Parasites and Cancer - A Molecular Insight

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Abstract: Cancer due to parasitic infection is one of the important causes of cancer. Parasites have an oncogenic potential of causing tumor formation in humans. Trematode parasite species such as *Schistosoma haematobium* and liver flukes such as *Opisthorchis viverrini*, *Clonorchis sinensis* are the major cause of bladder cancer. p53 is most widely used genetic marker in the bladder cancer. Micro RNA's that are differentially expressed in cancer cells, compared to that of normal cells could be used as marker for functional analysis of up regulation and down regulation of genes. Further research on functional characterization of Micro RNA's could eventually lead to the development of Micro RNA based therapeutics.

Keywords: Parasites, Cancer, Micro RNA’s, Therapeutics.

1. INTRODUCTION

Cancer is the global burden and it causes about 7.6 million deaths worldwide, with Most deaths occurring in low and middle income countries and it is projected to be rising at the Alarming rate to 11 million deaths in 2030 according to World Health Organization estimate [1]. Cancer due to infection is one of the most important causes of cancer and infection associated cancers are progressively increasing [2]. Cancer due to parasitic infections is found mostly among poorest people of the developing countries mainly in North African countries. Bladder cancer mostly occurs in men and chronic infection due to *Schistosoma haematobium* accounts for almost most of the deaths in developing countries [3]. In United States of America alone, it caused about 70,530 deaths for the year 2010 [1].

Parasites are the ones, which live in organism and derive food from the host; they lead a non-symbiotic relationship in which they derive food at the expense of the host. Parasites derive all the nutrients from the host organism. Parasites cause numerous diseases in human beings particularly in tropical and semi-tropical countries. Parasitical diseases are less in very well developed countries. Parasite fitness is determined by the high number of descendents and efficient exploitation of the host [4]. Macro parasites have very well developed dispersal stages, which help them to expand the parasites range, find host and facilitate the genetic exchange [5]. Monoxenous parasites complete their complete life cycle in one host, whereas the heteroxenous parasites have to change host several times in their life history [5]. The free-swimming stage in the life cycle of the parasite is for the efficient dispersal [6]. Host parasite interaction is the one in which every mammalian host is in the constant danger of being infected with viruses, bacteria, fungi and parasitic protozoan’s. The host- parasite molecular cross talk is largely shaped by evolutionary process, which is shaped by taking into the account of successful colonization of host tissue and successful exploitation [7]. In parasitism, there is not only impairment of host physiology and reproduction, but it even can lead to complete impairment and complete death [8]. In the case of cancer, parasitic behavior is exhibited by the malignant cells spreading across the organs and tissues of the host, resulting in a increase in the level of enzyme such as Gamma glutamyl transferase as the diseases progress ([9]. Recent studies have shown that the Gamma glutamyl transferase is released by the cancer cells including submicroscopic vesicles [10]. The Gamma glutamyl transferase activity on the cancer cells affect the redox equilibrium, producing extracellular effects on the S-thiolation status of extracellular proteins [11]. The exosomes rich in Gamma glutamyl transferase are shed by cancer cells facilitating the malignant cell survival and diffusion in the host tissues and this is similar to the one reported in Helicobacter Gamma glutamyl trans-peptidase [12].

The relationship between infectious agent and cancer provides valuable insight to understand the molecular basis of carcinogenesis [13]. Cell free lysate from the chicken sarcoma is shown to cause cancer, in an second animal and this was demonstrated for the first time by Rous in 1911, to prove the hypothesis that the cancer has an infectious origin [14]. Parasites have an oncogenic potential and their removal from the host may result in the reversal of tumor development [15]. Parasites induce carcinogenesis by chronic inflammation in which phagocytes at the site of inflammation...
produce reactive oxygen free radicals, reactive nitrogen free radicals which in turn can cause damage to DNA, Protein, Cell membrane, changes in gene expression, alter enzyme activities, ultimately resulting in cell damage and neoplasia [16]. Parasites have tendency to insert active oncogene into host genome, suppressing the tumor suppressor genes of the host organism and thereby inducing the mitosis [17].

2. CANCER CAUSING PARASITES

There are numerous reports of number of parasites causing cancer; the major ones are the trematode parasite species such as *S. haematobium* and liver flukes such as *O. viverrini, C. sinensis*, which actually cause cancer. *O. viverrini* and *C. sinensis* are flat worms, inhabiting the liver and they may cause bile duct cancer, which almost affects 20 million people, predominantly in northeastern part of Thailand [18]. Schistosomiasis is one of the most affected parasitic diseases in the world with 240 million people affected in 76 countries with almost about 3000000 deaths in Africa alone according to World Health Organization [19]. *S. haematobium* is a major cause of Bladder cancer [20]. *Toxoplasma gondii* infection causes ocular tumors, menigioma, leukemia and lymphoma [21]. *Trichomonas vaginalis* is the major cause of prostate cancer [22].

