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Do Non-Viral Microorganisms Play a Role in the Aetiology of Human Cancers? A Review

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ABSTRACT

The role of non-viral microorganisms (NVM) in oncogenesis has been remained as a subject of considerable debate. While Helicobacter pylori has been recognised as a carcinogenic agent, the role of other NVM in cancer has either been ignored or has not well been understood. Despite this, various mechanisms by which NVM might play a role in carcinogenesis included chronic inflammation and disruption of the cell cycle. The role of bacteria, in particular, in carcinogenesis has been increasingly justified. Growing evidence has provided links between human cancers and a diverse range of bacteria, including for example a role in lung cancer for Chlamydophila pneumoniae and Mycobacterium tuberculosis. Further research into this overlooked area is needed to understand the potential role of the infectious agents in carcinogenesis. The prevention and treatment of infectious diseases due to their microorganisms, by the use of vaccines and anti-microbial agents, may prove useful in the future to combat the increasing number of cancer cases, worldwide. The objective of this review was therefore to provide an update on the potential role of non-virus microbes in cancer.

Key words: *Non-Viral Microorganisms, Human Cancers, Carcinogenic Agent.*

INTRODUCTION

Cancer is the uncontrolled proliferation of abnormal cells that leads to a malignant growth, and ultimately severe morbidity and mortality. More than two hundred different cancers have been recognised, and while common, well-defined risk factors included smoking, an unhealthy diet and age [1-3], and infectious agents (mainly viruses) have been linked to over 20% of cancers [4]. Unhealthy diet might be resulted as a change in lifestyle confronting people with the challenge of doubling diseases [5]. In fact, Malignant neoplasms have remained as a leading cause of death worldwide [6]. Viral infection plays a significant role in the aetiology of hepatitis B (HBV) and C (HBC) and they are considered as one of the principal threats to human life and health worldwide [7]. These viruses can establish a chronic liver infection and, in severe cases, a hepatic carcinoma can be resulted [8]. Human papillomavirus (HPV), which is implicated in at least 90% of all cervical cancers, is yet another viral cancer [9].

While viruses are well characterised in carcinogenesis, the role of the other microorganisms has been less clearly understood and has largely been ignored. Several epidemiological studies have been done during the twentieth century and have associated bacteria with cancer [10]. The most significant studies on this potential role came in 1926, when Glover claimed that certain bacteria were consistently isolated from neoplastic tissue [11]. Since then, a diverse range of bacterial species has been isolated from cancers, therefore suggesting a link between bacteria (in particular) and specific types of cancer. Unfortunately, the role of non-viral microorganisms (NVM) in cancer has been still unclear [12], and such a role has been dismissed on the basis of non-cancer associated bacterial growth within tumours [13-15]; obviously, the presence of bacteria within a tumour has not necessarily suggested the causation. There has been increasing evidence suggesting that our own bacterial microflora have likely participated in carcinogenesis [16, 17].

Helicobacter pylori is the bacterium that has been most strongly associated with cancer, in this case, gastric carcinoma and lymphoma [4], but increasingly, evidence has suggested that other microorganisms play a role. *Porphyromonas gingivalis*, for example, has been linked to pancreatic cancer – a two-fold increase in the risk of pancreatic cancer has been suggested for those, currently, or previously, infected with this pathogen. Additionally, *Chlamydia trachomatis* DNA has been isolated from 80% of ovarian tissues from women with ovarian epithelial carcinomas, while all control tissue samples were negative for this organism [18]. Furthermore, studies on *Salmonella enterica* serovar *Typhimurium typhi* (the major causative agent of typhoid) suggested a strong link between infection and the advancement of gallbladder cancer [19, 20]. Despite such associations, however, the relationship between bacteria and cancer has still largely been disputed [1].

This review has been devoted to recent studies on the potential role of bacteria and other NVM in cancer, with particular emphasis being given to their role inducing genetic mutations and inflammation.

Bacterial Involvement in Carcinogenesis : Proposed Mechanisms

A variety of bacteria have been hypothesised to induce carcinogenesis via a range of different mechanisms, including, but not limited to, chronic inflammation, disturbance of the eukaryotic cell cycle, induction of immunosuppression, and down-regulation of apoptosis [21, 22].

