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## ***Streptococcus bovis/gallolyticus* Induce the Development of Colorectal Cancer**

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### **1. Introduction**

The role, of microbial agents and the infection of the intestinal mucosa in the carcinogenesis, or the development of colorectal cancer (CRC) is one of the hot topics in the field of CRC where much research has been done. However, this topic has long been underestimated by most of the related books. This chapter is intended to cover the relationship of CRC development with bacteria implicated in the development of CRC such as *S. bovis*, *S. gallolyticus*, *S. equines*, *S. infantarius*, *E. coli*, *C. difficile*...etc. However, *S. gallolyticus* and *S. bovis* will be discussed thoroughly in this chapter as they are considered the prototype for intestinal microorganisms related to CRC and colorectal premalignant lesions.

Studying CRC association with infection of intestinal mucosa is not complete without studying the underlying mechanisms. There is compelling evidence that CRC is largely affected by the status of intestinal bioflora. CRC has been found to be affected by certain microbial agents that have particular characteristics capable of inducing dysplastic changes in intestinal mucosa. However, the underlying mechanisms of the association of implicated infective agents with CRC development are yet not clear. In addition, the role of oncogenic factors, cell growth factors, and pro-inflammatory cytokines in the association of bacterial infection in intestinal mucosa with CRC has not yet been clarified well. Therefore, the current chapter attempts to scrutinize the nature and the underlying mechanisms of the association of infective agents represented by *S. bovis/gallolyticus* with CRC. Nevertheless, the association of *S. bovis/gallolyticus* with CRC is still under controversy regarding whether the bacterial infection of intestine, along with associated bacteremia/endocarditis, is a consequence or the etiological factor of CRC. Hence, this chapter also attempts to explore the facts available in the field to assess which scenario is more favorable for the association of *S. bovis/gallolyticus* with CRC namely, the consequence or the etiology scenario.

One of the bacterial agents that have been most associated with cancer is *Streptococcus bovis* (*S. bovis*). *S. bovis* has been shown to be important in human health because 25 to 80% of patients with *S. bovis* bacteremia had also colorectal tumor, and the incidence of association of colonic neoplasia with *S. bovis* endocarditis was shown to be 18 to 62% (Gupta et al., 2009; Kok et al., 2007; Leport et al., 1987; Malkin et al., 2008; Reynolds et al., 1983; Wilson et al.,

1981; Zarkin et al., 1990). Later, it was shown that a new species resembling *S. bovis* is actually most implicated in CRC development; *S. bovis* infecting human intestine has been named as *S. gallolyticus* (Osawa et al., 1995). More precisely, *S. bovis* biotype I and II/2 isolates were shown to be *S. gallolyticus* (Devriese et al., 1998). Accordingly, *S. bovis* biotype I was replaced by *S. gallolyticus* subspecies *gallolyticus* and biotype II/2 was replaced by *S. gallolyticus* subspecies *pasterianus* and *S. gallolyticus* subspecies *macedonicus* (Schlegel et al., 2003). *S. gallolyticus* subspecies *gallolyticus*, rather than other related taxa, have been found to be constantly associated with underlying colorectal cancer.

## 2. The association of colorectal cancer with *S. bovis/gallolyticus* bacteremia/endocarditis

*S. bovis*, has long been linked to the development of CRC. However, the extent, nature, and basis of this association are still not completely understood. *S. bovis/gallolyticus* became important in human health since it was shown that 25 to 80% of patients who presented *S. bovis/gallolyticus* bacteremia had also a colorectal tumor and the incidence of association of colonic neoplasia with *S. bovis/gallolyticus* endocarditis was shown to be 18 to 62% (Gupta et al., 2009; Kok et al., 2007; Leport et al., 1987; Malkin et al., 2008; Murray & Roberts, 1978; Reynolds et al., 1983; Wilson et al., 1981; Zarkin et al., 1990). The knowledge that there is an association between endocarditis from *S. bovis/gallolyticus* and carcinoma of the colon has important clinical implications (Boleij et al., 2009a; Kok et al., 2007). The majority of the studies that found clues on the association of *S. bovis/gallolyticus* with CRC was in Europe and North America. Actually, it is true that the association of *S. bovis/gallolyticus* bacteremia with colorectal cancer has been found variable among different geographical and ethnic groups (Boleij et al., 2009a), but this association is not restricted to certain geographical region. A recent study done in Malaysia found that 48.6% of *S. bovis* isolates was found in patients with colonic polyps, adenocarcinomas, inflammatory bowel diseases. It was also found that colorectal cancer incidence was 24.7%, adenocarcinomas accounting for 51% with the highest incidence in the sigmoid part of the colon (Al-Jashamy et al., 2010). This study indicates a strong relationship between *S. bovis/gallolyticus* and colonic premalignant as well as malignant lesions in a geographical region that was considered of low incidence for CRC cases associated with bacterial infections. Moreover, an epidemiological study conducted in Hong Kong on *S. bovis* bacteremia and its relation to colorectal cancer, confirmed the association of *S. bovis/gallolyticus* with CRC and found that *S. bovis* biotype II/2 is the dominant in Hong Kong rather than biotype I (*S. gallolyticus*) which is dominant in Western countries (Lee et al., 2003).