3. PARASITES AND CANCER

3.1. Schistosomiasis and Cancer

Granulomatosis inflammation and fibrosis in the bladder surrounding the eggs are the hallmarks of urogenital Schistosomasis. There is epidemiological evidence of oncogenesis suggesting the formation of Squamous cell carcinoma in the bladder due to *S. haematobium* infection. Schistosoma is recognised by World Health Organization as potential carcinogenic agent with potential risk to humans [23]. It is also recognized by American Cancer society as an infectious agent that increases cancer risk. The international agency for research on cancer (IARC) considers *S. haematobium* infection as definitive cause of urinary bladder cancer with five fold risk [24]. In china and japan, *S. japonicum* infection leads to hepatocellular carcinoma formation [25] the eggs which are deposited in the bladder cause florid tissue inflammation leading too much of morbidity of infection [26]. Urogenital schistosomasis leads to more aggressive forms of bladder cancer [27]. Animal models such as novel mouse model are recently used in research to understand the infection, in which injection of *S. haematobium* eggs into bladder wall of mice recreates the development of human disease, leading to bladder granulomata, bladder fibrosis and hematuria [28]. There is formation of granulomatous inflammation due to Schistosoma in the bladder wall. Inflammation due to this will bring with it certain growth factors and survival factors that encourage cell proliferation and the inflammatory cells also release reactive oxygen species that are potentially mutagenic. The immunobiology of Schistosomasis is related to the egg antigen or soluble extracts of worms being used in laboratory experiments, which may directly induce neoplastic transformation [29].

3.2. Liver Fluke and Cancer

The International Research agency on cancer has reported that *O. viverrini* is a potent human carcinogen and others such as *O. felineus* and *C. sinensis* has less carcinogenic effect. Cholangiocarcinoma, due to liver fluke *C. sinensis* infection is found in higher rate in Pusan, South Korea [30]. Liver fluke infection on the bile duct epithelium results in chronic irritation and inflammation resulting in hyperplasia and these cells are liable to induce DNA damage in the cells [31]. Neoplastic transformation is formed in the bile duct, due to the continuous production of nitrous oxide compounds by the inflammatory cells. Cholangiocarcinoma is further characterized by the increase of drug metabolizing enzymes such hepatic Cytochrome p-450 at the site of inflammation compared to than those of controls in adult male hamsters [32]. Extracellular vesicles from parasites are shown to influence host physiological processes including immunomodulation, adherence and communication between host and parasite [33]. O. viverrini secretes extracellular vesicles that are internalized by cholangiocytes *in vivo* thereby promoting the cascade of inflammatory and tumourgenic changes within cell thereby promoting the uptake of extracellular proteins by biliary cells of infected host leading to the development of Cholangiocarcinoma [34]. The release of Extracellular vesicles in the secretory products of carcinogenic liver fluke promotes inflammatory and modulatory response leading to the formation of biliary cancer [34].

3.3. Trichomoniasis and Cancer

*T. vaginalis* is a pathogenic protozoan, occurring in sexually transmitted disease worldwide and exists in female lower genitourinary tract. Trichomoniasis usually coexists with other sexually transmitted disease like gonorrhea, bacterial vaginosis [35]. The disease results
in the development of vulvavaginitis with yellowish frothy discharge. There are studies reporting close association between T. vaginalis and cervical neoplasia [36]. In Trichomoniasis infection, there is strong increase in antibodies against the T. vaginalis in patients with invasive cervical neoplasia compared to that of controls [37]. There is a tremendous increase in antibody titre against the T. vaginalis antigen in patients with squamous cell carcinoma [37]. The centre for disease control and prevention have reported that 5% of the T. vaginalis isolates have some kind of resistance against the drug Metronidazole [38]. Actin protein is major component of cytoskeleton, involving cellular mobility and cell interaction, affecting the variations in T. vaginalis on transforming from flagellate form to ameboid form [39]. Actin gene is used as a molecular marker to identify and investigate the molecular pathways of the parasite T. vaginalis by PCR-SSCP (PCR-Single stranded conformational polymorphism and DNA sequencing studies [40]. Recently RAPD studies on Iranian isolates of T. vaginalis confirmed the genetic variation among it and also concluded that there is no strong association between genetic variability and geographical origin of isolates [41]. HSP 70 gene analysis by RFLP in T. vaginalis indicated that there is considerable genetic diversity among the samples from USA [42]. T. vaginalis secretes a protein T. vaginalis macrophage migration inhibitory factor that is 47% similar to human macrophage migration inhibitory factor and is reported to be increased in the case of prostate cancers [43]. Human macrophage migration inhibitory factor has been reported to cause inflammation, autoimmunity, cell proliferation, angiogenesis and tumourigenesis [44].

