Single-Cell Biology

Tripathi et al., Single Cell Biol 2015, 4:3
DOI: 10.4172/2168-9431.1000117

Review Article Open Access

Helminth Infections Mediated DNA Damage: Mechanisms and Consequences

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Abstract

According to an estimate, the chronic infections caused by certain pathogens such as viruses, bacteria, fungi and parasites contribute to about 18% of the global burden of cancer; helminth infections attributing to only small part of it. Carcinogenesis associated with the helminthes infections induced development of cancer is a complicated event involving several different mechanisms varying from one species of parasite to another. Parasite infections evoke immune responses in the host which finally result into inflammatory reactions. The chronic inflammatory processes produce reactive oxygen species (ROS) and reactive nitrogen species (RNS). These free radicals may cause DNA damage resulting into genetic instabilities and occurrence of malignancy. The parasites or their eggs or their excretory-secretary products exhibit potential to induce proliferation of some cells in the affected tissues which harbor DNA damage. The existing reports indicate that helminth infections may trigger cancer in the organs of their infection for example Clonorchis sinensis and Opisthorchis viverrini may induce cholangiocarcinoma (cancer of gall bladder and hepatocarcinoma) and Schistosoma haematobium and its other species are known to cause urinary bladder cancer. In many cases of helminth infections mediated carcinogenesis, the DNA damage by free radicals or inflammatory responses at damaged host tissues is demonstrated. Therefore the knowledge about the mechanisms of helminthes mediated DNA damage may be of great importance in management of parasite infections and reduction of incidences of parasites induced cancer thereby improving the quality of human lives. This article presents an updated account of helminthes infection mediated genotoxicity, DNA damage mechanisms and consequences.

Keywords: Helminths; Infection; Inflammation; Genotoxicity; Reactive nitrogen species; DNA damage; Cancer

Introduction

The potential of DNA damaging agents was reflected in the heterogeneity of distribution of DNA corresponding to single-stranded breaks or double-stranded breaks [1]. However, the application of "Comet assay" technique was essentially helpful to detect division of DNA during mitotic division in liver cell suspension (Figures 1 and 2) of Clarias batrachus, that is fast becoming extinct in the region of Gangetic plains in U.P., India, as recorded in the present investigation.

It has been challenging to test the application of comet assay technique on resultant effects of genotoxic pollutants on DNA's integrity in fish cell constituents [2].

The method facilitated differentiation of larger number of single-stranded breaks in cells from those that were undamaged [3], in cases of exposure of cells to Bleomycin, a cancer therapeutic drug. Cancer is a condition in which cells starts dividing abnormally and invades other tissues as well. Cancer brings about changes at physiological, cellular and molecular level. The changes at molecular level lead to genotoxic changes. The genotoxic changes include breakage of DNA strands, genetic mutation, chromosomal aberrations etc. In recent years the focus of attention has been on parasitic determinants of cancer which affect global health [4]. Infections generally promote carcinogenesis by

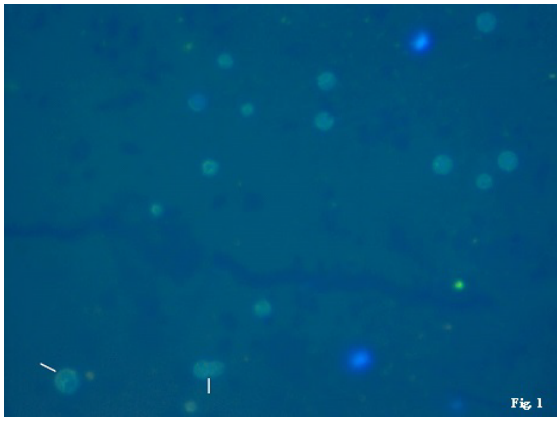

Figure 1: DNA during mitotic division in liver cell suspension.

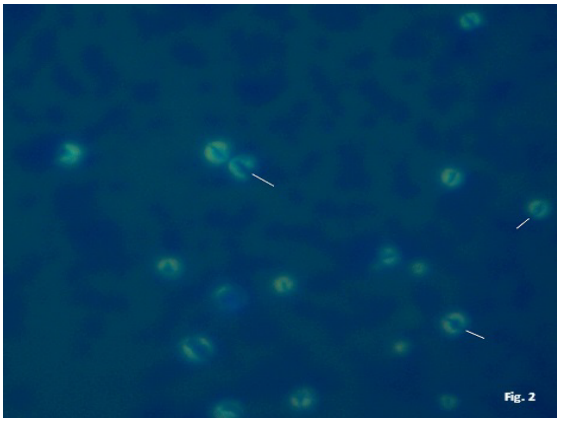

Figure 2: DNA during mitotic division in liver cell suspension.

