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Review Article

Microbial Aspects of Cancer Progression: A Conventional Approach

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Abstract

Cancer is defined as the uncontrolled proliferation of cells due to malignancy being caused due to certain factors such as genetic variations, mutations and Chemical factors that contribute to the increment of cancer as a worldwide disease making it one of the prominent disorders of the human body. However, in developed countries, worldwide cancer accounts for 20% of the deaths due to the lack of proper diagnosis or lack of proper treatment. In developing countries like India cancer is increasing at a fast pace most of the cases are arising and reported as lung cancer, liver cancer, and Cervical Cancer to name a few. There is one more aspect of cancer that is one of the most important parts which is the microbiota or microorganisms causing cancer, they play an important role as viruses, bacteria, and other such organisms holds a great potential to cause and generate optimum conditions for cancer. Bacteria can increase the development of cancer by manipulating animal cell signaling pathways, alteration in metabolites, and causing inflammation, however, these microorganisms can cause cancer under certain geographical and environmental conditions. Some of the prominent causatives in different areas of the body are *helicobacter pylori* for stomach cancer, Papillomavirus for cervical cell carcinoma, Epstein-Barr virus for Burkitt's lymphoma, and Streptococcus Ovis for Colorectal cancer. In recent trends it is being observed that the microorganisms are responsible for 15-20% increase in lung cancer, carcinoma, and liver cancer, major causative organisms are responsible also included the factors that these organisms are drug-resistant as well. This review aims toward the microbiological aspect of cancer and the analysis of detailed factors responsible for causing cancer progression.

Keywords: Cancer; Polyomavirus; Radiotherapy; Chemotherapy

Introduction

Cancer is one of the Foremost lethal disorders around the world, cancer is caused by genetic disorders or environmental impacts and is defined because of the uncontrollable and abnormal proliferation of cells. Additionally, ultraviolet rays in sunlight and chemicals, bacteria, and viruses play important roles in developing cancers. In many cancer cases, secondary tumors are formed because of late diagnosis which is the leading expression of high death rates. Common treatments like chemotherapy or radiotherapy have low viability rates due to drug resistance, tumor development, and low specificity of treatment. New studies suggest that the microbiome can be potentially employed in the treatment of many diseases including cancer. currently a large number of infectious agents have been identified which either cause or contribute to specific human cancers [1]. They include two members of the herpes virus family, Epstein–Barr virus and human herpes virus type 8, high risk and low risk human papilloma viruses (HPV), Hepatitis B and C viruses, a recently identified human polyomavirus, Merkel cell polyomavirus [2], the human T-lymphotropic retrovirus, and human immunodeficiency viruses (HIV). Other pathogens have also been identified. They include the bacterium *Helicobacter pylori*, a major contributor to gastric cancer, and parasitic infections, here in particular Schistosoma haematobium, a major cause of bladder cancer in Egypt, and liver

