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Editorial

India is a one of the biggest democratic nation and the Carnival of democracy is on. The citizens has to participate in this carnival by casting his/her most valuable vote to the party to whom one think appropriate to develop the nation. The question arises why the youngest nation with high potential is lagging behind in all the aspect of growth. Till date the participation of young voters of India are not adequate and India was ruled by inappropriate politicians.

Are we the voter of India born to listen only rosy speeches not to see the acts? For the sake of development of India we the vigilant citizen of India have to participate in this democratic process and elect politician who have a manifesto for development plan, good governance other than this morbidness of caste driven politics. Now this is the time to show the power of common man by casting our valuable vote to beguile the renaissance.

It is time to remind our politician about their duties and ask for good governance.

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Manuscripts submitted to Quest should adhere to below mentioned criteria.
Research News: About 400 words (1 page)
Research Article: About 2000 words (4 pages)

Common for all: -
Font: Calibri
Font Size: 14
Columns: 2
Line Spacing: 1
Margin: Narrow
References: 1) In text citing, S No, Superscript.
2) Author's name (s), *Journal name*, Volume No, Page No**,** (year).

Reasons Behind Cardiac Disorder

Cardiovascular disease (CVD) is globally considered as the leading cause of death with 80% of CVD related deaths being reported from low and middle income countries like India.

According to Medilexicon's medical dictionary, Cardiovascular means: "*Related to the heart and the blood vessels or the circulation.*"

Circulatory system, is the system that moves blood throughout the human body. *I*t is composed of the heart, arteries, veins and capillaries. It transports oxygenated blood from the lungs & heart throughout the whole body through the arteries.

The circulatory system may also include the circulation of lymph, which is essentially recycled blood plasma after it has been filtered from the blood cells & returned to the lymphatic system. Whereas the cardio vascular system doesn't include the lymphatic system.

The lifetime risk for cardiovascular disease is more than 50% for both men & women. Even among those with few or no cardiovascular risk factors, the risk is still more than 30%.

According to National Health Service (NHS), UK,; There are 9 risk factors associated with cardiovascular disease, they are:

- Hypertension (high blood pressure)
- Radiation therapy
- Smoking
- Lack of sleeping
- Hyperlipidemia(high blood cholesterol)
- Having a partner with cancer
- Diabetes
- Unhealthy eating
- Stress

Another are age, gender, tobacco consumption, alcohol consumption, sugar consumption, lack of physical activity, family history, obesity, psycho social factors, air pollution etc.

Hypertension (high blood pressure)

This is the one major risk factor for CVD. If hypertension is poorly controlled, the artery walls may be become damaged, raising the risk of developing blood clot.

Radiation therapy

Scientist from the Karolinska Institute, Sweden; reported that "radiation therapy can increase the risk of cardiovascular disorder"

Smoking

Regular smoking can narrow the blood vessels, especially the coronary arteries.

Lack of sleeping

People who sleep less than 7.5hours each day have a higher risk of developing cardiovascular disorder.

Hyperlipidemia (high blood cholesterol)

If the concentration of cholesterol is high in blood, higher chance of narrowing the blood vessels &blood clots.

Having a partner with cancer

A person whose partner has cancer has a nearly 30%higher risk of developing stroke or coronary heart disease.

Diabetes

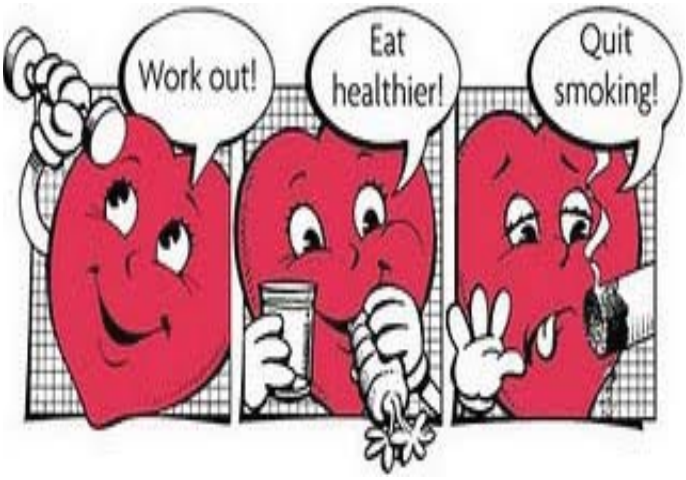
This includes both type1&2.high blood sugar levels can harm the arteries. People with type2 diabetes are often overweight or obese, which are also risk factors for cardiovascular disorder.

People with diabetes are 2 to 4 times more likely to die from heart disease than non diabetics.

Expert say that blood glucose control measurements can help predict a diabetes patient's cardiovascular disease risk.

