses continue to occur, with an increased prevalence in developing countries and immune-compromised patients [1]. Brain abscess has an incidence of about 1 in 100,000 persons per year in the United States. In Europe and other countries, 1,500–2,500 cases are reported per year [2]. Brain abscess is a focal infection that begins when organisms are inoculated into the brain parenchyma, usually from a site distant from the central nervous system (CNS). Abscess formation occurs through several stages. Inflammation during the "early cerebritis" stage evolves into a necrotic collection of pus, eventually surrounded by a well-vascularized capsule after 2 weeks [3]. Three mechanisms have been proposed as predisposing factors for brain abscess [4]. (1) Direct extension: infections stemming from the sinuses, teeth, middle ear, or mastoid may gain access to the venous drainage of the brain via valveless emissary veins that drain these regions. Because of improved antibiotic therapy for ear infections, this mechanism is decreasing in incidence, accounting for only approximately 12–25 % of cases. However, in developing countries, this is still a significant source, accounting for at least 50 % of cases [5]. (2) Hematogenous: seeding of the brain occurs from distant infection sites and often results in multiple brain abscesses. This remains an important cause of brain abscess. (3) Following penetrating head injury or neurosurgery: previously low in incidence, more brain abscesses are developing after head trauma and neurosurgical procedures. A case series found that 37 % of brain abscesses were associated with head penetration. However, up to 30 % of abscesses are cryptogenic and have no clear source [5].

Currently, more than 147 bacterial taxa have been reported to cause brain abscess, including 29 reported for the first time using a metagenomic approach [6]. These include 129 known species from 50 genera and 18 as yet unclassified and uncultured bacteria. Among the 50 genera involved in brain abscess, the most commonly represented was the *Streptococcus* genus, with 14 different species, followed by the *Nocardia*, *Staphylococcus*, *Clostridium*, and *Prevotella* genera (8 species each), the *Haemophilus*, *Citrobacter*, and *Neisseria* genera (5 species each), the *Salmonella* genus (4 species), and the *Fusobacterium*, *Enterococcus*, *Campylobacter*, *Enterobacter*, and *Proteus* genera (3 species). Each of the remaining genera was represented by one or two species. In this review, the role,

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mechanism of virulence of *Streptococcus intermedius* in brain abscess, and novel treatment is discussed.

Streptococcus intermedius and brain abscess

Streptococcus intermedius, together with *S. constellatus* and *S. anginosus*, is a member of the "*Streptococcus anginosus* group" (SAG) and is found at various mucosal sites, including the oral cavity, genitourinary system, and gastrointestinal tract [7]. However, this group of bacteria is also frequently encountered in invasive suppurative infections at a range of sites, including liver and brain abscesses, dentoalveolar infections, and infective endocarditis [8].

The SAG species also differ in terms of the virulence factors they produce. For example, the enzymes α-*N*-acetylneuramidase (sialidase) and hyaluronidase, which destroy host tissues and, presumably, convert them into small nutrients to be utilized in bacterial growth [9], are both known to be produced by *S. intermedius*, whereas *S. constellatus* produces only hyaluronidase and *S. anginosus* produces neither. Strains of *S. intermedius* also secrete a human-specific cytolysin, known as intermedilysin, and its expression has recently been correlated with strain pathogenicity or with the severity of *S. intermedius* infections [9].

The identification and speciation of the SAG species can usually be performed successfully using a commercial identification kit (API 20 Strep; bioMérieux, Lyon, France). The identification of the SAG species based on molecular biological techniques can be useful in both guiding the diagnostic investigation and providing insight into the possible role of coinfecting organisms and the probability of occult abscesses, which are more likely with *S. intermedius* infections [10]. The *ily* gene sequence has notably been shown to be specific for *S. intermedius*. The assay can be used for rapid identification through the use of polymerase chain reaction (PCR) with the *ily* gene as a species marker gene [11].