Thorough studies on *S. bovis* have shown that associations between *S. bovis* bacteraemia and carcinoma of the colon and infective endocarditis were biotype-specific. It was shown that there is 94% association between *S. bovis* biotype I bacteraemia and infective endocarditis and 71% association between *S. bovis* biotype I bacteraemia and colonic carcinoma. On the other hand, it is only 18% association between *S. bovis* biotype II bacteraemia and infective endocarditis and 17% association between *S. bovis* biotype II bacteraemia and colonic carcinoma (Murray & Baron, 2007). Following the description of *S. gallolyticus*, Devriese team used whole-cell protein analysis to show that all six bacterial isolates studied, which were derived from patients with endocarditis and identified by conventional techniques as *S. bovis*, were in fact *S. gallolyticus*. Therefore, they suggested that *S. gallolyticus* is more likely to be involved in human infections than is *S. bovis* (Devriese et al., 1998).

The underlying mechanisms for the association of CRC with *S. bovis/gallolyticus* bacteremia/endocarditis have been obscure for a long time. The possible reason behind that, maybe, *S. bovis/gallolyticus* is a member of intestinal flora in 2.5 to 15% of individuals which usually make scientists counteract any malicious role of this bacteria (Burns et al., 1985; Murray & Roberts, 1978). It was conceived in the beginning that the ulceration of neoplastic lesions might form a pathway for the microorganism to enter the bloodstream (Gupta et al., 2009). However, the latter scenario of bacterial access into the circulation does not explain the cases of patients with infectious endocarditis and non-ulcerated colonic polyps (Cutait et al., 1988). Furthermore, colonic neoplasia may arise years after the presentation of the condition of bacterial bacteremia or infectious endocarditis (Fagundes et al., 2000; Zarkin et al., 1990). For this reason, patients with infectious endocarditis and normal colonoscopy may be included in the group who present risk for developing colonic cancer because of the late appearance of such lesions after the infectious episode of *S. bovis/gallolyticus* (Fagundes et al., 2000). Moreover, in supporting the second scenario, it has been shown that the relative risk of developing infectious endocarditis from *S. bovis/gallolyticus* in the presence of carcinoma of the colon is merely 3 to 6% (Bisno & 12.ed. New York: , 1991) while 60 to 75% of patients with endocarditis by *S. bovis/gallolyticus* simultaneously present malignant gastrointestinal disease that was not previously diagnosed (Grinberg et al., 1990).

### **3. The association of premalignant colorectal lesions with *S. bovis/gallolyticus***

There is a high incidence of colorectal cancer in individuals with polyps; about 90% of preinvasive neoplastic lesions of the colorectum are polyps or polyp precursors, namely aberrant crypt foci (Nielsen et al., 2007). Neoplastic polyps are often referred to more specifically as adenomas or adenomatous polyps (Srivastava et al., 2001). Adenomatous polyps are considered as good and few surrogate end point markers for colorectal cancer (Kelly et al., 1989; Nielsen et al., 2007).

It would be of interest to substantiate any relationship between bacterial colonic carriage, colonic polyps and the type of polyp and its malignant potential (Boleij et al., 2009a; Schlegel et al., 2003). Contrary to the more commonly reported association between *S. bovis/gallolyticus* bacteremia and colorectal cancer, a link to pre-neoplastic adenomatous polyps was less frequently reported (Burns et al., 1985; Ellmerich et al., 2000a). Nevertheless, the relationship between colorectal bacterial infection and the progressive development of malignant disease in pre-neoplastic adenomatous polyps was supported by recent reports (Abdulmir et al., 2009; Kahveci et al., 2010; Murinello et al., 2006). Interestingly, benign lesions (diverticulosis, inflammatory bowel disease, cecal volvulus, perirectal abscess hemorrhoids, benign polyps) were found to be mildly associated with intestinal bacterial infections such as *S. bovis/gallolyticus* while a strong relationship between more malignant diseases of the colon (cancer and neoplastic polyps) and *S. bovis/gallolyticus* was found (Abdulmir et al., 2009; Burns et al., 1985; Klein et al., 1979; Nielsen et al., 2007; Reynolds et al., 1983; Smaali et al., 2008). It was also revealed that *S. bovis/gallolyticus* septicemia and/or endocarditis is selectively related to the presence of villous or tubulovillous adenomas in the large intestine (Fagundes et al., 2000; Smaali et al., 2008). In fact, Villous and tubulovillous adenomas, which have risk of malignant transformation about 15-25%, were found to be associated with *S. bovis/gallolyticus* bacteria more often than other types of adenomas (Bond, 2005). For example, Hoen team performed a case-control study on subjects underwent

