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Consequences of Chronic Bacterial Infections on Development of Cancer

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ABSTRACT

There is increasing evidence on the association of chronic bacterial infections with development of various types of cancers. Bacterial infections are involved in the processes and mechanisms leading to chronic inflammations, these are shown to cause molecular genomic damage and alterations which lead to transformation of normal cells to malignant cells. Moreover carcinogenic bacterial metabolites and toxins were found associated with development of various types of cancers. Furthermore recent findings are relating specific bacterial infections and inflammations with aberration of genomic DNA methylation. This article reviews various aspects which link chronic bacterial infections with chronic inflammations, development of cancers and their influence on aberration of genomic DNA methylation.

Key words: Bacterial infections, inflammations, cancer, DNA methylation

INTRODUCTION

Considerable number of pathogens have been linked to cancer development, it is has been reported that malignancies can be attributed to microbial infections in the range 15 to 25% in developing countries and 7 to 10% in developed countries with an overall worldwide average between 11 to 17.5% (Pisani *et al*., 1997; Kuper *et al*., 2000; Schottenfeld and Beebe-Dimmer, 2006; Zur Hausen, 2006; Bouvard *et al*., 2009). The link between bacterial infection and cancer was suggested as early as 1772, when tuberculosis was thought to cause malignancy (Parsonnet, 1995). Nowadays correlation between lung cancer and tuberculosis is not confirmed and there is no evidence yet to support involvement of *Mycobacterium* in development of cancer and it is more accepted that if there is any link it might be attributed to reactivation of infection in immunocompromised cancer patients rather than a cause and effect relationship between infection and neoplasm (Browne and Healy, 1982; Kung *et al*., 1985). Notwithstanding association of bacterial infections with carcinogenesis continues to be promulgated (Snyder *et al*., 1990; Ferreccio *et al*., 2007). There is increasing evidence that correlate inflammation with cancer, the published results indicate that inflammation can be caused by microbial infections (including bacterial infections) and also resulted in by other means. The aim of present study is to review up to date development of research work on the involvement of bacterial infections with occurrence of various types of cancers. Moreover the study will discuss the mechanisms related to chronic bacterial infections which might cause aberration in DNA methylation patterns of genomic DNA of cancer patients.

INFLAMMATION AND CANCER

Connection of inflammation with cancer was suggested by Virchow 147 years ago (Balkwill and Mantovani, 2001). Nowadays, the causal relationship between inflammation and cancer development has gained increasing acceptance and more indications are reported about the critical role of inflammation components in tumors progression (Coussens and Werb, 2002; Mueller, 2006). Chronic infections by bacteria, parasites or viruses and tissue inflammations are recognized risk factors for human cancers at various sites (Allavena *et al*., 2008).

The mechanism of inflammation involves complex reactions to various agents, these may include microbial, chemical, or physical agents in vascularized tissues (Schottenfeld and Beebe-Dimmer, 2006). It was proposed that chronic inflammations might give the suitable microenvironment for the transformation of cells by insertion of oncogenes and inhibition of tumour suppressors; these will lead to development of cancer (Kuper *et al*., 2000).

There are several key mediators of inflammation-induced cancer; these include leukocytes, cytokines, complement components (group of serum proteins) and are orchestrated by transcription factors, such as nuclear factor kappa B (NFkB) and Stat3 (Mantovani, 2010). Other key mediators of inflammation-induced cancer are reactive oxygen and nitrogen species, prostaglandins and specific microRNAs, these cause changes in DNA methylation, cell proliferation, cell death, cellular senescence, DNA mutation rates and angiogenesis (Schetter *et al*., 2010). The reactive oxygen and nitrogen intermediates, prostaglandins and inflammatory cytokines produced in infected and inflamed tissues were reported to contribute to the process of carcinogenesis (Ohshima and Bartsch, 1994; Shacter and Weitzman, 2002). Maeda and Akaike (1998) reported that the inflammatory responses induced by various pathogens might accelerate mutagenesis as well as tissue damage, whereas nitrogen oxide also sustains more effectively solid tumor growth when normal cells are transformed to tumor or carcinoma cells by the host-derived free radical species, moreover peroxynitrite formation caused DNA-strand breakage.

The results of several investigations showed chemokines (small cytokines) are key components of cancer-related inflammation, it is likely that the chemokines system contributes to this process by its ability to attract mononuclear cells to cancer sites, where they provide growth or angiogenic factors that enhance cancer development (Rollins, 2006; Mantovani *et al*., 2010a, b). One more investigation in this context reported that high levels of IL-6, another type of cytokine, were observed in patients with numerous chronic diseases and solid cancers (Hodge *et al*., 2001).

