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Relationship Between *Streptococcus bovis/Streptococcus equinus* Complex and CRC; An Overview

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Abstract

Streptococcus bovis/Streptococcus equinus complex (SBSEC) is a gram-positive coccus that belongs to group D of the Lancefield grouping. Most SBSEC strains have been characterized as commensal microorganisms, but some can cause severe infections, such as bacteremia and infective endocarditis (IE). Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the third leading cause of cancer-related death. The connection between SBSEC bacteremia, endocarditis, and CRC is well recognized. The presence of CRC is directly linked to the stage of diagnosis, with stage I disease associated with a 5-year survival rate of 90.1%. Epidemiological research has revealed that in CRC patients, the colon is infected with SBSEC, even in the early stages, in ulcer tissues. However, the molecular mechanism of the SBSEC connection in CRC has not yet been identified. According to some reports, there are geographical discrepancies in SBSEC bacteremia, including the occurrence rate and origin of infection. For instance, *Streptococcus bovis* endocarditis is more prevalent in the European population than in the United States, and within Europe, there is variation between the North and South. In this review, we focus on the major virulence factors, diagnostic methods used to identify SBSEC isolates, and risk factors for CRC.

Keywords: *Streptococcus bovis*, *Streptococcus equinus*, Colorectal Cancer

1. Context

Streptococci form a diverse genus that includes many pathogenic species in the lactic acid bacteria (LAB) group (1). Most *Streptococcus bovis/Streptococcus equinus* complex (SBSEC) strains are harmless commensal bacteria, but some can cause serious infections such as colorectal cancer (CRC), infective endocarditis (IE), and bacteremia in humans and animals (2, 3). The non-enterococcal group D *Streptococcus* (GDS) complex comprises several species and subspecies: *Streptococcus lutetiensis*, *Streptococcus alactolyticus*, *Streptococcus equinus*, *Streptococcus gallolyticus* subsp. *gallolyticus* (SGG), *Streptococcus gallolyticus* subsp. *macedonicus* (SGM), *Streptococcus gallolyticus* subsp. *pasteurianus* (SGP), and Streptococcus *infantarius* subsp. *infantarius* (SII) (3). The relationship between GDS bacteremia or IE and CRC is now well documented, and it is recommended that both CRC and IE be excluded in any patient diagnosed with GDS bacteremia (4).

More than half of the mortality associated with CRC is caused by preventable risk factors such as poor diet, smoking, alcohol consumption, lack of physical activity, and body weight (5). On the other hand, the human colon is characterized by various microbiota that play key roles in maintaining human health. Dysbiosis can suppress or potentiate health disorders (6). *Streptococcus bovis* is known as a bacterial agent that contributes to CRC due to its impact on health. According to reports, 25 - 80% of individuals with *Streptococcus bovis* have colorectal tumors (7). Colorectal cancer is a genetic disease that develops over several years and involves a series of genetic changes, known as the adenoma-carcinoma sequence. Emerging studies have closely linked CRC development with changes in the gut microbiota (8).

In this narrative review, we will discuss and focus on the major virulence factors, diagnostic methods used to identify SBSEC isolates, and risk factors for CRC.

2. Taxonomy and Identification of the *Streptococcus bovis*/*Streptococcus equinus*

Streptococcus bovis, synonymous with *Streptococcus equinus*, is now known as SBSEC and belongs to the non-enterococcal group D Lancefield. SBSEC consists of a heterogeneous group of commensal bacteria that colonize the gastrointestinal tract (GIT) of humans and animals (3, 9, 10). It has been noted that SBSEC classification is intricate and occasionally challenging.

SBSEC has been divided into three biotypes: Biotype I, biotype II/1, and biotype II/2. However, the categorization of SBSEC has undergone several taxonomical changes over the past 20 years, coinciding with the identification of new species (or subspecies) (11). Based on the latest taxonomical reconsideration using molecular methods such as single-gene PCR and qPCR analyses (e.g., 16S rRNA, sodA, and groEL), SBSEC is divided into seven species and subspecies: *Streptococcus equinus*, *Streptococcus infantarius* subsp. *coli* (formerly *Streptococcus bovis* biotype II/1), SII (formerly *Streptococcus bovis* biotype II/1), Streptococcus alactolyticus, SGG (formerly *Streptococcus bovis* biotype I), SGP (formerly *Streptococcus bovis* biotype II/2), and SGM (3, 11-13). In this scheme, *Streptococcus bovis* is considered a heterotypic substitute for *Streptococcus equinus*, while *Streptococcus gallolyticus* includes three subspecies: *Gallolyticus*, *pasteurianus*, and *macedonicus*. Subsp *infantarius* has been isolated from milk and fermented dairy products worldwide.