3.4. Toxoplasmosis and Cancer

Toxoplasma gondii infection and relative occurrence of tumors like primary ocular tumors, meningioma, and leukemia is relatively very rare in nature [45]. The toxoplasma cysts in the tumor cells were identified by using Toxoplasmic Antibodies [46] Toxoplasma gondii infection may promote initiation and progression of brain cancer by modifying miRNA ome in brain cells [47]. Differenthial expression of micro RNA's in brain tumors including glioblastoma, pituitary adenoma and medullablastoma, on comparison with normal tissues have been reported [48]. Toxoplasma infection has been shown to promote expression of anti-apoptotic proteins such as Bcl2, Bfl1,Bcl-x1,Bcl-w,Mcl-1,Bad and Bax in host cells [49]. Toxoplasma infection has been specifically shown to cause increase mature miR-17-92 derived micro RNA's in primary human foreskin fibroblasts [50]. Whole genome expression profiling per-
factor receptor (Her 2/ neu/ c-erb2) expression and efficacy of combining Trastuzumab (human monoclonal antibody that binds to her 2/ neu) with first line therapy of recurrent or metastatic her 2/ neu positive urothelial cancer was conducted [61]. Immunotherapy using BCG (Bacillus-calmette-Gurin) intravesical instillation remains one of most effective therapy for bladder cancer [62]. Aberrant epigenetic alterations observed in bladder cancer, are useful in finding out new Tumor biomarker for diagnosis [63]. Gene expression analysis by Microarray revealed the up regulation and down regulation of genes in bladder cancer in comparison with the normal tissue [64]. Methylation patterns were found to be altered in bladder cancer in comparison with normal urothelial epithelia, and DNA hypermethylation usually occurs in the specific regions (CpG islands) [65]. Epidermal growth factor receptor pathway (EGFR) is over expressed in bladder cancer and it is usually targeted with the help of drugs including tyrosine kinase inhibitors (Gefitinib, lapatinib, Sorafenib) and monoclonal antibodies such as cetuximab, trastuzumab [66]. Micro RNA’s function as negative modulator of gene expression by binding to complementary sites in target mRNA indicating that they also function as tumor suppressor genes [67]. Superficial bladder cancer is effective target for virus based gene and local immunotherapy, in which the patients with locally advanced bladder cancer, treated with replication defective CMV driven adeonoviral construct for vector delivery and gene expression results in patients showing transgene expression via RT-PCR [68]. Pro apoptotic drugs works well in improving the bladder cancer treatment in animal models, but so far no success had been made in the clinical trial involving humans [69]. Clusterin, an important chaperone protein is involved in proapoptotic treatment with apoptosis inhibition and chemo resistance in bladder carcinoma [70]. Drug resistance and treatment failure against the Trichomoniasis with only drug metronidazole had been reported [71]. The micro RNA’s that are differentially expressed in toxoplasma driven cancer cells could be used as markers and would be useful in the functional analysis of Micro RNA up regulation and down regulation in cell lines and experimental animals. These would further reveal toxoplasma modified micro RNA expression on survival and death pathways of brain cancer cells. This would further lead to micro RNA based therapeutics. Control of seizure is better in patients with neurocysticercosis after a course of anticysticercal drugs such as Albena-zole and Praziquentel [72]. A protective antigen from Taenia ovis oncosphere stage has been cloned to develop a recombinant vaccine against the ovine cysticercosis and this vaccine is commercially available in Newzealand [73].

5. FUTURE RESEARCH AND CONCLUSION

The molecular mechanism and other potential factors, which are causing the parasites to cause cancer have to be found out. Parasitic infections basically leads to chronic inflammatory response, the mechanism of infection related tumors has to be scientifically elucidated out. The basics of avoiding parasite associated cancer are avoiding exposure to parasite, reducing parasite transmission, treating the infected immediately are the some of things which help in the prevention strategy. Micro RNA’s in the bladder cancer are to be compared with that of the normal bladder epithelia to evaluate the up regulation and down regulation of the genes. Novel Drugs such as, inhibitors of EGFR pathway such as cetuximab and tumor angiogenesis inhibitor pathway such as bevacizumab and sunitinib have been recently used in the treatment of bladder carcinoma. More emphasis is to be carried out on drug development research in order to find out newer therapies. In order to personalize therapy of urothelial cancer, new molecular markers have to be developed. Subunit vaccines targeted against Extracellular vesicular surface molecules of carcinogenic liver fluke O. viverrini can be developed to control this deadly disease. In T. vaginalis actin gene is used as genetic marker, and further research is needed to understand the relationship existing between gene polymorphism and phenotypic behavior of the parasite. The relationship between T. vaginalis and prostate cancer can be further analyzed by using parasitic mimics of human cytokines, which would help us to understand the mechanism of chronically infective parasite affecting the host. Vaccination against the T. solium has not been made possible, due to the complex immunology of parasite making it difficult, but recent success in the development of vaccine against the porcine cysticercosis employing the Recombinant DNA technology paves way for similar success against the human cysticercosis.

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