colonoscopy comparing between patients with *S. bovis/gallolyticus* endocarditis and sex- and age- matched unaffected patients. This study showed that colonic adenomatous polyps were present in twice as many cases as controls (15 of 32 *vs* 15 of 64), and colorectal cancer was present approximately 3 times as often (3 of 32 *vs* 2 of 64) (Hoen et al., 1994). However, surprisingly, another study (Devis et al., 1989) found that the association between *S. bovis/gallolyticus* and adenoma was more evident than that with colorectal cancer; they reported that 36% of positive blood cultures of *S. bovis/gallolyticus* were found in proliferative lesions (15% of cancers and 21% of adenomas). A recent study (Abdulmir et al., 2009) supported this concept showing that the level of *S. bovis/gallolyticus* IgG antibodies in adenoma patients is much higher than in both colorectal cancer patients and control subjects. However, other reports did not reveal the same thing. (Burns et al., 1985) stated that the incidence of *S. bovis/gallolyticus* carriage in all colons with polyps was intermediary between normal colons and colons with carcinoma although the difference did not achieve statistical significance.

Regarding the fecal carriage of *S. bovis/gallolyticus*, (Burns et al., 1985) demonstrated that highly premalignant polyps were found to be more often associated with *S. bovis/gallolyticus* carriage than were benign polyps. A clue for the active role of intestinal bacteria in the development of CRC, *S. bovis/gallolyticus* endocarditis, rather than other members of group D Streptococcus, showed special predilection to colonic lesions. It was found that of 77 infections with group D Streptococcus endocarditis, colonic polyps and colonic carcinoma were significantly more frequent in the *S. bovis/gallolyticus* group (67 and 18%) respectively than in the Enterococcus group (21 and 2%) respectively (Leport et al., 1987). This indicates that certain bacteria have role in the etiology of CRC development from premalignant poly lesions.

The remarkable association between adenomatous polyps and *S. bovis/gallolyticus* seems to be of importance due to the compelling evidence that colon cancer progresses from normal tissue to adenoma and then to carcinoma through an accumulation of genetic alterations (Baron & Sandler, 2000). Although ulceration of the neoplastic lesion might form a pathway for the *S. bovis/gallolyticus* to enter the bloodstream (Gupta et al., 2009), the association of *S. bovis/gallolyticus* bacteremia with non-ulcerated colonic polyps indicates an etiological/promoter role of these bacteria in polyps progression (Cutait et al., 1988; Konda & Duffy, 2008). The possibility of *S. bovis/gallolyticus* to act as a promoter for the preneoplastic lesions is worthy to be considered. A remarkable study supported this hypothesis using rats treated with *S. bovis* wall extracted antigens (WEA), rats treated with a chemical carcinogen, rats treated with both WEA and chemical carcinogen, and untreated rats. All groups of rats did not develop hyperplastic colonic crypts except for the group treated with both WEA and the chemical carcinogen; about 50 % rats of this group developed neoplastic lesions (Ellmerich et al., 2000a). This indicated that *S. bovis* bacteria might exert their pathological activity in the colonic mucosa only when preneoplastic lesions are established. Another model supporting the promoter effect of *S. bovis/gallolyticus*, *H. pylori* infection and subsequent inflammation seem most likely to be promoters in the multistep development of carcinoma (from chronic gastritis to atrophy, intestinal metaplasia, dysplasia, and, ultimately, cancer) rather than the causative agents (Leung, 2006). Therefore, the association of *S. bovis/gallolyticus* in etiology and/or acceleration of the transformation of aberrant crypts to adenoma and to cancer is now being reconsidered.