Unhealthy eating

Diets which are high in fat combined with carbohydrates, especially of they consist mainly of fast-food, can accelerate the accumulation



of fatty acids inside the arteries, which can cause hypertension & stress.

Stress

Stress is normal part of life that can either help us learn & grow or can cause us significant problems.

Stress release powerful neurochemicals & hormones.

The individual contribution of each risk factor varies between different communities or ethnic groups. Some of the risk factors such as age, gender or family history are immutable. However many important cardiovascular risk factors are modified by life style change, social change, drug treatment etc like hypertension, hyperlipidemia and diabetes.

Contributed By Vidhi IGBT Sem IV

Stem Cell Targeted Gene Therapy of Cancer – A new frontier in personalized and targeted therapy.

Stem cell have the unique potential for self renewal and differentiation, stem cells are seen to carry suicide genes and thus used in 'suicide gene therapy of cancer'. It targets the cancer cell directly thus chemo-radiation therapies are cornerstones.

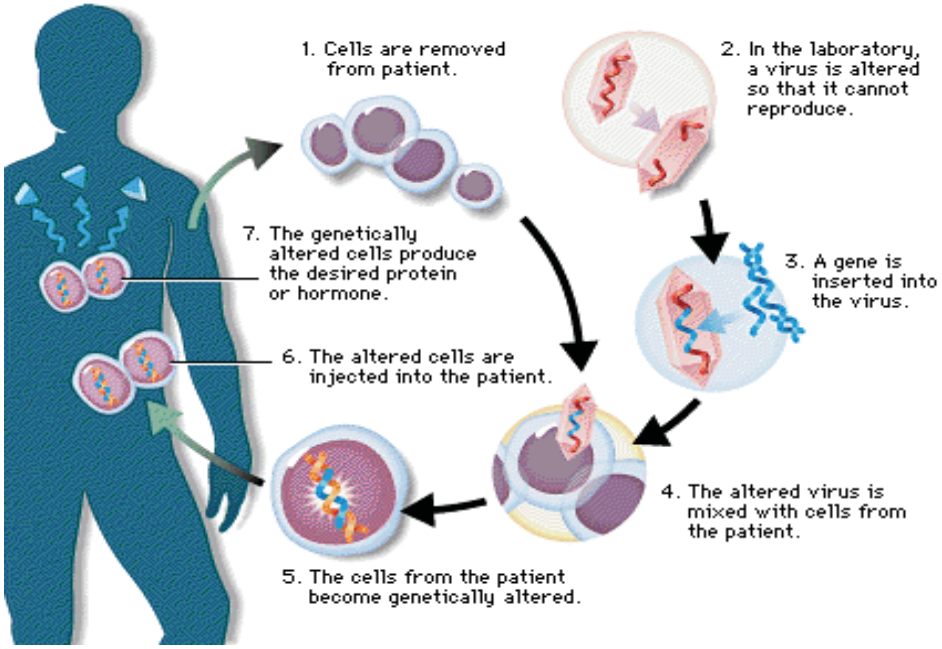
A number of suicide gene systems have been identified, including the herpes simples virus thymidine kinase gene, the cytosine deaminase gene, the varicella zoster virus thymidine kinase gene, the nitro-reductase gene, the e.coli GPT gene, and the e.coli deo gene. Various vectors including liposomes, retro viruses, and adeno virus have been used to transfer the suicide genes to tumors cells. These strategies have been effective in cell culture experiments, laboratory animals, and some early clinical trials. Advances in tissue-and cell specific delivery of suicide genes using specific promoters will improve the utility of suicide gene therapy.

Standard chemotherapeutic agents and ionizing radiations destroy dividing cells. Because tumor cells divide more rapidly than normal cells, there is a theaurapetic index in which damage to the cancer cells is maximized while keeping the toxicity to the normal host cells acceptable. Suicide gene therapy strives to deliver genes to the cancer cells which convert non toxic pro drugs into active chemotherapeutic agents. With this strategy the systemically administered pro drug is converted to the active chemotherapeutic agent only in cancer cells, thereby allowing a maximal therapeutic affect while limiting systemic toxicity.

Contributed By Parth Patel IGBT Sem IV

Gene Therapy

Gene therapy is the use of genetic manipulation for treatment of disease. The basic concept of gene therapy is to introduce a gene with the capacity to cure or prevent the progression of a disease. It is a method in which a genetically altered gene is inserted to replace a defective or mutated gene in order to cure a genetic disorder.



There are mainly two main types of gene therapy namely: -
Somatic cell gene therapy.

Germ-line therapy.

In somatic cell gene therapy the functional gene is introduced into the somatic cell of human body where its expression is critical for health. Its effect is not heredity.