Clinical evidence for association

The clinical association of *S. intermedius* with the tendency to form abscesses has long been recognized. The first case of brain abscess caused by *S. intermedius* was reported in 1975 [12], where it was found to comprise a population of approximately 5.4 % among other pathogens in 71 analyzed brain abscess samples. *S. intermedius* has been isolated from 50 to 80 % of brain abscesses [13]. Several recent studies have implicated *S. intermedius* infection in the pathogenesis of brain abscess. In 2006, a study reported the role of *S. intermedius* in cases of intracerebral abscess in children, resulting from hematogenous spread from a distant focus (e.g., congenital heart disease) or extension from a contiguous focus of infection (e.g., sinus, teeth, and middle ear). In this study, among children who developed brain abscess associated to *S. intermedius*, 58 % of 17 patients had a cyanotic congenital heart disease, while 42 % of patients had sinusitis, otitis media, or dental caries [14]. Another two cases of brain abscess in the left frontal lobe caused by *S. intermedius* were reported in 13- and 52-year-old males, respectively. In the former patient, the predisposing condition was a paranasal sinusitis of the frontal and ethmoidal sinuses. In the later patient, the source of the pathogen was not detected, despite extensive investigation [15].

In 2008, Petti et al. [16] described a 47-year-old patient who developed an altered sensorium, periodontal disease, and low-grade fever. Magnetic resonance imaging (MRI) of the brain showed 15 to 20 ring-enhancing lesions in both the cerebral hemispheres and the midbrain. Craniotomy and biopsy revealed multiple abscesses positive for *S. intermedius*. This patient was found to have multiple risk factors for the development of invasive CNS disease, including a congenital heart disease, sinusitis, otitis media, and dental caries [16]. Despite the prompt initiation of antibacterial therapy, this patient did not return to his baseline function [16], which also suggests a role of *S. intermedius* in chronic brain abscess and highlights the pathogenesis of intracranial abscesses in patients with concurrent sinusitis, and *S. intermedius* was reported to be the most prevalent pathogen associated with this contiguous infection [16]. In recent prospective studies of the identification of the pathogenic agent of brain abscess, using both culture and 16S rRNA-based detection, Al Masalma et al. [17] reported an association between brain abscess and *S. intermedius* in 25 % of patients and found that, in predisposed individuals, *S. intermedius*-associated intracerebral abscess had multiple known risk factors for the development of invasive CNS disease, including congenital heart disease, sinusitis, otitis media, and dental caries. Jan et al. [18] described a case of brain abscess associated with *S. intermedius* in a 47-year-old non-Hispanic white male, and their investigation revealed a patent foramen ovale with oral flora being the plausible explanation for the brain abscesses caused by *S. intermedius*.

Predisposition and pathogenicity factors

Various factors may predispose a patient to develop a cerebral abscess containing a member of the anginosus group. These include mucosal infection (paranasal sinusitis, periodontal diseases), pneumonia, alcohol abuse, and diabetes [19]. In the particular case of *S. intermedius*, another predisposition may be a prior liver abscess containing the bacterium [20]. Lung infection (e.g., abscess, empyema, bronchiectasis) caused by *S. intermedius* has been reported

to be a predisposing factor for brain abscess [21]. Unoperated cyanotic congenital heart disease (CCHD) is an important predisposing factor for brain abscess associated with *S. intermedius*, accounting for 25–46 % of cases, as areas of microinfarctions may predispose to bacteremic seeding with this bacteria, bypassing the pulmonary filter via right to left shunting [22]. Risk factors predisposing to the development of brain abscess associated with *S. intermedius* in CCHD include hypoxia and its consequent polycythemia and hyperviscosity. The latter results in sluggish blood flow in cerebral microcirculation that allows microthrombi formation, focal encephalomalacia, and alters the blood–brain barrier permeability [23]. A variety of intrinsic factors could also be responsible for the distinctive pathogenesis of this bacterial group

Growth requirement

Growth requirements of *S. intermedius* appear to be important in its pathogenicity. It is able to grow well in acidic environments [24] and, also, it has been suggested that, under certain circumstances, *S. intermedius* has the ability to migrate from its normal niche, reach a particular site, and rapidly decrease the pH of a localized environment, resulting in a subsequent release of iron (which is a constituent of important metabolic enzymes essential for growth) from host transferrin. This would facilitate bacterial growth and initiation of the infectious process [25]. Another study demonstrated synergy between members of the anginosus group and oral anaerobes, resulting in enhanced growth. The predominant species recovered from the abscesses described in this paper were anaerobic bacteria and the anginosus group, confirming the clinical importance of this phenomenon [26].