Some SBSEC members have been identified as causing severe diseases such as bacteremia and IE in individuals, while others have been recognized for their role in food preparation processes, such as fermentation, and are therefore considered harmless. Consequently, this group of bacteria includes both pathogenic and beneficial species (3, 11, 13).

3. Prevalence of *Streptococcus bovis*/*Streptococcus equinus* in Animals and Humans

Streptococcus bovis/*Streptococcus equinus* is a component of the microbiota of the human and animal GIT. Approximately 5% to 60% of healthy adults are fecal carriers of SBSEC, depending on the detection methods and geographic location. The carriage rate in humans is 23.8% in infants in the UK and about 5% in adults in France and the UK (14, 15). *Streptococcus bovis*/*Streptococcus equinus* complex is also widespread among most domestic and wild animals, including livestock, sheep, deer, cows, horses, camels, pigs, rodents, dogs, and birds (16). Additionally, SII and SGM are major bacteria in fermented food products. Several SII strains were recently found to be highly prevalent among LAB in African naturally fermented dairy products (FDP) made from cow, goat, and camel milk in some sub-Saharan African countries (15, 17, 18). Therefore, live SII is consumed by millions of people in this region (17). The intracellular transport of lactose and its uptake play a significant role in the growth of LAB, such as streptococci, in dairy. *Streptococcus bovis*/*Streptococcus equinus* complex demonstrates that a lactose transposition system, such as the phosphoenolpyruvate-dependent phosphotransferase system, results in decreased growth levels for *Streptococcus bovis* strains in the presence of lactose compared to glucose (19). Due to these metabolic properties, the observed predominance of SII in naturally fermented dairy and the factors responsible for this unexpected dominance could not be explained (19).

The carrier level of SBSEC varies due to differences in diagnostic methods, sex, age, and underlying diseases. Oral colonization is uncommon in humans; however, SII, SGP, and *Streptococcus equinus* have been isolated from dental plaques and root infections (16). Certain species of SBSEC, such as SGG, SGP, and *Streptococcus lutetiensis*, are associated with IE and infant meningitis, and *Streptococcus bovis* has been linked to cancer. Specifically, SGG has been associated with CRC in humans (20). Living in rural areas and contact with animals facilitate fecal-oral or food-oral transmission (16).

4. Virulence Factors and Pathogenicity of *Streptococcus bovis*/*Streptococcus equinus*

Recognized SBSEC virulence factors are limited to a small number of adhesion and pro-inflammatory agents (1).

4.1. Adhesions

After ingestion, oral epithelial cells are the first GIT cells to interact with SBSEC (16). The binding to GIT cells seems to be influenced by pH and cell type. For instance, in a study by Von Hunolstein et al., 1993 (as cited by Jans and Boleij), the adhesion of human oral cells to human IE-derived SB biotype I and II strains was about 2 - 3 times greater than that of the commensal strain SB DSM20480T = NCTC8177 (16). In a study by Styriak et al., 1994, the highest rate of adhesion of SB strains to GIT cells was found to occur at pH 7.0 - 7.3 (21). Extracellular matrix proteins (ECM), such as various types of

collagens, fibrinogen, and fibronectin, play an important role in binding bacteria to epithelial and endothelial surfaces and facilitating colonization. Collagen type I is present in organ capsules and wound tissues, such as injured heart valves. Collagen type IV is a major component of basal membranes and can be exposed at tumor sites (1, 16). Most SGG strains isolated from human blood cultures of IE or bacteremia patients, as well as fecal and dairy SBSEC isolates, showed binding to collagen type IV. In contrast, SGG, SGP, SII, and SL isolated from human blood bind to collagen type I (22, 23).