Accordingly, the knowledge of association of colorectal adenoma with *S. bovis/gallolyticus* has important clinical implications. If the lesion can be discovered at an early stage, curative resection may become possible (Waisberg et al., 2002). Thus, bacteremia due to *S. bovis/gallolyticus* should prompt rigorous investigation to exclude both endocarditis and tumors of the large bowel (Beeching et al., 1985; Konda & Duffy, 2008). Therefore, it was concluded that the discovery of a malignant or premalignant proliferative lesion in one third of the cases justifies the exploration of the colon by barium enema and/or colonoscopy in the case of *S. bovis/gallolyticus* septicemia (Beeching et al., 1985; Konda & Duffy, 2008). This would empirically aid for the early detection of adenoma in the gastrointestinal tract before its progression to cancer.

#### **4. The proposed mechanisms for the development of colorectal cancer by *S. bovis/gallolyticus***

Chronic inflammation is associated with malignant changes. Host genetic polymorphisms of the adaptive and innate immune response play an important role in bacteria-induced cancer formation (El-Omar, 2006; Hou et al., 2007; Karin & Greten, 2005). Therefore, studying the immunological responses to chronic bacterial infections is likely to yield important clues on both the mechanisms of persistent infection and the relationship between inflammation and cancer formation (Ernst et al., 2006; Monack et al., 2004). Clinical studies have shown that the use of non-steroidal anti-inflammatory drugs is associated with a reduced risk of gastric cancer (Dai & Wang, 2006). However, bacteria implicated in carcinogenesis, like *S. bovis/gallolyticus*, might use several mechanisms for carcinogenesis such as the colonization of epithelial surfaces and the use of virulence factors to chronically affect host cell cycle control, apoptosis, cell junction integrity or cell polarity ((Vogelmann & Amieva, 2007).

##### **4.1 Clues for etiological role**

The big question is whether bacteria play an etiological role in the carcinoma of colon or it is merely marker of the disease. There are many clues collectively provide evidence for the etiological role of bacteria in colon cancer development. The striking association between bacteremia caused by *S. bovis* biotype I and both colonic neoplasia (71%) and bacterial endocarditis (94%), rather than bacteremia caused by closely related organisms such as *S. bovis* variant and *S. salivarius*, suggests the possibility of specific bacterium-host interactions (Ruoff et al., 1989). Moreover, the appearance of new colonic lesions 2-4 after the incidence of *S. bovis/gallolyticus* bacteremia/endocarditis, provides more evidence that *S. bovis/gallolyticus* is not merely a consequence of the tumor lesion (Wentling et al., 2006). In terms of pathogenesis, as *S. bovis/gallolyticus* is a transient normal flora in the gut, researchers have postulated that the increased bacterial load of *S. bovis/gallolyticus* in colon might be responsible for its association with colon cancer. Several studies have shown that increased stool carriage of *S. bovis/gallolyticus* is particularly found in patients with inflammatory bowel diseases or malignant/premalignant lesions of the colon while *S. bovis/gallolyticus* bacteria were rarely isolated from normal subjects (Teitelbaum & Triantafyllopoulou, 2006). Another clue supporting the etiological role of *S. bovis/gallolyticus*, patients diagnosed with colon cancer have only 3-6% chance to develop *S. bovis/gallolyticus* endocarditis (zur Hausen, 2006), which is far lower than the percentage of the detection of

colorectal cancer in patients with *S. bovis/gallolyticus* bacteremia/endocarditis, which is more than 70%.

## **4.2 Mechanisms of the proposed etiological role of *S. bovis/gallolyticus* in the development of colorectal cancer**

### **4.2.1 Selective adherence to intestinal tumor cells**

Some bacteria such as *S. bovis/gallolyticus* are frequent colonizers of the intestinal tract, which can also cause endocarditis. However, their ability to adhere to and colonize host tissues is largely unknown. It was found that *S. bovis/gallolyticus* bacteria possess collagen-binding proteins and pili that are responsible for adhesion to colorectal mucosa as well as to endocardium (Sillanpaa et al., 2009). On the other hand, another study (Boleij et al., 2009b) found a histone-like protein A on the surface of *S. bovis/gallolyticus* able to bind heparan sulfate proteoglycans at the colon tumor cell surface during the first stages of infection; this cell surface protein in *S. gallolyticus* acts as one of the main heparin-binding proteins that is largely responsible for bacteria selective adhesive potential as well as entry to the blood circulation. Another study assessing 17 endocarditis-derived human isolates, identified 15 *S. gallolyticus* subspecies *gallolyticus*, one *S. gallolyticus* subspecies *pasteurianus* (biotype II/2) and one *S. infantarius* subspecies *coli* (biotype II/1) for their in vitro adherence to components of the extracellular matrix; this study provided evidence that *S. gallolyticus* subspecies *gallolyticus* bacteria possess very efficient adherence characteristics to the host extracellular matrix; this bacteria showed powerful adherence to collagen type I and type IV, fibrinogen, collagen type V, and fibronectin (Sillanpaa et al., 2008). These adherence merits render these bacteria successful colonizers in both intestinal and cardiac tissues which might explain the association between *S. bovis/gallolyticus* endocarditis and intestinal lesions.