Cell-associated virulence factor

The ability of bacteria to bind extracellular matrix (ECM) components is regarded as a significant factor in the development of streptococcal abscesses and endocarditis, since tissue damage often precedes bacterial colonization, thus, exposing ECM [27]. Recent studies have shown that *S. intermedius* expresses one or more members of a family of structurally and antigenically related surface proteins termed antigen I/II, which may have a potential role in *S. intermedius* pathogenesis. This antigenic protein is reported to bind to human fibronectin and laminin and induce IL-8 release from monocytes [28], which promotes neutrophil chemotaxis and activation (Fig. 1). The recruitment of new neutrophils at the site of *S. intermedius* infection results in the accumulation of proinflammatory cytokines that contribute to tissue damage and abscess development [29]. Another potential virulence factor is the presence of a polysaccharidic capsule in strains of *S. intermedius* that hinder phagocytosis. The ability to escape phagocytosis allows this pathogen to replicate after arriving at and adhering to a site of tissue damage [30]. The study conducted by Kanamori et al. [31] on encapsulated strains of *S. intermedius* for causing abscess in mice revealed the role of the capsule in its pathogenicity. Encapsulated strains produced larger abscesses, earlier spontaneous drainage, and a higher lethality than the unencapsulated ones. In addition, this study showed that encapsulated strains resisted the phagocytosis and phagocytic killing function of polymorphonuclear neutrophils. The capsular material itself inhibited the function of polymorphonuclear neutrophils and that inhibition was proportional to the polysaccharide concentration. Brook and Walker reported that encapsulated *S. intermedius* had a stronger ability to produce an abscess than unencapsulated ones [32]. However, the presence of a polysaccharide capsule might be a necessary virulence factor in suppurative infections, but not in lethal ones.

Extracellular virulence factors

Members of the anginosus group produce a wide variety of hydrolytic enzymes, such as hyaluronidase, deoxyribonuclease, and chondroitin sulfatase, which may contribute to their pathogenic potential [33, 34]. These enzymes may facilitate the liquefaction of tissue to form pus. Hyaluronidase has been found in pus and shown to be a growth factor, presumably, by mobilizing low molecular weight nutrients [35]. A strong association between brain abscesses and the production of hyaluronidase during infections by *S. intermedius* has been observed [36]. Isolates from brain abscesses and purulent lesions frequently produce hyaluronidase, and the deeper the abscess, the higher the frequency of hyaluronidase production. The products of hyaluronidase degradation are used as a nutrient source by the microorganism. In *S. intermedius*, the hyaluronidase, or proteins associated with the enzyme, is induced in the presence of substrate [37]. The addition of hyaluronate to growth media also results in increased levels of hyaluronidase in *S. intermedius* [38]. The depolymerization of hyaluronate by hyaluronidase results in a decrease in the viscosity of the ground substance. Decreased viscosity results in increased permeability of the connective tissues, and potentially increased spread of microorganisms and toxins through these tissues [39]. Hyaluronidase is also involved in biofilm formation through different mechanisms. The ability to form biofilms may also be critical for the pathogenesis of *S. intermedius*. Biofilm formation is a dynamic process which involves initial attachment of cells to the surface, production of extracellular polymers, maturation, and dispersion of single cells from the biofilm [40]. The establishment of biofilms by *S. intermedius* protects it from host defenses and antibiotics. Moreover, *S. intermedius* utilizes quorum-sensing communication to organize its behavior by monitoring the