flukes. The latter, Opisthorchis viverrine and Clonorchis sinensis are important factors of cholangiocarcinoma and hepatocellular carcinomas in South-eastern Thailand and Southern China. It is important to note that there exist vast gender differences within the global role of papillomaviruses in human cancers. This is mainly due to the role of this virus family in the induction of cancer of the cervix. over 50% of cancers linked to infections in females are caused by HPV infections. In males, only approximately 4.3% of cancers are linked to this virus family. In recent years, microbial metabolites have been shown to possess cariostatic as well as carcinogenic potentials, but many concepts of cellular regulation are derived from studies with microorganisms [3,4]. There are diverse areas in which recent progress in our understanding of the neoplastic process and its prevention has come from working with microorganisms as a therapeutic approach. The classical work on bacterial lysogeny and also the nature of temperate bacteriophages has provided the foundation for present-day theories on virus-induced neoplastic transformations, and moreover, it is being suggested studies on the physical state of the viral genome in the transformed cell. The present article will be confined to a consideration of only a limited number of aspects in which mostly microorganisms have played a role in cancer research. Moreover, the discussion will be limited to a consideration of prokaryotes (eubacteria). A prepore on the membrane surface; however, at 37 ◦ C this prepore then rapidly inserts into membranes to form an pre-active pore Formation of the CH-1 pore ends up in releasing in calcium influx, which (via calpain activation) leads to cell death at moderate CPE doses, where modest CPE pore formation allows only limited calcium influx, CPE-treated cells die from a classical caspase 3-mediated apoptosis. At higher CPE doses, where large amounts of CPE pore formation end up resulting in a massive calcium influx, cells die from onychosis's pore formation also leads to morphologic damage that exposes the basolateral surface of cells. This permits the formation of a second bigger (~650 kDa) large complex named CH-2 In addition to six copies of CPE and both receptor and nonreceptor claudins, CH-2 also contains another tight junction protein named occluding Formation of CH-2 leads to the internalization of occluding into the cytoplasm claudins are also internalized inside native CPE-treated cells although itis not clear if this is due to CH-1 formation, CH-2 formation, or to the formation of both complexes. These effects likely help to clarify the observed ability of native CPE to disrupt tight junctions [5]. However, This Article Aims Towards The Microbiological Aspect of Cancer and Microorganisms as Therapeutics towards Cancer.

Cancer scenario for India

India is a developing country and the present population is approximate 1.35 billion at which every year approx. 0.11 % (1.5 million) population is diagnosed with cancer every year and mortality from cancer is as high as 1.2 million. in recent decades, Head, neck, and lung cancer in males, and Cervix and breast are leading cancer among females [6]. Among males, lungs, mouth, esophagus, or in females, breast, cervix, uterus, and ovary is the most common sites for cancer development. Treatment in most of the cases is palliative and Due to poverty and illiteracy, there is an insufficiency of awareness which leads to progression at the advanced or metastatic stage [7].

Microorganism v/s Cancers

Bacteria can increase the development of cancer by manipulating animal cell signaling pathways, alteration in metabolites, and causing inflammation [8]. The larger number of infectious agents encountered, either cause or contribute to specified human cancer. They include Epstein-Barr virus, Human herpesvirus type 8, high-risk and low-risk human papillomavirus, recently discovered human polyomavirus, the human T-lymphotropic retrovirus type 1 (HTLV-1), and human immunodeficiency viruses (HIV) types 1 and 2. In addition, human endogenous retroviruses have been suspected to play a crucial role in human cancers [9]. Besides viruses, other pathogens have also capable to develop carcinoma, which includes *Helicobacter pylori*, a major causative individual of gastric cancer, and parasitic infections, here, in particular, Schistosoma hematobium, a major cause of bladder cancer. It is important to note that these microorganisms are able to cause cancer under certain geographical conditions such as *Helicobacter pylori* infection associated with peptic ulcer and gastric cancer in Eastern and Southern India due to consumption of meat, fish and north-western India is less susceptible to gastric cancer due to consumption of chili, black pepper, these appear to be protective against *Helicobacter pylori* [10].

In recent decades, many microorganisms are identified for the treatment of tumors, and researchers have prompted the development of many new approaches to the treatment of cancer, including the delivery of anti-cancer genes to the tumor

site in various gene therapy protocols [11]. Genetic approaches include delivering genes encoding pro-drug activating enzymes, cytotoxic anti-angiogenic proteins, or cell-targeted toxins to the tumor. However Current gene therapy protocols require local administration of vectors. Therefore, a systemic delivery system is required that will allow therapies to be carried to both primary and metastatic tumors. As a result, bacteria and their products have been investigated as DNA delivery vectors, cell-targeted toxins, and tumor targeting vehicles. Bacteria Such as Salmonella typhimurium A1-R, Clostridium perfringens have been used as cell-targeted toxins and *Listeria monocytogenes* [12], *Shigella flexneri* [13], Lactococcus lactis have been shown to deliver a DNA expression plasmid and cDNA encoding a human cystic fibrosis transmembrane intracellular conductance regulator into mammalian cells, respectively. A genetically modified strain of L. lactis with a synthetic human IL-10 gene represents a promising treatment for inflammatory bowel disease [14]. Toxoplasma gondii is an obligate parasite. Infection of toxoplasma controls several cellular communication pathways to establish an antiapoptotic environment and decimate immune cells as a conduit for the dissemination. Although, high degree of ambiguity in the molecular mechanism of *T. gondii* dissemination through the host [15].