4.2. Pili

Overall, SGG has three pilus loci named pil1, pil2, and pil3, each of which contains three genes. Among these, pil1 and pil3 are the most conserved in the clinical isolates of *Streptococcus gallolyticus*. The pil1 pilus has been shown to bind to collagen type I, supporting IE in a rat model of experimental endocarditis (16, 24, 25). In other SBSEC members, the three pilus loci demonstrated signs of genome decline, with several loci and genes being mutated, defective, or entirely missing. Most *Streptococcus equinus*, SII, and SGM strains carry only pil3, which is a complete locus. This may explain the low virulence of SGP. Remarkably, pil1 is expressed irregularly at the bacterial level through a new regulatory system in the promoter region (16, 26). This variable expression is controlled by phase variation in the leader peptide-coding gene through the insertion or deletion of 5-bp repeats, leading to the hairpin formation of the mRNA. This mechanism is believed to help bacterial overpopulation by providing a defense against the host immune system (1).

4.3. The Capsule

The capsular polysaccharides of the SBSEC group mainly contain galactose, rhamnose, and uronic acid, and are formed from glucose and other carbohydrates. Capsule characteristics vary among strains. Highly virulent strains of *SGG* produce a considerably thicker capsule, while defective genes in dairy-isolated strains of SII or SGM may prevent capsule production (16, 27). Genome information suggests a high diversity of capsular polysaccharides in SGG, SGP, and SII, which is linked to capsule inconsistency and variable antigenic features (16).

Many streptococci exhibit hyaluronic acid capsules, which are used for binding to host cells, colonization, and resistance to the innate immune system (28, 29). Capsule degradation by hyaluronidase is associated with reduced adherence to epithelial and endothelial cells (30). In contrast, SL can utilize host-derived hyaluronic acid to increase adherence and invasion, indicating a significant role for hyaluronic acid in SBSEC pathogenesis (16).

5. Biofilm Formation

Bacterial colonization in the GIT depends on its binding to the ECM and biofilm formation. These factors are crucial for the persistence of bacteria in injured or prosthetic heart valves (31). *Streptococcus bovis* contains two types of polysaccharides: (1) water-soluble glucans and (2) capsular polysaccharides (16). Glycosyltransferases (GFT) are responsible for the production of exopolysaccharide (EPS) glucan, thus contributing to biofilm formation (32). Pil1 also appears to play a role in biofilm formation, particularly on exposed collagen I of injured tissue, such as that found in damaged heart valves and colorectal adenomas (33).

Several studies (32) have shown that the SBSEC group isolated from the GIT, blood, and food can produce biofilms; however, the role of biofilm formation in IE is unclear, and the ability to form biofilms is not directly linked to virulence and needs to be carefully evaluated (32, 33).

6. Risk factors of Colorectal Cancer

The geographical diversity in the frequency of CRC strongly suggests the involvement of various risk factors, such as high-fat diets with saturated fats, overweight, diabetes, age above 50 years, smoking, alcoholism, and red meat consumption, particularly in Western countries (34-36). Various studies show that the intestinal microbiota plays an essential role in the origin, development, and metastasis of CRC (36). These investigations have revealed differences in the composition of the intestinal microbiota between patients with CRC and healthy individuals, including which microorganisms are increased or decreased in patients with CRC (36). Some bacteria, such as SBSEC, have also been linked to CRC (37). The association between SBSEC and CRC was first linked to SGG and SGP (34). Close contact with animals and the use of animal feces as plant fertilizers are important risk factors for the presence of SGG in human feces (32).

The association between GDS bacteremia or IE and CRC is well known, and it is recommended that both CRC and IE be excluded in any person diagnosed with GDS bacteremia. However, the extent of the link between GDS fecal carriage and CRC has been debated (38). Inflammation can also be a major risk factor for the progression of CRC and is a potential mechanism

through which bacterial infections may contribute to carcinogenesis. Changes in the colon tissue can compromise the colonic barrier entirely; as a result, certain opportunistic bacteria may infect the colonic tissue and potentially trigger an immune response (37).