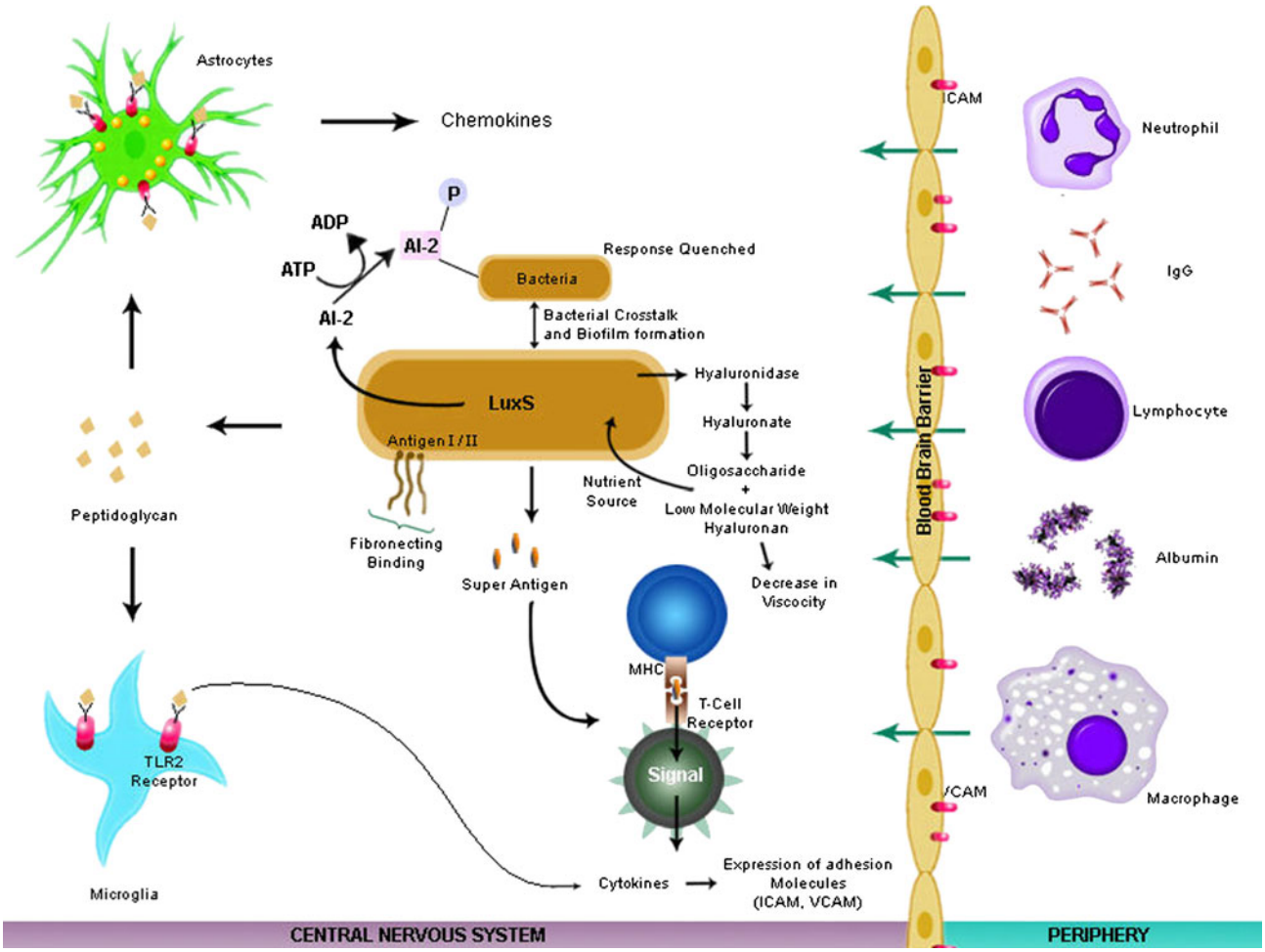

Fig. 1 Pathogenesis of *Streptococcus intermedius* in brain abscess. The polysaccharide capsule has been identified as an important virulence factor and contains antigen I/II surface protein that are involved in binding to fibronectin and laminin of brain tissues. The gene product of *luxS* is involved in biofilm formation and the recruitment of bacteria. The product of hyaluronidase is utilized as a nutrient source, for biofilm formation as well as decreasing the viscosity of ground substances. The superantigenic toxins stimulate T cells to proliferate and produce cytokines. Other important virulence factors include the capsule, ATP-binding cassette, fibronectin-binding protein, and hemolysin (ILY). Toll-like receptor 2 (TLR2) of astrocytes and microglia recognize peptidoglycan (PGN) from the bacterial cell wall and leads to the activation and elaboration of numerous proinflammatory cytokines and chemokines. Proinflammatory cytokine release leads to blood–brain barrier (BBB) compromise and the entry of macromolecules such as albumin and IgG into the brain parenchyma. In addition, cytokines induce the expression of adhesion molecules (ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule), which facilitate the extravasation of peripheral immune cells such as neutrophils, macrophages, and T cells into the evolving abscess. Newly recruited peripheral immune cells can be activated by both bacteria and cytokines released by activated glia, effectively perpetuating the antibacterial immune response that contribute to brain abscesses