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Received June 23, 2015; **Accepted** July 23, 2015; **Published** July 25, 2015

Citation: Tripathi R, Jaiswal N, Sharma B, Malhotra SK (2015) Helminth Infections Mediated DNA Damage: Mechanisms and Consequences. Single Cell Biol 4: 117. doi:10.4172/2168-9431.1000117

reduced immunosurveillance, by the insertion of oncogenes in the host genome or by chronic inflammation [5]. Parasitic worms infect billions of people worldwide and 15% malignancies worldwide are attributed to infections [5]. These worms include roundworms, flatworms and foodborne liver flukes causing particularly important diseases in human beings which are being neglected.

The parasites produce eggs that get lodged in the walls and leads to inflammation and fibrosis and may even lead to transformation. These inflammatory area are believed to be surrounded by cells of innate immune system and reactive oxygen species and was thought to be anti-tumour response but has been lately found to actually trigger tumour progression because the factors encourage cell proliferation and are also found to have mutagenic effect and are also found to induce genotoxicity. The genotoxicity is attributed to the presence of metabolites and reactive oxygen species that are triggered around the inflammation that lead to DNA mutagenesis. Phagocytes at the inflammatory site release reactive oxygen radicals and reactive nitrogen radicals having the potential to cause damage to the DNA by causing breaks in the strands, proteins alter enzymatic activities and also alter the genetic expression which leads to induction of carcinogenesis.

The prevalence of helminth infections and their products are known to induce carcinogenesis by a set of different mechanisms depending on the parasite species or the nature of their excretory and secretory products. The helminth infections may cause chronic inflammation due to their persistence in the host for the extended period of time. Under this condition the phagocytes at the site of inflammation generate reactive oxygen (ROS) or reactive nitrogen (RNS) species which cause damage to nucleic acids (DNA/RNA), enzymes and proteins and cell membranes resulting into cancer development [6]. The second possibility could be parasite infection mediated drastic reduction in defense system of the body which facilitates opportunistic infections by many pathogens including certain viruses which may evoke development of cancer [7]. The role of ROS and RNS was reviewed recently [8-10] in the inflammatory process in the host's body under pressure of infection by parasites.

In recent past, several authors have reviewed the published works from many authors on the helminth infection mediated carcinogenesis in the host, however, the exact mechanism of action of host-parasite interplay which could induce cancer in the host is not well known. Further, the knowledge about the helminth infection mediated carcinogenesis in host is important for productive management of the parasite infections and better quality of host health. The present article is an endeavour to bring out the updated information on the issue in a more systematic and precise manner.

Schistosomes as Carcinogens

Among the helminth infections, schistosomiasis, Opisthorchis, Clonorchis and Taenia solium infections have received wider attention. The schistosomiasis being the second most common parasitic infections after malaria, is caused by a trematode, blood flukes. The parasite completes its life cycle using a mammalian host and a fresh water snail. Schistosoma larvae (free-living cercariae) released from the snails penetrate the skin of the mammalian host where the parasite develops into schistosomulae which migrate into liver through blood stream. In liver it matures as adult and starts releasing eggs into blood. These eggs are either filtered out in urine through kidney or stay into hepatic tissues and produce inflammatory reactions. The eggs released in water get transformed into miracidia which reach into snails [11]. The infection by one of the several species of Schistosoma known so far, S. haematobium, is known to cause urinary bladder cancer. The mechanisms of development of urinary bladder cancer include fibrosis induced by schistosome eggs [12], production of nitrosamines (a potent carcinogen) due to bacterial infection [13], absorption of carcinogens from urine and exposure of bladder epithelium [14] and overexpression of parasite urinary beta-glucuronidase releasing carcinogenic amines in urine [15]. Presently S. japonicum can be considered a possible carcinogen for humans, which may cause hepatocellular carcinoma (HCC) [5,16].