Chronic inflammation

In 1863, Virchow proposed that cancer originates at sites of chronic inflammation, and this causal relationship has been getting increasingly accepted [22]. Inflammation leads to the production of a tumour microenvironment rich in white blood cells, and leukocytes generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can induce DNA damage in cells. Such damage can lead to the production of an abnormal cell, which may then undergo the proliferation to produce a neoplasm [22].

Disturbance of the cell cycle

There is increasing evidence to show that several species of bacteria produce toxins that interfere with the cell cycle; such toxins have been termed as cyclomodulins [12]. Cyclomodulins may stimulate or inhibit the cell cycle to result in the altered growth, which can cause the impaired cell cycle, leading to the uncontrolled cellular proliferation, leading to the beginning of tumour growth. Some bacterial products have been proven to stimulate the division of eukaryotic cells. For example, cytotoxic necrotising factors (CNFs) from *Escherichia coli* can lead to the constitutive activation of a common growth signalling pathway [23].

Bacterial metabolites as carcinogens

Some bacterial metabolites have been also suspected of increasing the risk of cancer. For instance, a few bacteria can metabolise bile salts to produce cytotoxic bile acids, a metabolite that has been thought to promote cellular proliferation. Additionally, bacteria may ferment polysaccharides and glycoproteins to fatty acids, which can alter the membrane structure, and potentially increase the cell proliferation [24], these are the changes which could all induce cancer formation.

***Helicobacter pylori* and its role in gastric carcinogenesis**

The bacterium *Helicobacter pylori* has been implicated in gastric carcinogenesis in various studies [25]. It is a Gram-negative rod-shaped bacterium that is able to colonise the stomach of humans and animals, where it can induce cancer [26]. Persistent *H. pylori* stomach infection by this organism has been associated with chronic inflammation, and the release of ROS and RNS. Its presence is often associated with the elevated blood levels of interleukin (IL-) 8, a pro-inflammatory cytokine [26]. Two independent groups found *H. pylori* antibodies in the sera of a high percentage of patients who went on to develop gastric carcinoma [27, 28], and a six-fold increase in gastric cancer rates have been reported in populations with a high *H. pylori* infection rate [29]. Sasaki *et al.* inoculated Mongolian gerbils with *H. pylori* and examined them for morphological changes occurring in the stomach. Stomach ulcers and severe active chronic gastritis were observed in a high proportion of the gerbils, and 37% developed adenocarcinoma of the stomach [25]. Considering that the Mongolian gerbil is an excellent animal model for the gastric studies, these results were highly suggestive of an involvement of *H. pylori* in gastric carcinogenesis in humans.

While *H. pylori* has been linked to over 60% of all stomach cancers, few infected individuals develop gastric cancer [26], largely because of the occurrence of distinct virulence factors in different strains of the bacterium. Some strains contain the *cagA* pathogenicity island (PAI), a significant virulence factor that induces the activation of mitogen-activated protein kinases (MAPK); the expression of transcription factors *c-fos* and *c-jun*, and simultaneous expression of the encoded proteins increases the cellular proliferation [30]. The affirmation of the engagement of *H.*

pylori in gastric cancer should have emphasised the potential role of the other microorganisms in the aetiology of human cancers, but surprisingly, this bacterium has been viewed as an exception, and the role of NVM, in general, has been largely ignored.

Lung Cancer

It has been well known that smoking is the largest risk factor, although other risk factors exist, including air pollution and exposure to asbestos or diesel exhausts [14, 31, 32]. There is also increasing evidence that infection with various bacteria (notably the two species discussed below) may be related to an increased risk of the disease.