In Germ-line therapy the functional genes are integrated into the germ cells i.e., the sperms and ovum. The change due to this therapy is heritable and passed on to coming generations.

In general, a gene cannot be inserted into a person's cell directly; it must be delivered through some carrier or vector.

Vector systems are divided in to two:

1. Viral vector
2. Non-viral vector

Viral vectors as the name suggest, viruses are used as vectors or carriers- the gene from the virus is removed and replaced with the genes encoding for the desired effect. Mainly adenovirus, retrovirus are only used as viral vectors.

Non viral vectors are by the use of naked DNA. The techniques involved are: electroporation, gene gun, blood occlusion, hydrodynamic injection, etc.

ADVANTAGES OF GENE THERAPY:-

It is used to cure genetic diseases such as Alzheimer's disease, Parkinson's, cystic fibrosis, sickle-cell anemia, etc.

In germ-line gene therapy the effect is passed on from generations to generations and hence a disease can be completely eradicated.

Disadvantages of gene therapy:-

There are many social and ethical issues related to this technique.

People do not consider it safe as virus itself is a threat to body.

When an unborn is detected with a genetic disorder, it can lead its parents to abort the child and hence ethically cannot be accepted.

Contributed By Nikita Bhatt IGBT Sem IV

Site Targeted Drug Delivery

Targeted drug delivery, sometimes called smart drug delivery, is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. The conventional drug delivery system is the absorption of the drug across a biological membrane, whereas the targeted release system releases the drug in a dosage form. The advantages to the targeted release system is the reduction in the frequency of the dosages taken by the patient, having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels. The system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue via the drug. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. For example, by avoiding the host's defense mechanisms and inhibiting non-specific distribution in the liver and spleen, a system can reach the intended site of action in higher concentrations. Targeted delivery is believed to improve efficacy while reducing side-effects.There are different types of drug delivery vehicles, such as polymeric micelles, liposomes, lipoprotein-based drug carriers, nanoparticle drug carriers, dendrimers, etc. An ideal drug delivery vehicle must be non-toxic, biocompatible, non-immunogenic, biodegradable, and must avoid recognition by the host's defense mechanisms. The discovery of drugs for Alzheimer's disease (AD) therapy that can also permeate the blood brain barrier (BBB) is very difficult owing to its specificity and restrictive nature. The BBB disruption or the administration of the drug directly into the brain is not an option due to toxic effects and low diffusion of the therapeutic molecule in the brain parenchyma. A promising approach for drug systemic delivery to the central nervous system is the use of nano-sized carriers. The therapeutic potential of certain nanopharmaceuticals for AD has already been demonstrated in vivo after systemic delivery. They are based on:

i) Conjugates of drug and monoclonal antibodies against BBB endogenous receptors;

ii) Cationized or end terminal protected proteins/peptides;

iii) liposomes and polymeric nanoparticles coated with polysorbate 80, cationic macromolecules or antibodies against BBB receptors/amyloid beta-peptides. Optimization and further validation of these systems are needed.

The blood–brain barrier (BBB) is the homeostatic defense mechanism of the brain against pathogens and toxins. Complex and highly regulated, the BBB screens the biochemical,

physicochemical and structural features of solutes at its periphery, thus affording barrier selectivity in the passage of desired molecules into the brain parenchyma. One potential in delivering drugs to the brain is the employment of nanoparticles. Nanoparticles can be synthesized from preformed polymers or from a monomer during its polymerization, as in the case of alkylcyanoacrylates. Finally, two main approaches have been proposed for the preparation of nanoparticles by synthetic polymers. The theory of the first scheme follows the emulsification of a water-immiscible organic solution of the polymer, in a surfactant-containing aqueous phase, and followed by solvent evaporation. The second approach follows the precipitation of a polymer after the addition of a non-solvent of the polymer.

Contributed By Anunay Sinha IGBT Sem VI

Nematophagous fungi -A potential bio-control agent for plant and animal parasitic nematodes

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Ashok and Rita Patel Institute of Integrated Study and Research in Biotechnology and Allied Sciences, New V. V. Nagar, Anand.

Abstract

Parasitic nematodes infect various crop and animals and causes huge economic looses. Due to development of resistant among nematode population towards pesticides and environmental pollution is concern research are now aiming to use of biocontrol agent for management of parasitic nematodes. Nematophagous fungi are one of the most prominence nominees to be used for biocontrol purpose. Several researchers have studied this group of fungi, however very few products have been commercialized. Considerable amount of research and development still required to make sure the undefeated use of nematophagous fungi for management of nematodes.