7. Invasion and Infection Establishment

CRC development is a complex, multifactorial process that occurs over several years, involving an accumulation of genetic and epigenetic alterations in proto-oncogenes, tumor suppressor genes, and/or DNA repair genes. These changes lead to the transformation of colonic epithelial cells into tumorous structures known as adenocarcinomas (24). Epidemiological research has shown that in CRC patients, colon lesion tissues are infected by *Streptococcus bovis*, even in the early stages of CRC (39). Subspecies *gallolyticus* is more strongly linked to CRC and IE compared to SGP and *Streptococcus infantarius* branch members and is a major cause of endocarditis, an inflammation of the inner layer of the heart called the endocardium (24, 40). Pathogenicity and virulence are associated with several factors, including adhesion, evasion of the immune system, competition, inflammation, invasion, translocation, and cytotoxicity. To date, defined virulence features of SBSEC are generally restricted to adhesion and proinflammatory elements (1).

There are four critical steps for initiating endocarditis from the GIT: Firm attachment to the enterocyte ECM, translocation across the epithelial barrier, evasion of immune cells in the lamina propria, persistence in the bloodstream, and the ability to establish a secondary infection (41).

Binding of SGG to eukaryotic cells is facilitated by ECM proteins in eukaryotic cells, such as collagen, fibronectin, and fibrinogen, along with its ability to adhere through pili and form biofilms (42). Typically, ECM proteins are not freely accessible unless tissue is damaged, such as in imperfect heart valves or colon adenomas (1). The next step is the invasion and translocation of the epithelial barriers (16). The intestinal mucosal barrier in a healthy colonic environment has several protective strategies against bacterial invasion, including an inner water layer, an epithelial outer layer with phospholipids, a mucous gel layer, epithelial cells, subepithelial connective tissue, and capillary endothelium. Goblet cells secrete a mucosal layer into the epithelium to protect it and aid in the transport of gut substances, while enterocytes release antimicrobial peptides, cytokines, and immunoglobulin A. In CRC patients, several alterations occur in this barrier, such as increased tight junction permeability and altered mucus production and composition (16, 41, 43).

Bacteria must then evade the host's immune system. Subspecies *gallolyticus* alters IL-8 and IL-1β gene expression, and epithelial cells are unresponsive to SGG compared to other bowel microorganisms (41). The increase in infection by this bacterium is related to delayed epithelial response following the delayed recruitment of tissue macrophages, which enhances the ability of SGG to enter the bloodstream after translocation of the intestinal wall. The final stage is the survival of bacteria in the bloodstream, infection of the heart endothelium, and endocarditis (41, 44, 45).

The attack by commensal bacteria and their structures activates TLRs on tumor-infiltrating myeloid cells, leading to the activation of the myeloid differentiation factor 88 (MyD88)-facilitated production of inflammatory cytokines, most notably interleukin (IL)-23. IL-23 then induces the production of IL-17A, IL-6, and IL-22, ultimately stimulating tumor cell proliferation by activating nuclear factor-kB (NF-kB) and STAT3 signaling pathways. Additionally, commensal microorganisms and their components similarly upregulate IL-17C in transformed IECs (Intestinal Epithelial Cells) through TLR/MyD88-dependent signaling. IL-17C promotes the production of B-cell lymphoma-2 (Bcl-2) and Bcl-xL in IECs, stimulating tumor cell survival and tumorigenesis (7, 46).

8. Diagnosis

Colorectal cancer is one of the three most prevalent forms of cancer and the second most common cause of cancer-associated mortality worldwide (47). Late-phase detection is the main reason for CRC-related deaths. It is widely believed that the disease burden can be reduced through proper population-based screening approaches that can identify precancerous lesions and early-phase diseases (47). Dysbiosis is a disorder in the composition, structure, or function of the colonic microbiota that disrupts the normal microorganism-host homeostatic association. It remains unclear whether dysbiosis is the result or cause of food-induced inflammation. Limited data are available on the behavior of microorganisms in a complex microbial environment and their changing characteristics in response to nutrition and the host immune response (48, 49).

The intestinal microenvironment of CRC patients is significantly altered compared to that of healthy mucosal environments. Key changes include a marked decrease in glucose and pyruvate levels and an increase in lactate (low pH), amino acids, lipids, and fatty acids. Moreover, the rate of SGG colonization in CRC patients

with a history of bacteremia was significantly higher than in patients without such a history. Additionally, SGG colonization is mostly detected in tumor lesions rather than in the mucosal area (50, 51).