### **4.2.2 Changing the intestinal bacterial flora and alterations in the local vascular attributes**

Increased incidence of hepatic dysfunction has been reported in patients with bacterial infectious endocarditis (Fagundes et al., 2000). It has been speculated that *S. bovis/gallolyticus* affects portal circulation through bacterial translocation, thereby determining hepatic alterations. Modifications in the hepatic secretion of bile salts and the production of immunoglobulins contribute towards increasing the participation of *S. bovis/gallolyticus* in abnormal changes in the bacterial flora of the colonic lumen which might then promote carcinogenesis of the intestinal mucosa (Beeching et al., 1985; Gupta et al., 2009).

It has been suggested that alterations in local conditions and disruption of capillary channels at the site of neoplasm allowed *S. bovis/gallolyticus* to proliferate and gain entry into blood stream (Biarc et al., 2004; Ellmerich et al., 2000a; Nguyen et al., 2006). The local action of cytokines or of chemical mediators able to promote vasodilatation and the enhancement of capillary permeability, may support the bacterial entry at tumor sites, and increase bacterial adherence to various cells (Biarc et al., 2004; Ellmerich et al., 2000b).

### **4.2.3 Promoting/propagating effect on preneoplastic lesions and inflammation-driven carcinogenesis**

A series of interesting experiments was conducted for investigating the role of *S. bovis/gallolyticus* in the initiation and development of colorectal cancer. Chemical carcinomas

were induced by giving adult rats intraperitoneal injections of azoxymethane (15 mg/kg body weight) once per week for 2 weeks. Fifteen days (week 4) after the last injection of the carcinogen, the rats received, by gavage twice per week during 5 weeks, either *S. bovis* ( $10^{10}$  bacteria) or wall-extracted antigens (WEAs) (100 µg). One week after the last gavage (week 10), it was found that administration of either *S. bovis* or its antigens promoted the progression of preneoplastic lesions into neoplastic lesions through the increased formation of hyperproliferative aberrant colonic crypts, which enhanced the expression of proliferation markers and increased the production of IL-8 in the colonic mucosa (Biarc et al., 2004; Ellmerich et al., 2000b). Therefore, this study suggests that *S. bovis/gallolyticus* bacteria act as potential promoters of early preneoplastic lesions in the colon of rats, and their cell wall proteins are more potent inducers of neoplastic transformation than the intact bacteria. This study also revealed that the development of colonic adenomas increased remarkably in 50% of the tested rats and the expression level of proliferation markers, the polyamine content and proliferating cell nuclear antigen was also increased (Biarc et al., 2004; Ellmerich et al., 2000a; Nguyen et al., 2006). This provided extra evidence that *S. bovis/gallolyticus* acts more likely as promoter/propagator of colorectal carcinoma rather than just a consequence of the tumor lesion. These studies might suggest that bacteria, in general, are often not capable to induce cancer without the presence of other predisposing factors for carcinogenesis. In this regard, it was conceived that the transformation process of colorectal tumors associated with *S. bovis/gallolyticus* is more likely accompanied with long-lasting bacterial promoting/propagating effect along with chronic inflammation status in intestinal mucosa. This conclusion was supported by Balkwill et al. stating that tumor formation might require independent mutations in oncogenic signaling pathways in addition to chronic inflammatory conditions which are needed to promote transformation process (Balkwill et al., 2005).

*In vitro* experiments showed that the binding of *S. bovis* wall extracted antigens to various cell lines including human colonic cancer cells (Caco-2) stimulated the production of inflammatory cytokines by those cells (Biarc et al., 2004; Nguyen et al., 2006). Earlier it was found that the production of inflammatory cytokines in response to *S. bovis/gallolyticus*, such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6, and the chemokine IL-8, were found to contribute to the normal defense mechanisms of the host (Ellmerich et al., 2000b; Travers & Rosen, 1997) leading to the formation of nitric oxide and free radicals such as superoxide, peroxy nitrates, hydroxyl radicals as well as alkylperoxy radicals (Nguyen et al., 2006; Ohshima & Bartsch, 1994). Owing to their potent mutagenicity, all these molecular species can contribute to the neoplastic processes by modifying cellular DNA. On the other hand, in the colonic mucosa, the production of angiogenic factors, such as IL-8, triggered by *S. bovis/gallolyticus* antigens may also favor the progression of colon carcinogenesis (Eisma et al., 1999; Ellmerich et al., 2000b; Norrby, 1996). This resembles *H. pylori* infection for the development of chronic inflammation in the gastric mucosa (Dixon et al., 1996); therefore, it seems that chronic infection and subsequent chronic inflammation are responsible for the maintenance and development of pre-existing neoplastic lesions (Shacter & Weitzman, 2002).