Ectopic lymphoid follicles are additional key feature of chronic inflammatory autoimmune and infectious diseases, such as rheumatoid arthritis, Sjögren's syndrome and *Helicobacter pylori*-induced gastritis; the chemokine receptor CXCR5 was reported being pivotal for ectopic mucosa-associated lymphoid tissue neogenesis in chronic *Helicobacter pylori*-induced inflammation (Winter *et al*., 2010).

There are results which showed that the longer the inflammatory process persists, the more likely malignancy is to develop (Payne *et al*., 1992), thus it is expected a thorough understanding of the molecular basis of inflammation-associated neoplasia and progression can lead to novel approaches to the prevention and treatment of cancer (Shacter and Weitzman, 2002).

BACTERIAL INFECTIONS ASSOCIATED WITH CANCER

Several bacterial infections have been shown as being risk factors for development of cancers at various sites. In the following the reported and documented results on association of bacterial infections with various types of cancers will be reviewed.

***Helicobacter pylori*:** Research work on possible association between bacterial infections and development of cancer are coming mainly from overwhelming evidence of the association of *Helicobacter pylori* and cancer. At least 50% of the world's population harbors this bacterium (Taylor and Blaser, 1991; Orlicek *et al*., 1993). It is a motile Gram-negative rod bacterium lives in a neutral pH between the mucus layer of the stomach and the gastric epithelium, never found distant from gastric epithelium and does not invade tissue; it neither enters epithelial cells nor penetrates the basement membrane (Parsonnet, 1995). Despite this bacterium being non-invasive, *H. pylori* infection is associated with inflammation and capable invariably to induce pathological changes (Valle *et al*., 1991; Di Napoli *et al*., 1992; Stanley *et al*., 1994; Dore *et al*., 2002). It is believed that *H. pylori* infection and its associated inflammation last for lifetime (Taylor and Blaser, 1991; Kiehlbauch *et al*., 1994; Ponzetto *et al*., 2000).

Various groups of investigators reported the association of *H. pylori* infection with the development of gastric malignancy (Enroth *et al*., 2000; Crowe, 2005; Sasazuki *et al*., 2006). An investigation was carried out by Chiba and his colleagues to explain the pathway leading to cancer following infection. The study showed two major pathways for the development of gastric cancer by *H. pylori* infection: the indirect action of *H. pylori* on gastric epithelial cells through inflammation and the direct action of the bacteria on epithelial cells through the induction of protein modulation and gene mutation. Both pathways work together to promote gastric carcinogenesis (Chiba *et al*., 2008).

These findings might suggest taking precautionary measures to treat and prevent further progress of *H. pylori* infection to become chronic infection. These measures might start with diagnosis of infections caused by this bacterium to prevent subsequent development of malignancy. Various methods were developed for detection of *H. pylori*. A study was carried out to identify best combination of media for the primary isolation of *H. pylori*. Six media, Egg Yolk Emulsion agar (EYE), Skirrow' s medium and modified Thayer-Martin medium were used as selective media; whereas Modified Chocolate agar (MCHOC), Triptycase Soy Agar (TSA) and brain heart infusion agar were used as nonselective media, these were used to recover *H. pylori* from biopsy samples (Alikhani *et al*., 2007). The investigators were able to recover, *H. pylori* from biopsy specimens from 48 of 97 patients, yielding an isolation rate of 49%. Moreover their results showed that the highest rate of isolation of *H. pylori* was 100% (48 of 48) with EYE-MCHOC, followed by 97% (47 of 48) when EYE-SK was used. Other group of researchers investigated another approach for identification of *H. pylori* and they found histopathology method was useful method for diagnosis of *H. pylori* (Sadeghifard *et al*., 2006). In this context, it is worth mentioned the novel application of molecular bio-techniques for identification of *H. pylori*; several research works have developed Polymerase Chain Reaction (PCR) methods for detection of this bacterium from various clinical samples (Grahn *et al*., 2005; Falsafi *et al*., 2009; Guarner *et al*., 2010).

Characterization of *in vitro* susceptibility testing of *H. pylori* to antibiotics will assist in selecting useful antibiotics for treatment; moreover such investigation will help monitoring the evolution of the pattern of antibiotic resistance conferred by this bacterium to various antibiotics. Khedmat *et al*. (2007) isolated *H. pylori* from one hundred forty nine patients and studied the resistance rates of the bacterial isolates against several antibiotics; their obtained results as expressed in percentage of resistance toward tested antibiotic were as follows: MTZ (60.4%), CIP (40.3%), AMX (15.4%) and TC (10.7%). On the other hand other group of investigators showed that twenty two (56.41%) of 39 pure isolates of *H. pylori* were resistant to metronidazole, the authors concluded that determination of metronidazole sensitivity of *H. pylori* isolates before treating patients is essential (Moghaddam and Moghaddam, 2008).