Chlamydophila pneumoniae

Previously known as *Chlamydia pneumoniae* [33] (NCBI, 2009), *C. pneumoniae* is a Gram-negative intracellular bacteria [34] that is transmitted via respiratory secretions and aerosol, and can cause a variety of infections including the chronic obstructive pulmonary disease (COPD), bronchitis and pneumonia. This bacterium appears to persist in the lungs, and induce pulmonary inflammation [34-36]. Research has also suggested an involvement of *C. pneumoniae* in lung cancer. In a 2004 study, which involves 520 individuals with confirmed diagnoses of lung cancer being serologically tested [37], *C. pneumoniae* IgA antibodies were detected at much higher levels in people living with lung cancer compared to the control group. Another study used an alternative serological technique: antibodies complementary to the *Chlamydophila* heat shock protein-60 (CHSP-60) were employed as biomarkers for the chronic infection [35]. CHSP-60 has been consistently expressed during persistent infection, and has been an important protein in inflammatory-induced tissue damage. The CHSP-60 enzyme-linked immunosorbent assay (ELISA) used a recombinant *Chlamydia trachomatis* HSP-60 antigen, which shares 90% homology with CHSP-60 from *C. pneumoniae*. Individuals seropositive for CHSP-60 IgG antibodies were shown to have a significantly increased risk of becoming diagnosed with lung cancer in later years of their life.

The marked association between *C. pneumoniae* and lung cancer has been highly suggestive of its role in the aetiology of lung cancer, and the link between chronic infection and inflammation has provided a highly plausible mechanism for such carcinogenesis. Although the relationship between *C. pneumoniae* and the corresponding increased lung cancer risk is somewhat variable, the estimates of an elevated risk of lung cancer due to the presence of this bacterium ranged between 0.7- and 9.0-fold [35].

Mycobacterium tuberculosis

Mycobacterium. tuberculosis has currently infected some 33.3% of the world's population [38]. This intracellular bacterium persists in the lungs [39] and causes symptoms including a cough, fever and weight loss. Chronic inflammation caused by a latent infection triggered by this bacterium has been considered to lead to tissue damage, fibrosis and genetic alterations [38]. Additionally, tuberculosis scars and deforms the blood and lymphatic vessels, which may allow carcinogens to enter the lungs more easily and bring about cancer [40, 41].

Tuberculosis has been associated with a two-fold increase in the risk of lung cancer, and a 3.7-fold increase in the risk of squamous cell carcinoma [38], though some researchers have disputed against such an association[37-41].

Oesophageal Cancer

Two major types of oesophageal cancer exist in squamous cell carcinoma and adenocarcinoma [4]. Squamous cell carcinoma happens more often in the upper and middle regions of the oesophagus, whereas adenocarcinomas tend to occur in the lower region [42]. Risk factors for this type of cancer include smoking, alcohol consumption and a high body mass index (BMI) [43]. It has been suggested that *Campylobacter concisus*, *Campylobacter rectus* and *Streptococcus anginosus* are likely to be involved in carcinogenesis of the oesophagus [4].

Campylobacter concisus

Campylobacter concisus is a common mouth commensal, which is rarely found in the oesophagus [44] but which has been discovered to play a key role in acute and chronic gastrointestinal diseases [45]. An increase in the occurrence of *C. concisus* in oesophageal biofilms has been reported in those suffering from adenocarcinoma of the oesophagus [44-47].

Macfarlane *et al*. collected oesophageal biopsy and aspirate specimens from 14 individuals diagnosed with gastrointestinal problems; this included seven patients suffering from Barrett's oesophagus (BO), a common precursor of oesophageal adenocarcinoma [46]. Total counts of bacteria in specimens from patients with BO were higher than those from the control group – 18 different bacteria were detected in the control group, compared to 28 in those suffering from BO. High levels of *Campylobacter* species were also found to colonise 57.1% of the patients with BO, while these bacteria colonised none of the control group.

A transcriptomic and proteomic study found that macrophages infected with *C. concisus* assembled the IFI16 inflammasome [45]. The inflammasome is a multiprotein complex that is expressed during the innate immune response, and plays a major role in the inflammation [48]. *Campylobacter concisus* was also found to affect the expression of p53, tumour necrosis factor alpha (TNFα), and IL-18 in FLO-1 cell lines (immortalised BO epithelial cells) significantly [47]. This study showed that *C. concisus* might stimulate cellular proliferation within the oesophagus by causing a decrease in the expression of p53 (a tumour suppressor protein), and an increase in the expression of both TNFα and IL-18. Evidence has also been found for elevated levels of IL-18 in patients with oesophageal cancer, thereby suggesting a relationship between IL-18 and cancer [49]. While some researchers were convinced of a link between *Campylobacter* infection and oesophageal cancer, others were less convinced of such an association [50].