Introduction

As the population of word is increasing the demand for food is also escalating high. The main sources of rations are agriculture and live stock production. Both these are affected by infectious diseases which ultimately leads to deprived production. Parasitic nematodes are one of the pests which cause major loss in agriculture[1] and livestock production[2]. The common practice to overcome this problem is use of chemical pesticides and anthelmintics. However most of them are unaffected on nematodes as they are acquiring resistance towards pesticides[3]. Moreover these chemicals are not eco friendly and toxic to soil and environment[4]. These issues have increased awareness of soil ecology and the importance of maintaining soil health has become crucial now. Alternative way is use of bio-control agents to manage the population of parasitic nematodes and simultaneously health of environment. Bio-control of pest using their natural antagonist is well established and rapidly evolving field of science.

Plant and animal parasitic nematodes and their control strategies

Plant-parasitic nematodes cause diseases and damages food and fibre crop worldwide. The root-knot nematode, *Meloidogyne* spp. infects a variety of crop plants and it has been considered the most damaging plant parasitic nematodes[5]. The total global potential loss in agriculture due to pests varied from about 26 –29% for soybean, wheat and cotton, and 31, 37 and 40% for maize, rice and potatoes, respectively[6] among these losses, Root Knot Nematodes (RNK) are estimated to cause 70% of these loose. Cyst nematodes also cause considerable loss. Several strategies are been employed to control plant parasitic nematodes[7]. These include sanitation, use of resistant verities, soil management, crop rotation, fumigaton, organic amendment, soil so-

larization, chemical nematicides, biological control and others[8-9].

On the other hand livestock industry worldwide is severely affected by parasitic nematodes; they affect animal productivity and thus cause a great economic loss. The most frequent one is gastrointestinal parasitic nematodes[10]. Nematodes belonging to the group of trichostrongylids are of major concern because its blood-sucking feeding habits cause anemia, resulting in the death of the animal. Anthelmintics are widely used to control these parasites. However the overuses of anthelmintics have resulted in the development of resistance. In addition, there has been an increased public concern about chemical residues in animal products.

Biocontrol of nematodes

Biocontrol is the use of living organism especially natural antagonist to control other. Because nematodes often occur in high numbers in soil, it is not astonishing that a variety of soil organisms make use of nematodes as food for nutrition. Soil harbours diverse range of organism which are predators of nematodes Viz., mites, collembolan, flatworms, protozoa, and other predacious nematodes or parasites include fungi and bacteria[11]. Among this diverse range of fungi which are parasites on nematodes known as nematophagous fungi are important group of microorganism. This group of fungi are promising candidate to be used as biocontrol of nematodes in plants and animals.

Nematophagous fungi

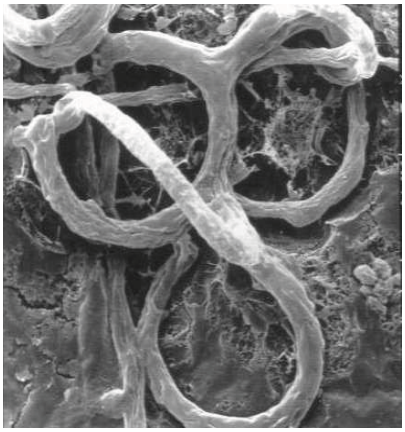
Among microorganisms regulating nematodes population in soil, fungi play a vital role due to their parasitic, antagonistic or predatory behavior. Nematophagous fungi are carnivorous fungi specialized in trapping and digesting nematodes. This group of fungi has been the subject of research over several decades including fundamental studies and their potential as biological control agents against plants and animals parasitic nematodes. Nematophagous fungi comprising a diverse range of species which are able to kill nematodes. Based on the infection mechanism, nematophagous fungi can be sub divided into four categories, nematode-trapping fungi, endoparasitic fungi, eggs parasitic and toxin-producing fungi[12]. These categories of fungi differ in their reliance on nematodes for growth and survival. Nematode-trapping fungi can grow as saprophytes in soils, however when the prey nematodes are present they enter the parasitic stage by developing special hyphal structures called traps, with the help of which it traps nematodes. The killed nematodes offer the fungi with an additional nutrient source that is rich in nitrogen. The endoparasitic fungi are often obligate parasites and are dependent on nematodes for their survival. They infect nematodes with adhesive or non-adhesive spores adhere to the nematode surface followed by growing within prey. The third category is the egg and cyst parasitic fungi that parasitize these non-motile stages of nematodes with their hyphal tips. The last categories of fungi i.e. toxin producing fungi produces toxic substances which are paralyze or kill nematodes.

Nematophagous fungi comprise more than 200 species of taxonomically diverse fungi that all are capable of attacking living nematodes or their eggs and use them as nutrients. The reason for the continuing interest in these fungi is their potential as biocontrol agents against plant and animal parasitic nematodes. From this point of view particularly, the egg-

and cyst-parasitic fungi as well as nematode trapping fungi have been investigated in depth because of the promise of these fungi as bio-control agents. Another reason for the continued attraction in nematophagous fungi is the amazing morphological variation of trapping weaponry and the dramatic capturing of nematodes.