Moreover, it was found that WEAs of *S. bovis* induced *in vitro* overexpression of cyclooxygenase-2 (COX-2) (Biarc et al., 2004; Nguyen et al., 2006). COX-2, via prostaglandins, promotes cellular proliferation and angiogenesis and inhibits apoptosis, thus acting as a promoter in the cancer pathway (Tafte & Ruoff, 2007). It is noteworthy to mention that non-steroidal anti-inflammatory drugs (NSAIDs) were found to decrease the relative risk of gastrointestinal carcinomas and their main target was found to be



cyclooxygenase 2 (COX-2) that is over-expressed in up to 85% of colorectal adenocarcinomas (Kargman et al., 1995). Moreover, (Haqqani et al., 2000) revealed that the activation of leukocytes by *S. bovis/gallolyticus* was found to release various other inflammatory mediators (NO, free radicals, peroxy nitriles, etc.) which could interfere directly or indirectly with the cell proliferation process. A recent study conducted by our team, *S. gallolyticus* has shown a specific association with colorectal cancer and colorectal adenoma when compared with the more dominant intestinal bacteria, *B. fragilis*. This provided evidence for a possible important role of *S. gallolyticus* in the carcinogenesis of colorectal cancer from pre-malignant polyps. In addition, it was also found that NF- $\kappa$ B and IL-8 rather than other transformation factors p21, p27 and p53 act as important mediators for the *S. gallolyticus*-associated transformation of adenoma to carcinoma (Abdulmir et al., 2009). Moreover, it was concluded that NF- $\kappa$ B exerts most probably a promoting carcinogenic effect and IL-8 exerts mainly an angiogenic-based propagating effect on colorectal mucosal cells (Abdulmir et al., 2009). In addition, a more recent study done by our team showed a direct and active role of *S. bovis/gallolyticus* in colorectal cancer development through inflammation-based sequel of tumor development or propagation via IL-1, COX-2, and IL-8 (Abdulmir et al., 2010). By these studies, a strong relationship was shown to be evident between the proinflammatory potential of *S. bovis/gallolyticus* bacteria and their carcinogenic properties confirming the linkage between inflammation and colon carcinogenesis.

In the presence of WEAs proteins of *S. bovis/gallolyticus*, Caco-2 cells exhibited enhanced phosphorylation of 3 classes of mitogen activated protein kinases (MAPKs) (Biarc et al., 2004). Several reports showed that MAPKs activation stimulates cells to undergo DNA synthesis and cellular uncontrolled proliferation (Hirata et al., 2001; Ihler, 1996; Smith & Lawson, 2001). Therefore *S. bovis/gallolyticus* proteins could promote cell proliferation by triggering MAPKs which might increase the incidence of cell transformation and the rate of genetic mutations. Furthermore MAPKs, particularly p38 MAPK, can induce COX-2 which is an important factor in tumorigenesis (Lasa et al., 2002; Wang & Dubois, 2010) and up-regulate the expression of NF $\kappa$ B which is considered the central link between inflammation and carcinogenesis (Karin & Greten, 2005). Accordingly, the pro-inflammatory potential of *S. bovis/gallolyticus* proteins and their pro-carcinogenic properties as well as the chronic inflammation and the leucocytic recruitment driven by *S. bovis/gallolyticus* provide strong evidence on the possible causal link between *S. bovis/gallolyticus* inflammation and colonic carcinogenesis. Therefore, the above data support the hypothesis that colonic bacteria can contribute to cancer development particularly via chronic infection/inflammation where bacterial components may interfere with cell function for long time (Biarc et al., 2004; Wang & Dubois, 2010).