Helicobacter pylori and stomach cancer

Helicobacter pylori is a Gram-negative pathogen and have a unique ability to colonize the mucosal lining of the human stomach. This bacterium shows urease, catalase, and oxidase activity, it is spiral shape and possesses 3 to 5 flagella that are used for motility. *H. pylori* has evolved the ability to colonize the highly acidic environment found within the stomach by metabolizing urea to ammonia via urease, which generates an neutral environment enveloping the bacterium [16]. Helicobacter is a very important pathogen in the development of cellular gastric carcinoma, the growth of stomach cancer differs in different regions. Though anti- *H. pylori* treatments have been shown to be successful in preventing stomach cancer, the risk of this type of cancer initiated by *H. pylori* would be significantly decreased. *H. pylori* infection may be acquired during childhood, persists lifelong if not eradicated, and is associated with chronic gastritis and an increased risk of peptic ulcer disease and further gastric cancer [17]. Although, *H. pylori* colonization does not cause any symptoms in most persons [18]. *H. pylori* has several pathogenicity factors such as OipA, BabA, VacA, CagA, which are connected to the gastric epithelial cells by the receptor molecules on their surface, and this interaction creates a series of intracellular signaling cascade pathways, causing cell changes and ultimately damage to the cell such as CagA phosphorylation-dependent host cell signaling, CagA phosphorylation-independent host cell signaling, etc. [19]. CagPAI (The cag pathogenicity island (*cag* PAI) is a 40-kb DNA insertion element which contains 27 to 31 genes flanked by 31-bp direct repeats and encodes one of the most intensely investigated *H. pylori* proteins, CagA), VacA, Paptitoglycan, BabA, DupA, SabA, FlaA that are the virulence factors of the *helicobacter pylori* [20]. OipA is an inflammation-related protein. *H. pylori* contains either a functional or non-functional OipA gene and the functional OipA gene is significantly related associated with the presence of duodenal ulcers, gastric cancer, and increased neutrophil inflammation [21,22]. DupA increases Interleukin-8 production and it expresses the OipA gene of the *H. pylori* [23,24]. The chance of gastric carcinoma is induced not only by *H. pylori* strain and genetic makeup of the host cell but also by the environmental factors, high dietary salt intake of them can able to increase the risk of gastric cancer with the association of *H. pylori* [25,26]. A subsequent study on a Japanese population and a case-control study in South Korea each give an account that *H. pylori*-infected subjects consuming a high-salt diet had an increased risk of gastric cancer compared to *H. pylori*-infected subjects who consumed lower levels of salt [27,28], while another study reported a positive correlation between the prevalence of *H. pylori* infection and levels of dietary salt intake [29]. The result of this study indicated that many factors are involved in virulence and *H. pylori* is capable to cause peptic ulcers as well as gastric cancer.

Papilloma virus and cervical cell carcinoma

Papillomavirus is a tiny, epitheliotropic, non-enveloped, double-stranded DNA virus that infects cutaneous and mucosal epithelia in a species-specific manner except bovine papillomavirus (BPV_s) 1 and 2 are known to infect Mesenchymal tissues and to show inter species transmission. More than 100 types of Human papillomaviruses have been identified and half of them cause infection in the urogenital tract [30]. According to WHO statistics, high-risk HPV DNA is found to be present in 99.7% of cervical cancer specimens [31]. HPV infection types are divided into two groups based on their carcinogenic properties: these are high risk and low risk. High-risk type (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, and 59), Others are classified as potential high risk