Trapping structures and mechanism of killing nematodes by nematophagous fungi

Nematophagous fungi possess the unique ability of trap nematodes and kill them. To capture nematodes they produce different types of trapping structure including adhesive networks (most of *Arthrobotrys* species), adhesive columnar (*Monacrosporium cionopagum*, *M. gephyropagum* and *Dactylella lobata*), constricting (*A. dactyloides, Dactylaria brochopaga, M. doedycoides*) and non constricting rings (*Dactylaria candida* and *D. leptospora*) or they use spore (*Drechmeria coniospora, Paecilomyces lilacinus, Hirsutella rhossoliensis, Haptoglossa dickii* and *Catenaria anguillulae*) as infectious agents[13]. Nematophagous fungi present a high diversity not only in respect of taxonomic distribution but also in respect of the trapping structures. The type of nematode-trapping structures formed depends on species as well as on environmental conditions. The most important factor is nutrient level and living nematodes. In the presence of nematodes fungi get induced and form massive number of trapping structures. Previously a protein known as nemin was found to inducing factor. Recently researchers have identified pheromones (ascarocides) which are responsible induction in *A. oligospora*[14]. After recognizing the host nematodes, nematophagous fungi secrets various proteases to digest host cutical and nutrients. Proteases form nematophagous fungi have been studied in detail by many researchers[15-17].



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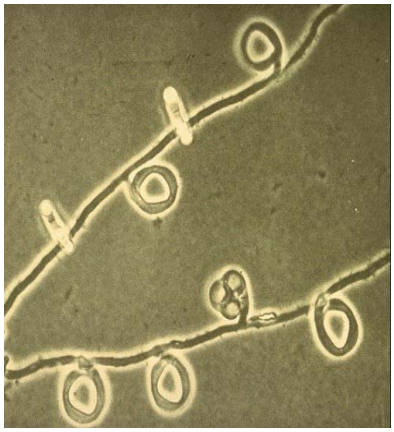

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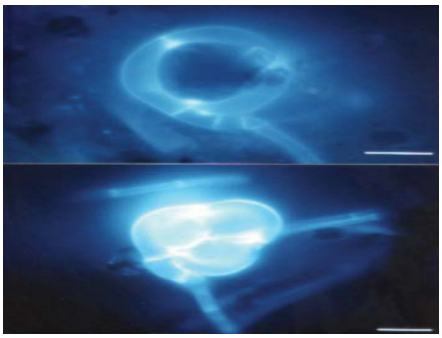

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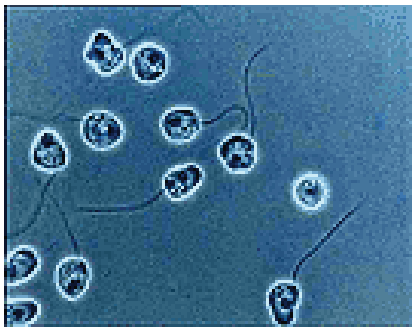
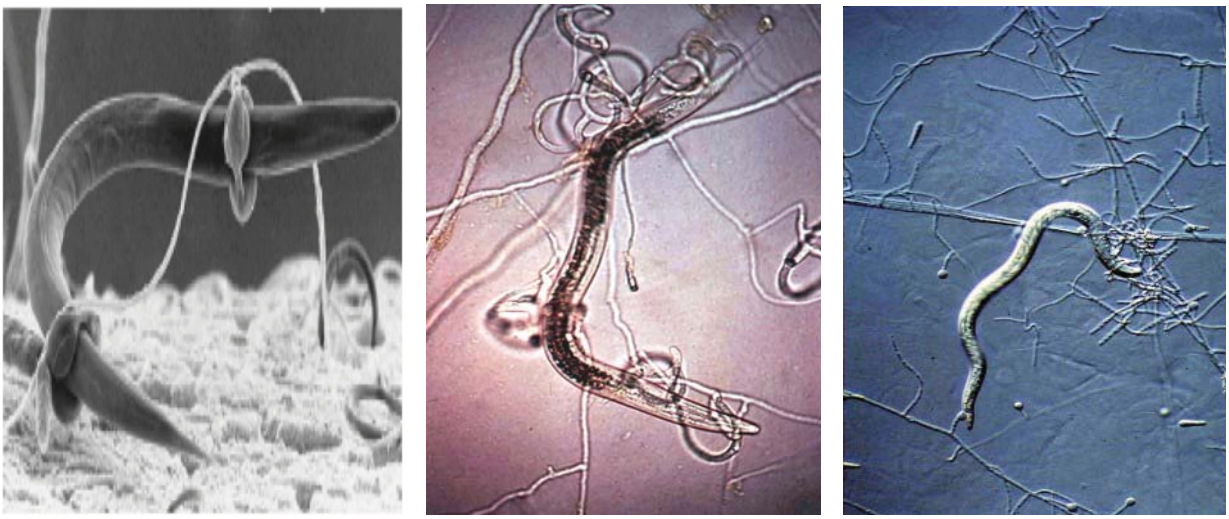