## 5. Selective colonization of *S. bovis/gallolyticus* in colorectal mucosa

The association of bacteria with colorectal cancer has always been described through the incidence of *S. bovis/gallolyticus* bacteremia and/or endocarditis (Leport et al., 1987; Murray & Roberts, 1978; Reynolds et al., 1983; Wilson et al., 1981; Zarkin et al., 1990). On the other hand, little bacteriological research has been done on elucidating the colonization of *S. bovis/gallolyticus* in tumor lesions of colorectal cancer in order to confirm or refute, on solid bases, the direct link between colorectal cancer and *S. bovis/gallolyticus* (Norfleet & Mitchell, 1993; Potter et al., 1998). A recent study of by our team was conducted to assess the colonization of *S. bovis/gallolyticus* bacteria in colon by detecting *S. bovis/gallolyticus* DNA in

colorectal cancer tumors using advanced molecular assays (Abdulmir et al., 2010). In Abdulmir et al. study, *S. bovis/gallolyticus*-specific primers and probes were used in PCR and in situ hybridization (ISH) assays, respectively, to detect *S. bovis/gallolyticus* DNA from feces, tumor mucosal surfaces, and from the inside of tumor lesions. In addition, bacteriological isolation of *S. bovis/gallolyticus* was conducted to isolate *S. bovis/gallolyticus* cells from feces, tumor mucosal surfaces, and from the inside of tumor lesions. In this study, *S. bovis/gallolyticus* was successfully isolated, via bacteriological assays, from tumorous and non-tumorous tissues, of colorectal cancer patients with bacteremia, 20.5% and 17.3%, and of colorectal cancer patients without bacteremia, 12.8% and 11.5%, respectively while only 2% of control tissues revealed colonization of *S. bovis/gallolyticus*.

On the other hand, the positive detection of *S. bovis/gallolyticus* DNA, via PCR, in tumorous and non-tumorous tissues of colorectal cancer patients with bacteremia, 48.7 and 35.9%, and without bacteremia, 32.7 and 23%, respectively, was remarkably higher than that in control tissues, 4%. And the positive detection of *S. bovis/gallolyticus* DNA, via ISH, in tumorous and non-tumorous tissues of colorectal cancer patients with bacteremia, 46.1 and 30.7%, and without bacteremia 28.8 and 17.3%, respectively was remarkably higher than that in control tissues, 2%. In addition, by using absolute quantitative PCR for *S. bovis/gallolyticus* DNA, the *S. bovis/gallolyticus* count, in terms of copy number (CN), in tumorous and non-tumorous tissues of colorectal cancer patients with bacteremia, 2.96-4.72 and 1.29-2.81 log<sub>10</sub> CN/g, respectively, and colorectal cancer patients without bacteremia, 2.16-2.92 and 0.67-2.07 log<sub>10</sub> CN/g, respectively, showed significantly higher level of colonization in tumorous than in non-tumorous tissues and in colorectal cancer patients with bacteremia than in colorectal cancer patients without bacteremia. Accordingly, this study provided several new observations. First, *S. bovis/gallolyticus* colonizes selectively tumorous tissues of colorectal cancer patients rather than normal mucosal tissues. Second, the colonization of *S. bovis/gallolyticus* is mainly found inside tumor lesions rather than on mucosal surfaces of tumors. Third, the titer of the colonizing *S. bovis/gallolyticus* bacteria in colorectal cancer patients with bacteremia/endocarditis was much higher than in patients without bacteremia/endocarditis; this explains why some colorectal cancer patients develop concomitant bacteremia of *S. bovis/endocarditis* while others do not. Actually, the newly discovered selective colonization of *S. bovis/gallolyticus* explains the conclusions of an earlier report (Tjalsma et al., 2006) stating that colonic lesions provide a suitable microenvironment for *S. bovis/gallolyticus* colonization resulting in silent tumor-associated infections that only become apparent when cancer patients become immunocompromised, as in bacteraemia, or have coincidental cardiac valve lesions and develop endocarditis.

## 6. Using *S. bovis/gallolyticus* in the early detection of colorectal tumors

For a long time, it has been conceived that there is a need to establish a good screening test for colonic cancer patients, particularly a test which could detect early lesions. It has been suggested that the presence of antibodies to certain bacterial antigens or the presence of certain bacterial antigens in the bloodstream may act as markers for carcinogenesis of the colon (Beeching et al., 1985; Potter et al., 1998). The serology-based detection of colorectal cancer has advantage on other tests such as fecal occult blood which is neither sensitive nor specific or carcinoembryonic antigen which is regularly detectable in only advanced diseases (Tafte & Ruoff, 2007). Darjee and Gibb stated that it might be possible to develop a

test to screen patients for the presence of colonic cancer by measuring IgG antibody titer of *S. bovis/gallolyticus* (Darjee & Gibb, 1993). Hence, since the association between slow evolving bacterial inflammation and colorectal cancer takes long time, it is prudent to seek specifically for IgG antibodies. Furthermore, IgG antibodies reflect an image of the past and the chronic presence of *S. bovis/gallolyticus* antigens in the circulation.