concentration of bacterial signals and biofilm formation, by using signals molecules referred to as autoinducers (AIs) [41]. The autoinducer-2 (AI-2), a furanosyl borate diester synthesized by the product of the *luxS* gene acts as an inter- and intraspecies communication signal. In addition to its role in signaling, AI-2 may be involved in the regulation of various genes related to the pathogenic capabilities of several bacteria, including proteolytic and hemolytic activities, iron acquisition, antibiotic production, carbohydrate metabolism, and biofilm formation [41]. The biofilm formation in *S. intermedius* may explain its reduced susceptibility to ampicillin, ciprofloxacin, and tetracycline [42].

In addition, deoxyribonuclease and chondroitin sulfatase activities are also found in *S. intermedius* [37]. Other enzymes produced by *S. intermedius* are a novel glycosaminoglycan depolymerase, which acts on both chondroitin sulfate and hyaluronic acid [43], and sialidase (neuraminidase), which also acts as a growth factor [44]. All these enzymes may play an important role in the ability of microorganisms to proliferate and, thus, participate in pathogenesis. Superantigens should probably be considered as one of the most important virulence factors of the *S. intermedius*. These consist of a diverse group of molecules able to stimulate the apoptosis of specific lymphocyte subsets [45]. A 90-kDa protein that suppresses

lymphocyte and fibroblast proliferation has also been recovered from *S. intermedius* [46]. Another group of proteins called histone-like DNA binding proteins (HLPs) was studied in *S. intermedius* (Si-HLP). This nucleoid-associated protein governs the nucleoid architecture, controls the gene transcription profile in *S. intermedius*, and stimulates cytokine production in human macrophages at the site of the brain abscess [47]. Specifically, the continued release of proinflammatory mediators by activated glia and infiltrating peripheral immune cells may act through a positive feedback loop to potentiate the subsequent recruitment and activation of newly recruited inflammatory cells and glia. This would effectively perpetuate the antibacterial inflammatory response via a vicious pathological circle, culminating in extensive collateral damage to normal brain tissue.

Intermedilysin

The cytotoxin, intermedilysin (ILY), which can directly damage host tissues and immune defense cells and participate in bacterial pathogenicity, was first identified as a cytolytic factor of *S. intermedius* strain UNS46, causing human cell death with membrane bleb formation [48]. This gene exists only in *S. intermedius* strains and no homolog to the toxin gene was detectable in a collection of *S. anginosus* and *S. constellatus* isolates [9]. The unique feature of intermedilysin was its species-specific cytolysis.

The production level of ILY from isolates found in deep-seated brain abscesses is 6.2- to 10.2-fold higher than that from the strains found in normal habitats, such as dental plaque, in contrast to the expression levels of other potential virulence factors, such as hyaluronidase and sialidase, where no significant difference in levels has been found [9]. Moreover, an *ily* knockout strain showed greatly decreased adherence, invasion, and cytotoxicity of human liver (HepG2) cells, and incubating ILY^{+} strain UNS38 with antibody to ILY caused drastic reductions in adherence and invasion of the HepG2 cells [49]. These facts suggest that ILY acts as a major virulence factor, essential for the invasion of and cytotoxicity to human cells. *S. intermedius* can modulate *ily* expression and growth rate through catabolite control protein A-mediated monitoring of the extracellular glucose/utilizable carbohydrate concentration that offers two modes of growth: a rapid growth and lower-virulence mode under preferred carbohydrate-abundant conditions and a slow-growing and highly virulent mode under carbohydrate-limited conditions [50].

ILY was potently hemolytic on human erythrocytes but was 100-fold less effective on chimpanzee and cynomolgus monkey erythrocytes, and did not induce significant hemolysis on horse or sheep blood agar [48]. The susceptibility of human erythrocytes to ILY was not dependent on the ABO blood type of the cell [48]. As most diagnostic laboratories use sheep or horse blood agar to screen for hemolysis, the *S. intermedius* strains that invariably expressed hemolysis against human RBC without affecting animal RBC are identified as "non-hemolytic *streptococci*". β-hemolytic streptococci are investigated in detail more frequently than non-hemolytic streptococci in diagnostic laboratories [48]. Thus, the real incidence of *S. intermedius* in clinical samples might have been underestimated [48].