(e)

Fig. 1: Trapping weaponry of nematophagous fungi.
Different types of trapping structure of nematophagous fungi. (a) adhesive network (http://www.biological-research.com), (b) attaching knob http://mic.sgmjournals.org/content/151/3/789.full), (c) Non constricting ring (http://nematology.ucdavis.edu/faculty/westerdahl/courses/slides/fromCD/1939/35B.GIF), (d) constructing ring (http://www.biological-research.com/Fungi/Mycologist) and (e) Adhesive- zoospores (http://lib.jiangnan.edu.cn/asm/305-Introduce.htm).



(b) (c)

Fig. 2: Trapped nematodes inside different trapping strictures.
Mechanism of trapping nematodes. (a) nematode trapped inside constituting ring (http://microbewiki.kenyon.edu/index.php/Nematode_trapping_fungi), (b) nematode trapped within adhesive network (http://plpnemweb.ucdavis.edu/nemaplex/Ecology/anta) and (c) nematode trapped by adhesive hyphal knobs. (http://plpnemweb.ucdavis.edu/nemaplex/Ecology/anta).

Nematophagous fungi as biocontrol agent

Many species of *Arthrobotrys* have been found to show the predatory activity against both plant and animal parasitic nematodes[18-19] (Kumar and Singh 2006; Carvalho *et al*., 2011 and Wang *et al*., 2013). Several researchers have studied different nematophagous fungi against root-knot nematodes[20-21] (Usman and Siddiqui 2012; and Singh *et al*., 2013). For animal parasitic nematodes, *Duddingtonia flagrans* has been extensively for is superior activity in reducing nematode larvae[22-23]. This fungus has also been reported to produce chlamydospores which can survive gut passage in small ruminants[24-25]. These studies reveal that nematophagous fungi are potential biocontrol agent against parasitic nematode infection.

Current status of use of nematophagous fungi

However nematophagous has been extensively studied, there are very few products has been commercialised[26]. In addition to the lack of commercial biological control organisms, relatively low efficacy to trap nematode is major blockage to the use for managing parasitic nematodes. Research aimed at understanding the ecological factors affecting reliable and effective biological control of nematodes, as well as research to improve the effectiveness

of specific antagonists is still indispensable. In recent years, molecular tools have been developed and are beginning to be used to answer critical questions related to biological control of nematodes. Moreover, organisms can be engineered to over-express certain genes that enhance their activity against nematodes[27].

The past few years have seen an increased concern in research related to biological control of nematode. Surveys and empirical tests are being replaced by quantitative experimentation and basic research on the modes of action, host specificity and epidemiology of selected organisms. Such basic data is important for a practical assessment so as to improve the microbial agent at the genetic level. Current experience suggests that biological control agents won't replace the utilization of nematicides however, integrated with alternative control measures including chemicals; they may play a vital role in the development of integrated control strategies in both developed and developing agriculture.

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Epigenetics of Acute lymphocytic leukemia

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Abstract

Epigenetic defines heritable changes in gene expression without the primary DNA sequence alterations. Epigenetic modifications considerably contribute to development and progression of leukemogenesis. Two major mechanisms that cause epigenetic changes are DNA methylation and post-translational histone modifications. Acute lymphoblastic leukemia (ALL) is the commonest childhood malignancy. Studies suggest that epigenetic alterations play important role in occurrence of ALL. In this review, we focus on the current knowledge and major works done on epigentic alteration study and their role in treatment of ALL.

Introduction

Leukemia the most common blood cancer occurs in haematopoietic tissue[1]. Leukemia causes one-third of all cancer deaths in children younger than 15 years. According to National Cancer Institute, the mortality rates have fallen since 1991. In 2013, 48,610 new cases and 23,720 deaths of leukemia were estimated in the United States[2].

The two major types of leukemia are acute and chronic. Acute further includes acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML)[1]. ALL is the most common cancer among children accounting for approximately 75% of all childhood leukemias[2].

Several studies have cleared that heritable changes in gene expression capacity without DNA alterations are associated with tumour progression. These alterations are called epigenetics. Epigenetic alterations causes deregulation of genes which involves aberrant over expression or silencing of gene that participate in development and progression of cancer. It is now clear that epigenetic modifications contribute to the development and progression of carcinogenesis particularly leukemogenesis[3,4].