(which are 53,56,70,73, and 78). HPV16 and HPV18, it has been proven that both of strains are most virulent and high-risk human papillomavirus [32]. The available literature indicates that there are two discrete intraepithelial processes in the cervix associated with human papillomavirus. One is the classical condyloma. The other is intraepithelial neoplasia, like classical infection, which may be mature [cervical intraepithelial neoplasia (CIN) with koilocytosis] or immature (high-grade CIN or carcinoma in situ). HPV16 and HPV18 are the only existing HPV types With DNA that can integrate their DNA with the host cell [33]. Many studies have been confirmed that persistent infection with an oncogenic HPV type, mainly 16 and 18 is the main risk factor for the development of cervical intraepithelial neoplasia (CIN) that may range from CIN1 to CIN3 and cancer [34]. Oncogenic ability of HPV16 depends on the regulation of viral transcriptional factors. At the initiation of viral infection, the HPV16 genome can be presented as an unintegrated small DNA molecule also called episome, and results in benign and precancerous lesions of the cervix. However, HPV16 can integrate its genome into the host genome, which in turn can lead to the development of cervical carcinoma and cervical intraepithelial neoplasia grade III [35]. E6 is an envelope protein, that binds with E6-associated binding protein (E6AP), a ubiquitin ligase leading to a structural change in E6 allowing it to bind with p53(guardian of the genome), the cell cycle control tumor suppressor protein to form a trimeric complex E6/E6AP/p53. This binding leads to the degradation of P53 and the result is cell proliferation. On the other hand, E7 binds with pRb causing its degradation and inactivation [36]. At normal physiology of the cell, pRb downregulates E2F a transcription factor. As pRb is deactivated by E7, E2F is upregulated and cell proliferation genes are activated, furthermore, E6 and E7 have been shown to form complexes with hundreds of other proteins in the host cell [37,38]. However subsequent study shows that E6/E7 deregulates the mi RNA linked to carcinogenesis [39]. miRNA plays an important role in the posttranscriptional control of the expression of host genes. Many recent studies proposed that E7, E6, and E5 oncoproteins regulate the host mi-RNA profile. In HPV-associated cervical cancer cells, a number of miRNAs such as miR-21, miR-143, and miR-9 are overexpressed, thus targeting CCL20 (chemokine (C-C) motif ligand) and promoting the migration of HPV16-positive cancerous cells. However, overexpression of some miRNAs such as miR-203 inhibits HPV amplification (Figure 1). Thus miR-203 is suppressed by the overexpression of HPV E7 [40].

Figure 1: Progression of cervical carcinogenesis, Which involves HPV gene integration leads to the degradation of P53 and inactivation of pRb, mi-RNA by the binding of E6 and E7 viral protein tends to the uncontrolled cellular proliferation, tumor suppression evasion, and other feature of tumorigenicity [41].

Epstein-Barr virus and Burkitt's lymphoma

Epstein-Barr virus(EBV) is the first human virus that is proved to be carcinogenic. a double-stranded linear DNA genome and is enclosed by capsid proteins [42]. Primarily EBV is found associated with Burkitt's lymphoma, but now we have a lot of evidence that EBV is linked to a remarkably wide range of lymphoproliferative lesions and malignant lymphomas of B-, T- and NK-cell origin. Latent infection of EBV express a variety of genes which includes, six EBV nuclear antigens such as EBNA-1, -2, -3A, -3B, -3C, and EBV nuclear antigen-leader protein(EBNA-LP), three EBV latent membrane proteins such as LMP-1, -2A, and -2B, two short non-coding RNAs like EBV-encoded small RNA, EBER-1 and -2 [43,44]. EBV can infect various cell types, so human EBV_s infection leads to the development of various cancers. Due to the preferential infection of B cells, the most common forms of EBV-associated lymphoproliferative disorders are B-cell lymphomas. Some epidemiological studies show that the Epstein-Barr virus is restricted to the geographical region where Plasmodium falciparum malaria is holoendemic [45]. This virus is potentially able to infect epithelial cells as well as B cells [46]. Burkitt's lymphoma and Epstein-Barr virus have a strong relation in the immuno-compromised person [47]. Epstein-Barr virus related to Burkitt's lymphoma according to its epidemiologic and clinical characteristics is classified into three groups including HIV associated Burkitt's lymphoma, endemic Burkitt's lymphoma, and sporadic Burkitt's lymphoma. Endemic Burkitt's lymphoma engages the jaw and facial bones and sporadic Burkitt's lymphoma engages the upper respiratory tract and intestines, both leading to tumors in those areas [48]. The last two decades of Studies show that the interactions between the virus and B cells prepare the ground for the development of Burkitt's lymphoma and the key factor in tumorogenic of Burkitt's lymphoma is the activation of C-myc (C-myc is a proto-oncogene may convert into oncogene which encodes a nuclear phosphoprotein that plays a Crucial in cell cycle progression, apoptosis, and cellular transformation) oncogene through its transfer into the immunoglobulin region.