The epithelioproliferative potential due to the disorders triggered by eggs of Schistosoma was recently acknowledged [4]. The malignant growth transformation of one type of transformation of one type of transitional epithelial cells to another form of squamous epithelial cells under influence of an abnormal stimulus is associated with the eggs of Schistosoma that are retained back into the tissues of liver, and do not reach into the lumen of urinary bladder with the normal outflowing stream of laterally spined eggs penetrating through the walls of blood vessels, to enter into the urinary bladder before exiting with urine.

The enhanced levels of biomarkers of oxidative stress and carcinogenesis, 8-hydroxy-2'-deoxyguanosine (8-OHdG) in urinary bladder cells were reflected in the failure in the immunopathological control mechanism in the hosts infected by Schistosoma spp. [17]. The initiation of this activity commenced with chronic inflammation that followed infection by Schistosoma spp. and resultant release of potential source of free radicals i.e. eosinophils in urine. This demonstrated influence of reactive Oxygen species in etiology of cancer. Their presence in higher numbers in urine was associated with exorbitant overexpression of DNA-repair genes 8-oxyguanine-DNA-glycosylase and apurinic/apyrimidinic endonuclease (Schemes 1a and 1b) [18]. The genetic heterogeneity was linked with DNA single strand breaks and malignancies that resulted from the oxidization of free radicals and nitrogen species generated from inflammatory mechanism.

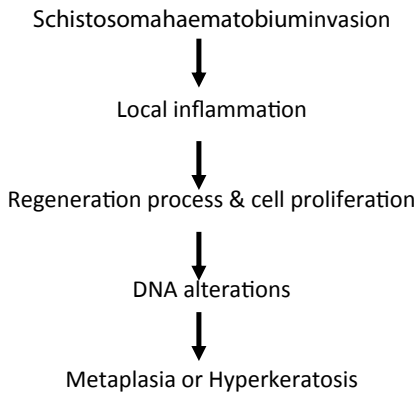
Opisthorchis and Clonorchis Helminthes as Carcinogens

Another group of helminthes causing cancer in humans are the flatworms which harbor in the liver of human, dogs, cats and other wild and domestic animals. These worms are O. viverrini, O. felineus and C. sinensis. Out of these three flatworms, O. viverrini is recognized as a human carcinogen causing cancer of bile duct e.g. cholangiocarcinoma, which is a very rare tumour. Another parasite, Clonorchis sinensis, has also been associated with the cholangiocarcinoma. As reviewed by [5], the mechanisms (Scheme 2) associated to the liver fluke infections include (1) chronic inflammation making bile duct epithelium vulnerable to carcinogens which may cause DNA damage [19], (2) enhancement of endogenous carcinogen such as N-nitroso compounds formation by parasites at the site of inflammation which culminates into neoplastic transformation [6], (3) upregulation of metabolic enzymes such as cytochrome p-450 isoenzyme in hepatocytes which metabolises N-nitrosodimethylamine and transforms into a product which is a potential DNA methylating agent causing DNA damage [20]. It can also induce RNS, like NO, which may cause DNA damage. It was however, elaborated recently [21] that high cell turnover in hepatocarcinoma genes induced several critical alterations for malignant transformation, including structural and/or functional modifications of proteins involved in cell-cycle control, apoptosis, oxidative stress, lipid peroxidation, and DNA repair damage [22,23]