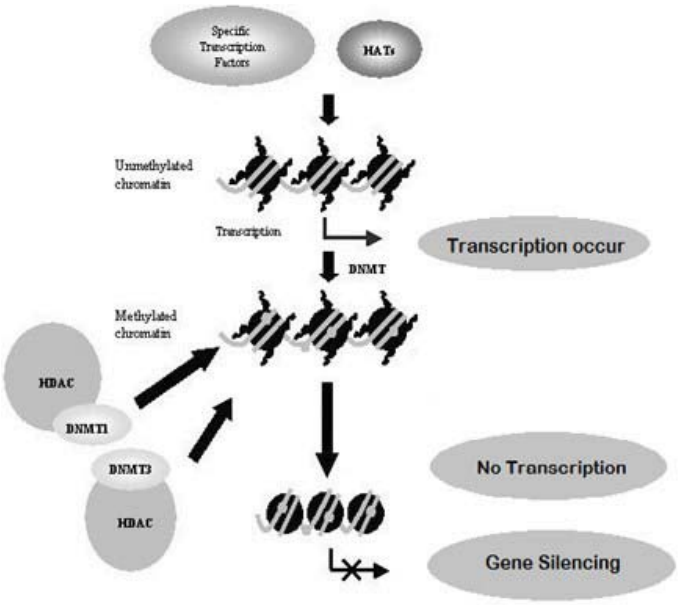

Figure 1: Epigenetic regulation of gene expression

Two major mechanisms that cause epigenetic changes are DNA methylation and post-translational histone modifications. Hypermethylation of CpG islands within gene promoter regions along with deacetylation and other modifications of histone amino acids are associated with transcriptional inactivation (Fig. 1). It represents an important mechanism of gene silencing in the pathogenesis of

human cancer [5].

Epigenetic alterations in ALL

DNA Methylation

DNA methylation is well defined epigenetic alteration which involves addition of a methyl group to cytosine bases preceding guanidine (CpG) residues occurring in CpG islands which cover 60% human gene promoters. DNA methyltransferases (DNMTs) are enzymes that mediate DNA methylation[6]. These catalyze the addition of a methyl group at the 5' carbon of cytosine residues that precede guanosine (CpG) islands[7].

Compared to normal cells, cancer cells display aberrant methylation of cytosine residues both in gene promoters or coding regions, leading to a transcriptional silencing of tumor suppressor gene[8].

Acute lymphoblastic leukemia (ALL) arises by the rapid proliferation of immature lymphoblasts (B- or T-cell progenitors) which fail to differentiate into mature cells[9]. ALL is the commonest childhood malignancy. Studies suggest that epigenetic alterations are involved in occurence of ALL.

In 1999, Paul G. Corn and colleagues found that *p73* was aberrantly methylated in approximately 30% of acute lymphoblastic leukemias (ALLs). Methylation was associated with transcriptional silencing of p73 gene which is a tumor suppressor gene and is a part of cell cycle regulation[10].

LanLan Shen et. al. in 2003, observed aberrant DNA methylation in p57KIP2 (a cyclin-dependent kinase inhibitor), which causes silencing of its gene expression and leads to a variety of human malignancies. In ALL, a region surrounding the transcription start site of p57KIP2 was found to be frequently methylated in adult patients with ALL. Twenty two percent of Philadelphia chromosome negative patients showed methylation of p73, p15, and p57KIP2. Inactivation of this pathway predicts for poor prognosis in Pheladelphia-negative patients[11].

Jose Roman-Gomez and colleagues in 2007 analyzed the regulation of the Wnt/β-catenin pathway ALL and its role in the pathogenesis of the disease. It was found that expression of the Wnt inhibitors *sFRP1*, *sFRP2*, *sFRP4*, *sFRP5*, *WIF1*, *Dkk3*, and *Hdpr1* was down-regulated due to abnormal promoter methylation in ALL cell lines and samples from patients with ALL. Methylation of Wnt inhibitors was associated with activation of the Wnt signaling pathway as demonstrated by the up-regulation of the Wnt target genes *WNT16*, *FZ3*, *TCF1, LEF1*, and cyclin D1 in cell lines and samples and the nuclear localization of β-catenin in cell lines. Treatment of ALL cells with the Wnt inhibitor quercetin or with the demethylating agent 5-aza-2-deoxycytidine induced an inactivation of the Wnt pathway and induced apoptosis of ALL cells[12].