Salmonella: Caygill *et al.* (1995) studied the risk of cancer at various sites in a cohort of chronic carriers of *Salmonella typhilparatyphi*. They observed a greatly increased risk of cancers of the biliary tract and also of cancers of the colorectum, pancreas, lung and all sites tested. These results supported an earlier documented case of *S. enteritis* which resulted in a chronic typhoid carrier; the recurrent cholangitis progressed to sclerosing cholangitis, with subsequent development of cholangiocarcinoma (Robbins *et al.*, 1988).

Shukla *et al.* (2000) studied the association of typhoid carrier state in patients with cholelithiasis, carcinoma of the gallbladder and controls using indirect haemagglutination assay measuring antibodies against highly purified *S. typhi* Vi polysaccharide antigen. They observed a significantly high Vi positivity in patients with gallbladder carcinoma (29.4%) compared to controls (5%) and patients with cholelithiasis (10.7%). They reported there is 8.47 times more risk of developing carcinoma of the gallbladder in culture-positive typhoid carriers than the non-carriers and concluded that the typhoid carrier state to be one of the possible mechanisms of gallbladder carcinogenesis. Kumar *et al.* (2006) suggested possible role of chronic inflammation and degradation of bile caused by mixed bacterial and *Salmonella* infections in the carcinogenesis of gallbladder cancer.

Other bacterial infections: Since the early reports which had shown the association of *H. pylori* chronic infections with gastric cancer and possibly *Salmonella* chronic infections with gallbladder cancer, other chronic bacterial infections have been shown to cause cancer. An investigation showed that most lung cancers arise among patients with chronic lung disease for example bronchitis and chronic infection (Schwartz *et al.*, 2002). Recent study indicated that *Mycobacterium tuberculosis* is associated with lung cancer, albeit probably not etiopathogenetically (Samaras *et al.*, 2010). Possible correlation between *Mycoplasma* infections and different cancers was reported, which suggested the possibility of an association between the two (Huang *et al.*, 2001). An experimental study in rats had shown that *Streptococcus infantarius* might be associated with colonic cancer; the researchers were able to identify and purify cell wall proteins putatively involved in colorectal inflammations and carcinogenesis (Nguyen *et al.*, 2006).

Bacterial metabolites and toxins: The bacterial and host molecular mechanisms remain unclear in respect of development of cancer. Recent studies suggested bacteria have been linked to cancer by two mechanisms: induction of chronic inflammation (Crowe, 2005) and production of carcinogenic bacterial metabolites (Salaspuro, 2003). In this respect, it had been demonstrated that bacteria can produce very potent carcinogens (N-nitroso compounds), from nitrite and suitable amines (Lijinsky, 1976; Caygill *et al.*, 1995). Carcinogenic compounds might arise as a result of microbial metabolism, in this respect a research work was carried out to ascertain production of acetaldehyde by bacterial infection. Acetaldehyde is considered a local carcinogen and might be produced in the digestive tract in humans. The obtained results showed that microbial ethanol metabolism leads to high intragastric acetaldehyde levels after ethanol drinking in achlorhydric atrophic gastritis patients. This could be one of the factors responsible for enhanced gastric cancer risk among atrophic gastritis patients (Vakevainen *et al.*, 2002).

Many bacteria that cause persistent infections produce toxins that specifically disrupt cellular signaling to perturb the regulation of cell growth or to induce inflammation, whereas other bacterial toxins directly damage DNA, such toxins mimic carcinogens and tumor promoters and might represent a paradigm for bacterially induced carcinogenesis (Lax, 2005).

EFFECT OF CHRONIC BACTERIAL INFECTIONS AND INFLAMMATIONS ON DNA METHYLATION

Research works during last two decades have succeeded to establish the correlation between cancer and aberration in DNA methylation. DNA methylation is one of three epigenetic mechanisms which have important roles in gene expression. Various investigations showed that this molecular mechanism is controlling gene expression and associated with various biological phenomena and diseases. One of important consequences of DNA methylation aberration is associated with development of cancer (Ibrahim, 2010a, b).

There are reports indicating possible connection between inflammation and DNA methylation aberration. Such possible link was reported by Stenvinkel and his colleagues, the results of their research showed changes in the genomic methylation in peripheral blood leucocytes from three different groups of Chronic Kidney Disease (CKD), changes were evaluated by measurement of HpaII/MspI ratio using the Luminometric Methylation assay method. The obtained results showed global DNA hypermethylation is associated with increased mortality in Chronic Kidney Disease (CKD) (Stenvinkel *et al*., 2007).