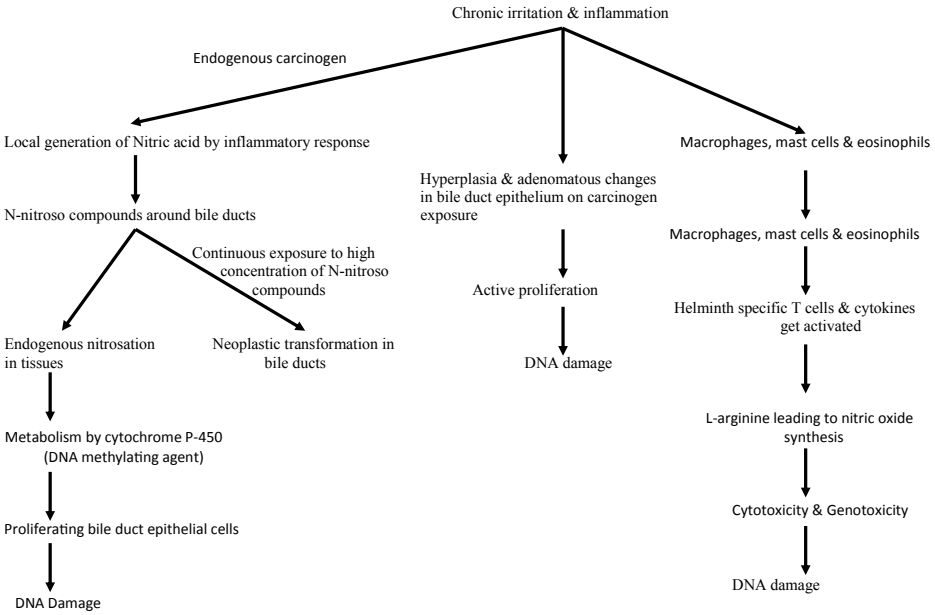
Cestode Mediated Carcinogenesis

Another helminth, Taenia solium, has also been found to induce

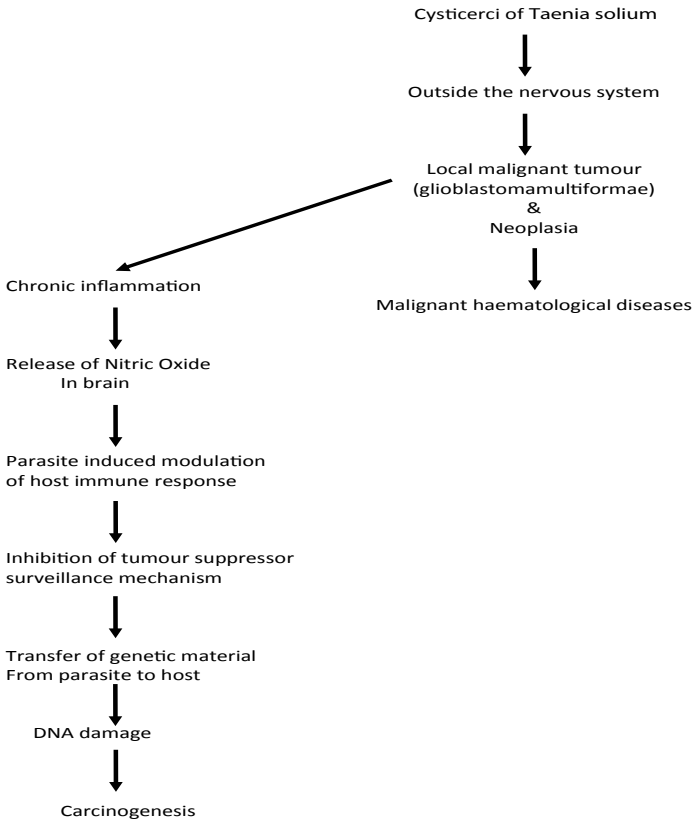
Scheme 1a: Development of urinary bladder cancer by infection of eggs of *Schistosoma haematobium* [18] The recent evidences were quoted [18] to elaborate secretion of mitogenic proteins by *O. viverrini* in liver tissues to promote cell proliferation, mutagenesis followed by carcinogenesis, while in *C. sinensis* infections, up-regulation of cyclin B and transcription factor E2F1 also co-occurred.



Scheme 1b: Development of Metaplasia or Hyperkeratosis due to cancer by infection of Schistosoma haematobium [18].



Scheme 2: Development of liver cancer by infections of adult flukes of Opisthorchis viverrini and Clonorchis sinensis [5]. The neoplasia affirmatively appeared extraneous to nervous system [5] that was associated with glioblastoma multiformae triggered by neurocysticercosis.



Scheme 3: Development of Neurocysticercosis in rats due to cancer by infection of cysticerci of Taenia solium [5]. Khurana et al. stressed on the positive evidence associating parasites with tumour development by illustrating its removal with cell proliferation & inflammation in the event of the worms of potential carcinogenic induction properties.

tumours after infection and the disease condition is known as neurocysticercosis. The mechanism (Scheme 3) of generation of cancer due to the infection of this parasite include (1) chronic inflammation and release of a potential carcinogen such as nitric oxide [24], (2) parasite mediated inhibition of tumour suppressors [24] and the interaction of excretory-secretory products of the parasites to the host

or transfer of its genetic material from parasite to the host causing DNA damage [25]. The role of larval forms of Taeniataeniae formis in hepatic sarcoma of rat was reported in natural hosts [26], and later confirmed experimentally by metastasizing tissues and malignant nature of lesions [27]. The genesis of multiple peritoneal sarcomas was associated with the active constituents of Taenia larvae [28,29].