Later in 2008, a genome-wide analysis of promoter associated CpG island methylation was performed using methylated CpG island amplification (MCA) or DNA promoter microarray in ALL. Sixty five potential targets of methylation were identified using the MCA/RDA approach, and 404 using the MCA/array, out of which 31 genes were validated and 26 were confirmed as being hyper-methylated in leukemia cell lines. Fifteen genes were validated in primary ALL samples for DNA methylation that includes GIPC2, RSPO1, MAGI1, CAST1, ADCY5, HSPA4L, OCLN, EFNA5, MSX2, GFPT2,

GNA14, SALL1, MYO5B, ZNF382 and MN1[13].

In 2009, Yang et al. reported that detection of epigenetic alterations allows the identification of ALL patients with poor prognosis[14].

More recently, Milani et al. (2010), analyzed the methylation patterns of CpG sites in 416 genes and have found different methylation patterns in a large number of samples of ALL patients. They identified 20 genes with DNA methylation levels capable to predict leukemia relapse. These observations suggest that methylation analysis should be explored to identify ALL patients at different risk[15].

Recently a genome-wide analysis of methylation across the spectrum of B-ALL and T-ALL subtypes has been performed. It is the first integrated genome-wide analysis of cytosine methylation, DNA copy number alterations, and gene expression in childhood ALL. Genes with recurring DNA copy number alterations exhibit aberrant methylation. DNA methylation profile of 71 genes in ALL blasts was compared with their status in normal B cells and found that approximately one-third was susceptible to aberrant DNA methylation. Promoter regions of *CDKN2A*, *CDKN2B*, and *PTEN* are found to be hypermethylated and promoter region of *KRAS* to be hypomethylation[16].

Histone Modifications

Histones form the core of nucleosomes and maintain the structure by interacting with DNA. Studies have shown that histones have long amino-teminal tails protruding out of nucleosome which are more prone to post-translational modifications. These modifications include acetylation, methylation, phosphorylation, ubiquitination, and ADP-ribosylation. These modifications are associated with activation and inactivation of gene transcription and influence many other biological processes such as, DNA repair, DNA replication, chromatin condensation etc. Methylation on lysine 4 of histone 3 (H3) activates gene while methylation of lysine 9 on histone 3 is associated with inactivation of gene[4,17,18]. Histone acetylation along with DNA methylation acts to regulate gene expression.

Several data have demonstrated that HATs (histone acetyl-transferases) catalyse histone acetylation and activate transcription[4]. In contrast, histone deacetylation (HDAC) removes acetyl groups from histone tails and thus maintains genes inactivated and silenced. Many studies show high level of HDAC expression that leads to aberrant activity of several proteins involved in proliferation, differentiation, apoptosis, adhesion, etc. in cancer cells[19,20]. In lymphomas also high expression of HDAC has been studied but not much in ALL[21].

Moreno et. al. (2010) reported a higher expression of HDACs in T-ALL. These higher expression of are associated with poor prognosis both in the overall group of childhood ALL and in B-lineage cases[20].

Role of epigenetics in treatment of ALL

Several data have indicated that DNA methyltransferase inhibitors (DNMTi), such as azacitidine, decitabine, and other derivative, are able to restore tumor suppressor gene expression and exert antitumor effects *in vitro* and *in vivo* by inhibiting hypermethylation or causing demethylation of subsequent gene[4]. Also DNMTi, used alone or in combination, may benefit patients with hematological malignancies, the application of this therapeutic strategy to ALL patients is so far limited.

Schafer et. al. (2010) showed that decitabine preferentially kills MLL-r lymphoblastic leukemia cell lines and this response is related with

the upregulation of several silenced genes. This indicates that these demethylating agents have efficacy for this category of infant ALL[22].

More recently, Stumpel et. al. (2011) studied the same category of MLL-r infant ALL patients and observed that eleven miRNAs were downregulated as a consequence of hypermethylation and seven of these were reactivated after exposure to a demethylating agent.[23].

HDAC inhibitors (HDAC-Is) are a class of agents that induce acetylation of histone proteins in tumor cells. Several studies intensively investigated them in preclinical models as well as in clinical trials for a variety of malignancies[24]. In vitro studies showed that novel HDAC-Is are potent growth inhibitors and inducers of apoptosis in human leukemia cells, including ALL cell lines. This can be used as therapeutics for patients with leukemias[8].

Conclusion

Epigenetic modifications consid-erably contribute ALL by causing heritable alteration not in primary DNA sequence. Here, we have summarized data that shows that many genes expressions and molecular pathways are altered by DNA methylation at promoter sites and histone modifications. As methylation, acetylation and other modifications causes alterations that can be relapsed, inhibitors of enzymes catalysing these reactions found to benefit patients with malignancies. This shows that thera-peutic targets regulating epigenetic pathways, demethylating agents and HDAC inhibitors, alone or in combination, will undoubtedly provide further advance in the treatment of hematological malig-nancies, including ALL cases.

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