Some studies showed the possibility of constructing a serology test for the successful detection of colonic cancer based on the detection of antibody to *S. bovis/gallolyticus* or *Enterococcus faecalis* (Abdulmir et al., 2009; Groves, 1997). Therefore, a simple ELISA test with no more than 2 ml of patient's blood might be a good candidate for screening high risk individuals for the presence of premalignant neoplastic polyps, adenomas, and cancers. However, some other studies of antibody response to *S. bovis/gallolyticus* and other streptococci have found that antibody is detectable in endocarditis but not in either clinically insignificant bacteremias (Burnie et al., 1987), or colonic cancers ((Kaplan et al., 1983) by using immunoblotting, immunofluorescence and other techniques. In a recent study of our team (Abdulmir et al., 2009), the serum level of IgG antibodies against *S. gallolyticus* subspecies *gallolyticus* antigens adsorbed on solid phase of ELISA was found to be significantly higher in colorectal cancer patients than in control subjects. This is in full agreement with the study of (Darjee & Gibb, 1993) who showed that patients with colonic cancer had higher median IgG antibody titers to *S. bovis* and *E. faecalis* preparations than did the control samples. Accordingly, the applicability of using ELISA as a cheap and effective assay for the early detection of colorectal cancer using IgG antibodies against *S. bovis/gallolyticus* has been tested and proven (Abdulmir et al., 2009). Therefore, the early detection of colorectal cancer using simple means of testing opens doors to monitor high risk groups of colorectal cancer more efficiently.

## 7. Conclusions

Colorectal tumors, adenoma or carcinoma, are associated remarkably with bacterial infections of intestine. The manifestation of this association is usually observed as concurrent bacteremia or endocarditis of *S. bovis/gallolyticus*. The association of *S. bovis/gallolyticus* bacteria with colorectal cancer is more likely etiological in nature rather than a consequence of the disease. The proposed etiological role of *S. bovis/gallolyticus* in the development of colorectal cancer might be attributed to many factors including selective adhesion potential of *S. bovis/gallolyticus* to tumor tissues, the selective colonization of *S. bovis/gallolyticus* inside tumor tissues, the suitable microenvironment of tumors for *S. bovis/gallolyticus* proliferation, the local disruption of tumor tissues and capillaries which allow the entry of *S. bovis/gallolyticus* into blood circulation leading to bacteremia and endocarditis, and the bacterially-induced cytokines and transcriptional factors, such as IL-1, IFN- $\gamma$ , IL-8, and NFkB, which induce and propagate the chronic inflammatory environment which promote/propagate premalignant intestinal lesions to malignant ones. This is a very important role of *S. bovis/gallolyticus* in the carcinogenesis of colorectal tissues since the majority of cases of colorectal cancer are sporadic cancers arising through the transformation of normal colorectal tissues to premalignant lesions, adenomas, and finally to malignant tissues. Besides, the early detection of colorectal adenomas or carcinomas via detection of *S. bovis/gallolyticus* DNA or their specific IgG antibodies might be of high value in screening the high risk groups for colorectal cancer. More in-depth research is needed to

exploit the association of bacteria with colorectal cancer in terms of early diagnosis of the disease as well as understanding the bacterial carcinogenic potential to determine the appropriate means to prevent and/or treat bacterially-associated cancers.

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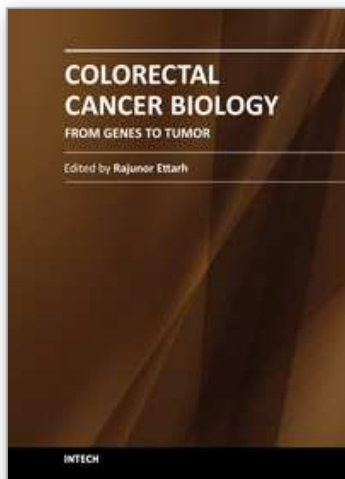
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Colorectal cancer is a common disease, affecting millions worldwide and represents a global health problem. Effective therapeutic solutions and control measures for the disease will come from the collective research efforts of clinicians and scientists worldwide. This book presents the current status of the strides being made to understand the fundamental scientific basis of colorectal cancer. It provides contributions from scientists, clinicians and investigators from 20 different countries. The four sections of this volume examine the evidence and data in relation to genes and various polymorphisms, tumor microenvironment and infections associated with colorectal cancer. An increasingly better appreciation of the complex inter-connected basic biology of colorectal cancer will translate into effective measures for management and treatment of the disease. Research scientists and investigators as well as clinicians searching for a good understanding of the disease will find this book useful.

### **How to reference**

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