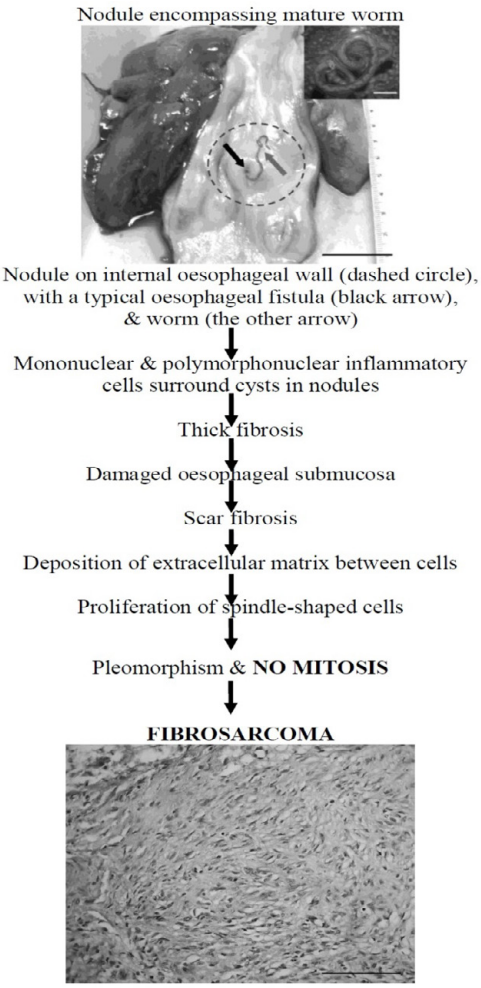


Figure 3: Development of oesophageal cancer by infections of adult worms of *Spirocerca lupi* [30].

Nematode Mediated Carcinogenesis

The manifestations of *Spirocerca lupi* in dogs (Figure 3) [29] were the oesophageal fibrosarcomas and osteosarcomas with metastasis to lung and other viscera, as reported [30]. The study [30] conducted on *Spirocerca lupi* in dogs emphasized occurrence of spindle-shaped cell formation, with elements typical of fibrosarcoma, encompassing little pleomorphism, without mitoses.

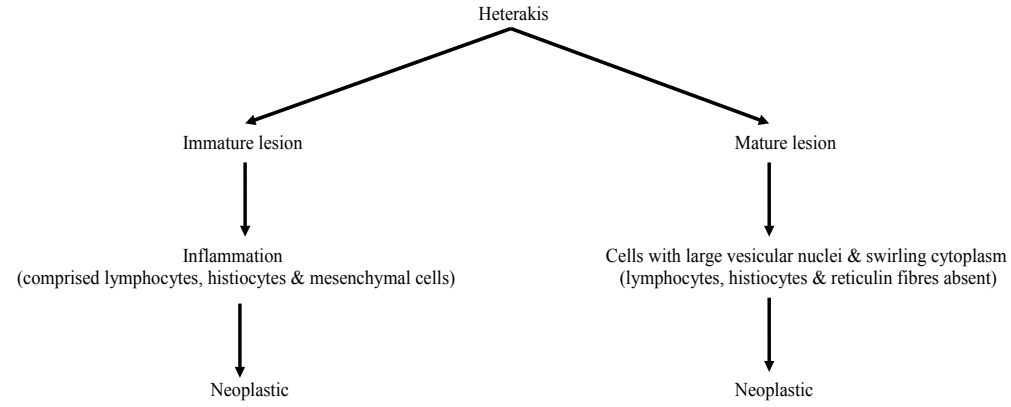
The peculiar fistula on oesophageal wall internally, was linked, on one hand, with a nodule, while continued with oesophageal lumen harbouring worms of *S. lupi*, on the other hand. The most significant observation of Da Fonseca [29] on deposition of extracellular matrix between cells, that did not undergo mitosis, and proliferation of spindle-shaped cells occurred with little pleomorphism in the host infected by *S. lupi*, was comparable with the present findings, in which somatic division represented by division of DNA has been demonstrated (Figures 1 and 2).