The results of other group of investigators led by Hodge showed that Interleukin 6 (IL-6), which is an inflammatory cytokine and is believed to have a role as mediator of inflammation, plays an important role in the growth and survival of many types of tumors. Their results showed that the promoter region of p53 in the IL-6–responsive human multiple myeloma cell line KAS 6/1 was found epigenetically modified by methyltransferases, resulting in decreased levels of expression. Furthermore, cells treated with IL-6 exhibit an increase in the expression of the DNA maintenance methylation enzyme, DNA methyltransferase (DNMT-1). The investigators concluded that the results of their study demonstrated that high IL-6 expression was linked to the hypermethylation of p53 gene and decrease in tumor suppressor's expression. Moreover their data demonstrated a clear association between mediator of inflammation and DNA methylation in the process of epigenetic control of tumor cell functions and provided possible explanation of the inflammatory mediated initiation of neoplastic growth (Hodge *et al*., 2005). Other study reviewed the molecular basis of development cholangiocarcinomas which are malignant epithelial liver tumors arising from the intra- and extra-hepatic bile ducts. The study illustrated those epigenetic changes (hypermethylation of specific gene promoters) which contributed to the carcinogenic process in cholangiocarcinoma (Stutes *et al*., 2007).

In this context it is worth mentioned the results of other recent studies investigated the correlation between bacterial infections and aberration of genomic DNA methylation. Bobetsis and his group assessed whether *C. rectus* infection mediates changes in the murine placenta Igf2 methylation patterns, they were able to observe that infection induced hypermethylation in the promoter region-P0 of the Igf2 gene (Bobetsis *et al*., 2007). A more recent study carried out by Shin *et al*. (2010) investigated methylation profiles of six genes namely p16, LOX, HAND1, THBD, p41ARC and APC along multistep gastric carcinogenesis and determined their association with *H. pylori* infection. Their results showed that active *H. pylori* infections were significantly increased methylation levels in three genes (THBD, LOX and HAND1) and hypermethylation of THBD, HAND1 and APC was associated with Intestinal Metaplasia (IM). Furthermore they observed that aberrant DNA hypermethylation was correlated with activity of *H. pylori* associated gastritis.

An investigation was carried out to ascertain methylation patterns of six genes (DAPK, TWIST, HIN-1, RASSF1A, RARbeta2 and APC) in Inflammatory Breast Cancer (IBC) and non-IBC patients using quantitative methylation-specific PCR. The methylation frequency of two genes,

Table 1: Inflammations and bacterial infections which might alter normal genomic DNA methylation profiles see the text for details.

Group	Agent	Disease, cancer or cell line	DNA methylation aberration	References
Inflammation	-	Chronic kidney disease	Global DNA hypermethylation	Stenvinkel *et al.* (2007)
factors	IL-6	Human multiple myeloma cell line KAS 6/1	Maintaining promoter methylation	Hodge *et al.* (2005).
	-	Inflammatory breast cancer	Hypermethylation	Van der Auwera *et al.* (2009)
Bacteria	*H. pylori*	Intestinal metaplasia and gastritis	Hypermethylation of promoter regions	Shin *et al.* (2010)
	C. rectus	Placental and fetal infection	Hypermethylation of promoter regions	Bobetsis *et al.* (2007)

RARbeta2 and APC, was significantly increased in IBC when compared to non-IBC (Van der Auwera *et al.*, 2009).

Table 1 summarizes main reported results on various agents whether chronic bacterial infections or inflammations associated with appearance of aberrant genomic DNA methylation profiles.

FURTHER WORKS

There have been vast amount of research works investigating the possible link of DNA methylation aberrations with various malignancies. The obtained results by various groups of researchers gave evidence on such possible connection; as a result research in this specific field of molecular epigenomic has seen a stream of interest among cancer researchers. Currently aberrations in this epigenomic molecular phenomenon has become known as one of the most consistent observed molecular genomic mechanism in neoplasm. Molecular studies have shown strong evidence which have correlated changes in normal pattern of DNA methylation with various types of cancers.

Recent studies suggested bacteria have been linked to cancer by two mechanisms: induction of chronic inflammation and production of carcinogenic bacterial metabolites, moreover the research in this field showed possible effect of bacterial infections on promotion of DNA hypermethylation (Bobetsis *et al.*, 2007) and aberration of DNA methylation (Shin *et al.*, 2010). These results support the correlation between aberration of DNA methylation caused by bacterial infections and cancer. It is expected that future studies will concentrate the efforts of research on these two mechanisms to investigate whether other types of bacteria have similar mechanisms linked to development of cancer.