Streptococcus bovis and Colorectal cancer

Streptococcus bovis is currently named *Streptococcus gallolyticus.* As the third most common malignancy and the second most deadly cancer, colorectal cancer (CRC) induces an estimated 0.9 million deaths and 1.9 million new cases were reported worldwide in 2020. The incidence of CRC is higher in highly developed countries, and it is increasing in middle and low-income countries due to western food habits [49-51]. *S. gallolyticus is mainly associated with colonic neoplasia and extracolonic malignancy. However, all genospecies are not closely related to the CRC.* A study conducted by Tsai., *et al*. in 2016 showed that between 25 and 80% of patients with *S. bovis* bacteremia have concomitant colorectal tumors. In this study, a total of 107 patients with *S. bovis* bacteremia were identified and investigated with colonoscopy, 15 of these patients (30.6%) had colorectal adenocarcinoma [52]. *Another study conducted by* Jason S. Gold., *et al.* in 2004 showed that Forty-five patients (41 adults, 4 children) with documented *S. bovis* bacteremia during 12 years were identified, and 17 (41%, adults) out of 45 underwent colonoscopy. Colonic neoplasia was present in 16 patients (39% of adults), with 3 of these patients having invasive colorectal cancer (7% of adults). Invasive cancer was present in 13 patients (32% of adults). Eight patients had malignant lesions arising within the gastrointestinal tract, and 5 patients had extraintestinal malignancies. All the data related to *S. bovis* bacteremia conclude that it is associated with colonic neoplasia and extracolonic malignancy.

Discussion

The Microbial aspect of the cancer plays an important role in inducing cancer as various microorganisms affect different mechanisms of the body to induce malignancy in cells. The type of microorganisms being listed in the above review article shows that how different types of microorganisms alter gene mechanisms, make fool out of the immune system, alterations in signaling pathways, increased the rate of growth signal inhibitors, and many such factors. However, another area of research interest that can be of great importance is the therapeutic aspect of microorganisms towards the cure of cancer as the healing mechanisms of cancer would be inward driven resulting in the cure of cancer while causing no harm to the human body as the treatment used in present scenario have side-effects and are not reversible. So microbial aspects of cancer hold great potential in both diagnosis and treatment.

Conclusion

In recent times the advancements are such that cancer can be diagnosed and treated as well. However microbial agents play an equally important for research, some of the deeper research is

required in order to get a better understanding of the microbial aspect of cancer because microbe and other microbial flora hold the potential to induce cancer, and modify body cells, genetic mechanisms, body environments. These are the small key factors that also play an important role in cancer to get induced. Another important key factor is the effect of microbes on the body and how the makeup of the body cell gets changed. Another aspect of research can be the therapeutic aspect of microbes towards cancer as the treatment used today such as chemotherapy, cyto proteins, they may be cytotoxic and the changes it does to the body are non-reversible further research towards this aspect via advanced biotechnological approach and microbiological practices would make advancements further.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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