Currently, CRC screening strategies consider colonoscopy the gold standard for identifying morphological changes in the mucosa, with fecal immunochemical testing (FIT) as an initial option (52, 53). Numerous studies have confirmed the association between CRC and the presence of *Streptococcus bovis* in stool samples; therefore, various forms of stool specimens, such as intestinal suction materials, can be used to identify high-risk individuals for advanced colorectal lesions (54). This can serve as a preferred investigative tool as an alternative to repeated colonoscopy in patients who have undergone treatment for advanced colonic lesions by endoscopy or surgical procedures (55). Several investigations have examined intestinal metabolic and genomic factors as markers of CRC. Blood-based methylated Septin9 in DNA is an FDA-approved test for the early detection of CRC, which requires confirmation by colonoscopy (56). Activation of MET, a receptor of hepatocyte growth factor (HGF), is observed in several cancers, including CRC (57). Overexpression of vascular endothelial growth factor (VEGF) has been found in many types of CRC (58).

Based on this information, the IgG fraction obtained from the serum of individuals with early-stage CRC contains antibodies that specifically recognize *Streptococcus bovis* surface antigens (59). IgG against four SGG pili proteins was observed in single and multiplex analyses. The IgG response to Pil1B was the best predictor of tumor presence but did not produce the same response in all IE-infected individuals. Colorectal cancer patients typically responded to only one of the four antigens, with an overall sensitivity of 20 - 43% when combined (16). Specific methods have demonstrated that the HlpA and RpL7/L12 wall antigenic proteins of *SGG* can be used for CRC identification (60). The use of tumor markers such as carcinoembryonic antigen (CEA) may increase in CRC, but they are not definitive for CRC diagnosis. Although levels of tumor markers like CEA can be elevated in CRC, they are used primarily for post-treatment monitoring and surveillance (61).

9. Treatment

Currently, surgery, chemotherapy, and radiotherapy are the standard treatments for CRC. Depending on the location and progression of the disease, these treatments can be used in combination. Laparoscopic resection of CRC has been shown to be as effective as open surgical procedures; however, it is not always possible to remove all malignant cells. Most patients in stages II and III undergo additional treatments, which can have various side effects. Immunotherapy is an alternative cancer treatment that utilizes the patient's immune system to target malignant cells (61). Research has demonstrated that alterations in the gut microbiota and its metabolism can affect the efficacy of immunotherapy and chemotherapy in CRC (62). Nutritional interventions, increased physical activity, aspirin, and NSAIDs can be used to regulate the intestinal microbiota in patients receiving cancer treatment. A higher intake of foods such as fiber, omega-3 fatty acids, vitamin D, coffee, or a plant-based diet has been associated with improved survival rates in CRC patients (63).

Antibiotic therapy is a common approach used to eliminate carcinogenic microorganisms in animal models, but it can potentially exacerbate dysbiosis and increase susceptibility to invasive bacteria (64). Monoclonal antibodies (mAbs) were developed using the hybridoma technique and phage display *in vitro*. mAbs can recognize and bind to tumor-specific antigens (TSA) or tumor-associated antigens (TAA). Cetuximab is an example of an FDA-approved chimeric mAb used in the treatment of CRC (65).

10. Conclusions

The development of CRC in individuals depends on several factors, with increasing evidence suggesting that the intestinal microbiome may play a significant role. Although the incidence and mortality rates of CRC have declined over the past decades, epidemiological studies suggest that the frequency of CRC will rise in individuals under 50 years of age. Nutrition, dietary habits, physical activity, and other lifestyle changes have been shown to be linked to the pathogenesis of CRC. For many years, clinical studies have strongly associated the presence of SGG with CRC. While it is not consistently found in association with cancers in microbiome studies, it may have increased colonization levels at tumor sites. A potential tumor-promoting capability of SGG may alter its microenvironment, further emphasizing its association with tumor locations. Elevated immune responses to SGG in CRC patients suggest a strong link with these sites.

Therefore, more rapid and affordable bacterial tests are needed to facilitate the integration of the intestinal microbiome into routine clinical practice. Additional assessments could also be used to evaluate the incidence of bacteremia related to intestinal microorganisms and subsequent CRC diagnosis.

Footnotes

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