The cystic fasciculated nodules that harboured worms of *S. lupi* in dogs comprised mononuclear and polymorphonuclear inflammatory cells with thick fibrosis, were recorded in cases of canine spirocercosis in Guapimirim city [30]. The emergence of granulomas in the presence of inflammatory cells, and fibrosis were the noticeable features, and spindle cell clusters were generated, that were compatible with formation of typical esophageal fibrosarcoma. The inflammation (Scheme 4) [31] caused by another nematode, Heterakis sp. results into neoplastic development of tissues after immature and mature lesions are observed in mammalian liver.

Immunological Consequences of Helminth Infections Leading to Cancer

The cellular toxicity induced by nitric oxide (NO) that is synthesized from L-arginine released due to the digenean infestation of liver and macrophages, mast cells, eosinophils etc. encountered around the chronic inflammatory zone, under activation by parasite specific T cells and cytokines, resulted into DNA damage [6,32]. Therefore, genotoxic effects of such cytotoxic activities were propounded as promoters of cholangiocarcinoma due to liver fluke infections. Scientists have not agreed to their role as 'initiators' mainly because of the essential presence of cofactors as a prerequisite [5] along with carcinogens to induce carcinogenesis in liver fluke (Clonorchis and Opisthorchis) infected bile ducts of animals.

The possible mechanisms of helminthes mediated carcinogenesis



Scheme 4: Development of liver cancer by infections of adult flukes of Heterakis sp. in mammals [24].

Mechanism	Constituents	Host(s)	Organism(s)	References	Type of Cancer
Inflammation mediated response mechanism		Human beings	*Schistosoma* spp.	[12]	Urinary bladder carcinoma
a) Host immune response mediated	Inflammatory factors			[33]	Squamus cell carcinoma (SCC) of urinary bladder
b) Immunopathological response mediated	Inflammatory factors			[13]	*Schistosoma* associated-bladder cancer
				[34]	*Schistosoma* associated-bladder cancer
				[14]	*Schistosomiasis* induced carcinoma
Metabolic activation of procarcinogens and DNA damage	Aflatoxins, Nitrosamines from Nitric Oxide (absorbed from bladder epithelium)	Rodents, dogs	*Schistosoma* spp.	[12-14,33,34]	Squamus cell carcinoma (SCC) of urinary bladder
Genotoxic factors mediated DNA damage	Eosinophils, Reactive Oxygen Species	Human beings	*Schistosoma* spp.	[17]	Hepatobiliary carcinoma
Oxidative DNA damage	Reactive Oxygen Species, Reactive Nitrogen Species	Mammals	*Schistosoma haematobium*	[35]	Urinary bladder carcinoma
Inactivation of protooncogenes mediated response	Oncogenes, Protooncogenes	Mammals	*Schistosoma* spp.	[33,36,37]	Squamus cell carcinoma (SCC) of urinary bladder; Hepatobiliary carcinoma
DNA modification mediated damage	DNA methylation	Mammals	*Schistosoma* spp.	[38]	Chemokine induced immunopathogenesis
		Humans	*Opisthorchis viverrini, Clonorchis sinensis*	[39]	Cholangiocarcinoma, Hepatocarcinoma

Table 1: Helminths infections mediated genotoxicity, associated mechanisms of DNA Damage and carcinogenesis.

are summarized in Table 1.

Conclusion

The information available as on date reflects that some helminth infections may directly get involved in releasing carcinogens or mediating release of carcinogens or producing immunocompromised state in the host inviting opportunistic infections by the viruses which may induce cancers, whereas there are some other helminth infections which may indirectly induce cancers in the host. Mitosis was not reported in the cells of dog hosts afflicted with spirosarcoma, while dividing DNA in the somatic cells of the liver of Clarias batrachus have been recorded in the current investigation. However, intensive research is required to be done to delineate the underlying mechanisms involved in occurrence of helminth infection mediated carcinogenesis. It may also help in early diagnosis, prompt treatment and prevention of such infections.

Acknowledgements

SKM is thankful to University Grants Commission, New Delhi for financial support Grant No. 41-17/2012 (SR). NJ is thankful to UGC for a Post-Doctoral research fellowship.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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