Streptococcus *anginosus*

Evidence provided by a number of studies suggested that S. *anginosus* is involved in early stages of oesophageal cancer, as well as having a potential role in the induction of gastric cancer [51-53]. The *Streptococcus anginosus* (SAG) group of bacteria includes *S. anginosus*, *S. constelatus* and *S. intermedius*. Like *C. concisus*, these microorganisms are commensal pathogens, although they are normally found in the oropharynx and gastrointestinal (GI) tract [54].

Sasaki *et al*. (1998) found that *S. anginosus* DNA was frequently detected in DNA samples from oesophageal and gastric cancers, but not in samples from cancers of the lung, cervix, bowel or bladder. These results were consistent with a previous study that isolated *S. anginosus* DNA in over 20 percent of people living with gastric cancer [51, 52, 55].

In conclusion, the increased abundance of *S. anginosus* in oesophageal biofilms of individuals with gastric and oesophageal cancers was highly suggestive of it playing a role in neoplasia.

Colorectal Cancer

Age has been the largest risk factor for this type of cancer, with some 90% of those diagnosed being over 60 ; other risk factors have included the lack of exercise, a diet high in red or processed meats, and obesity. *Streptococcus infantarius* has been linked to bowel cancer as an additional risk factor.

Streptococcus infantarius

Streptococcus infantarius, formerly *S. bovis*, has been implicated as the cause of endocarditis, neonatal meningitis and bowel cancer [1, 56-59]. Biarc *et al.* (2004) [56]inoculated male Wistar rats with this bacterium, and colonic mucosa samples were taken. The proteins of each sample were determined, and it was found that proliferation markers, such as a proliferative cell nuclear antigen (PCNA), were increased [56]. The presence of *S. infantarius* may, therefore, change the eukaryotic gene expression and lead to the cellular proliferation within the colon. Gold *et al.* (2004) reported that 28.9% of patients suffering from *S. infantarius* bacteremia were diagnosed with a malignancy within one month of infection [60]. Three patients were diagnosed with colorectal adenocarcinoma while other malignancies, including gallbladder adenocarcinoma, pancreatic adenocarcinoma and ovarian cancer, were detected in the remaining 13 patients. A similar case study detected *S. infantarius* in the stool samples of 48.6% patients with either colorectal cancer or inflammatory bowel disease [61]. A final case study reported 165 cases of colorectal cancer associated with *S. infantarius* bacteremia [62]. Such case studies provided compelling evidence of an association between *S. infantarius* and colorectal cancer. Although the relationship between *S. infantarius* and bowel cancer has been still unknown, it has been widely accepted that physicians should screen patients suffering from *S. infantarius* bacteremia for colorectal cancer [60].

Concluding Remarks

The role of non-viral microorganisms in the aetiology of human cancers has been overlooked or, where considered, been the subject of considerable controversy. The link between *H. pylori* and gastric cancer is now widely accepted ; there is, therefore, no reason to believe that other NVMs cannot be involved in the development of cancer. Throughout this review, the evidence for the role of a diverse range of microorganisms in carcinogenesis has been discussed. However, despite the accumulating evidence, the connection remains poorly understood. Although signs of bacteria and parasites in cancers have been observed, this does not prove causation, since the microorganisms may readily infect the tumour microenvironment.

Early treatment of the infections may prevent a large proportion of cancers. Considering that at least 20% of cancers have been likely to be caused by the infectious agents [4], the early eradication of such infections may protect against carcinogenesis. For example, *C. pneumoniae* has been commonly treated using tetracyclines and

erythromycin [63]. Treatment of the individuals infected by *C. pneumoniae* using these antibiotics may decrease the prevalence of lung cancer. Additionally, treatment of *T. vaginalis* infection with metronidazole [64] may reduce the number of cervical cancer cases. Furthermore, vaccination would provide an important prospect in the prevention of such infections, which may lead to the reduction in cancer cases [65].

Furthermore, studies and research are needed to gain a full understanding of the role of NVM in cancer development. A subset of cancer researchers should focus solely on the role of these organisms as the infectious agents in carcinogenesis. Given the increasing evidence of a causal link between NVM and cancer, it has been hoped that within the next ten years, the role of these organisms in carcinogenesis would be fully understood and recognised.

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