Another area of future research which requires further investigation is to clarify the complex relationship between bacteria and cancer and the possibility of discovering other therapeutic approaches (Hirayama and Rafter, 1999). These were discussed by Mager (2006), he demonstrated that research has shown that *H. pylori* can cause gastric cancer or MALT lymphoma in some individuals, yet exposure to *H. pylori* appears to reduce the risk of esophageal cancer in others. On the other hand *S. typhi* infection has been associated with the development of gallbladder cancer; however *S. typhi* is considered a promising carrier of therapeutic agents for melanoma, colon and bladder cancers.

The growing evidence which suggests that cancer-related inflammation promotes genetic instability will have impact on future molecular investigations in connection with new of strategy of cancer therapy. An important field of applied medical biotechnology research is emerging to study various aspects of cancer-related inflammation. This area will represent a target for innovative diagnostic and therapeutic strategies (Mantovani, 2010). There are considerable amount of evidence reported in the literatures emphasizing on the influence of chronic inflammation on

development of cancer, these data support the reported conclusion by various investigators the longer the inflammation persists, the higher the risk of associated carcinogenesis, this requires molecular investigation at the genomic level to explains various aspects related to the problem. Furthermore inflammatory mediators are known to contribute to neoplasia by inducing proneoplastic mutations, adaptive responses, resistance to apoptosis and micro-environmental changes such as stimulation of angiogenesis (Shacter and Weitzman, 2002). All these reported and suggested mechanisms need further research, since these problems worth investigation to clarify the molecular mechanisms associated with development of cancer.

Another area of future research is to investigate molecular basis of gallbladder cancer which is although relatively rare form of malignancy; there are unique combination of influencing factors which give rise to this type of cancer. It is worth mentioned the main associated risk factors identified so far include cholelithiasis (especially untreated chronic symptomatic gallstones), obesity, reproductive factors, chronic infections of the gallbladder and environmental exposure to specific chemicals (Lazcano-Ponce *et al*., 2001). However, there are more unique combination of influencing factors reported by other investigators these include genetic predisposition, geographic distribution, female gender bias, chronic inflammation and congenital developmental abnormalities, all these factors and possibly other unreported factors make this type of cancer unique and offers new approaches and potential for understanding cancer pathogenesis in general. It has been suggested that an understanding of how these risk factors contribute to the molecular basis of the disease is essential for understanding the origins of this unusual cancer (Rosin *et al*., 1994; Wistuba and Gazdar, 2004).

Suzuki *et al*. (2009) suggested that the frequent observed occurrence of aberrant CpG hypermethylation in correlation with chronic inflammation and precancerous lesions, might be useful in detection of early events in tumorigenesis and that could serve as a useful tumor marker. The authors indicated this is possible in presence of a variety of screening techniques which have been developed for genome-wide screening of methylation status. They emphasized on one of new novel molecular technique, namely transcriptome analysis coupled with pharmacological unmasking, the authors suggested that this molecular bio-technique is a powerful tool for revealing DNA methylation patterns in cancer cells and identifying new tumor marker candidates.

Results of several investigations carried out by Ibrahim and colleagues showed the possibility of detection of cancer by measurement of protein or identifying molecular markers in the genomic DNA. One investigation showed the observation of higher protein values in saliva of Primary Brain Tumors (PBT) patients as compared with healthy individuals; this might be considered a preliminary indication of diagnosis of PBT (Hamad *et al*., 2009). Other investigations had shown the possibility of identifying molecular markers in the genomic DNA associated with various types of leukemia including aberration in the genomic DNA methylation profile (Ibrahim *et al*., 2009, 2010a, b; Saleh *et al*., 2010). It might be useful to ascertain these methods in investigation of changes in the DNA methylation profiles of cancers associated with chronic bacterial inflammations.

CONCLUSIONS

The research during last few decades showed the correlation between chronic inflammation caused by *H. pylori* and probably of other types of pathogenic bacteria with cancer development. Molecular investigations have demonstrated the role of bacterial metabolites, toxins and other factors involved in the chronic inflammation which might be associated with development of cancer. It is suggested that some of these factors were engaged in changing the normal methylation profiles

of cells and promoting the development of malignant cells. It is increasingly clear and accepted nowadays, that aberrant DNA methylation is the most common molecular lesion of cancer. It is expected that understanding the molecular mechanisms at genomic level will prompt new guidelines in innovative development of new diagnostic and therapeutic strategies for cancers associated with chronic bacterial inflammations.

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