Observations that *S. intermedius* plays an important role in the induction and exacerbation of brain abscess opened the possibility of novel treatment strategies for brain abscess.

Antibiotic treatment

The antimicrobial management of brain abscesses has changed dramatically in recent decades, with the introduction of newer agents and different treatment strategies, including opportunities for outpatient delivery of care. A neurosurgical intervention plus an antibiotic regimen is warranted for most abscesses [51]. However, conservative management with antibiotics may be appropriate in patients too unwell for surgery and with significant co-morbidity. In particular, when multiple small cerebral lesions less than 5 mm in diameter are present on computed tomography (CT) imaging, patients may be successfully managed conservatively with antibiotics alone. Many different antibiotic regimens have been advocated to control the brain abscess caused by *S. intermedius*.

The mainstay of previous standard antibiotic regimens for brain abscess associated with *S. intermedius* was penicillin with chloramphenicol. This drug exhibits a broad spectrum of activity, good CNS penetration, and excellent bioavailability, but poor bactericidal activity, coupled to significant side effects. However, this regimen has withstood the test of time, with the possibility of antagonism between penicillin, a bactericidal agent, and chloramphenicol [52]. In addition, some more reports have documented an increasing resistance by *S. intermedius* against a number of antibiotics [53, 54]. Reviewing susceptibilities in studies from 1996 to 1999, there has been decreasing susceptibility of *S. intermedius* to penicillin, cephalosporins, macrolides, ciprofloxacin, and clindamycin [53, 54]. Susceptibilities of *S. intermedius* associated with brain abscess for third-generation cephalosporins, cefotaxime and cefepime, are reported to be from 97 to 98 % [55]. Gentamicin and streptomycin have poor activities against *S. intermedius* [53, 54], but aminoglycosides have been shown to be synergistic with penicillin [53]. Antibiotics that are constantly active against *S. intermedius* are vancomycin, teicoplanin, and imipenem [53, 54]. The use of a non-β-lactam antibiotic, such as vancomycin, may be warranted in patients with *S. intermedius*-associated brain abscess.

A combination of cefotaxime and metronidazole has demonstrated good intracerebral penetration and activity on *S.*

intermedius [56]. The Working Group of the British Society of Antimicrobial Chemotherapy (BSAC) recommended that brain abscess may be treated with a combination of a β-lactam antibiotic and metronidazole for 3 to 4 weeks parenterally when abscesses have been excised or between 4 and 6 weeks for those that are aspirated. Twenty-two cases of brain abscess patients tested positive for *S. intermedius* infection were treated with a high dose of cefotaxime and rifampicin and showed significant improvement [51]. However, the data support the recommendations of the BSAC guidelines that an *S. intermedius* brain abscess should be treated with cefotaxime and metronidazole [51]

Conclusions and perspectives

Considering, as a whole, the information presented throughout this review, *S. intermedius* appears to be a major agent of brain abscess, as this bacteria possesses many virulence factors coupled with the recent emergence of its antibiotic-resistant strains. Therefore, understanding the roles of both host antibacterial immune responses along with its virulence factors may lead to the establishment of novel therapeutic treatments for brain abscess. Moreover, understanding the roles of microarray technology may be useful in identifying genes that are up-regulated or down-regulated in different cell types from animals sensitized and challenged with *S. intermedius*. Such genes may then become novel therapeutic targets. The ability to sense the environment and mount an appropriate adaptive transcriptional response may be of crucial importance for *S. intermedius* colonization and pathogenicity. The AI-2/*luxS* system in *S. intermedius* involved in increased biofilm formation protects them from host defenses and susceptibility to various antibiotics at several sub-minimal inhibitory concentrations (MICs). Thus, the drug, either combating biofilm formation or disrupting intercellular signaling mediating by the AI-2/*luxS* system, may provide important advances in therapeutic strategies for brain abscess caused by *S. intermedius*. In addition, elucidating the molecular mechanisms involved in *S. intermedius* communication is important for understanding its commensalism and possible pathogenic transition. This knowledge may lead to novel strategies to fight against brain abscess.

Conflict of interest Authors declare that they have no conflict of interest.

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