CHAPTER 59

ZOOLOGY

Doctoral Theses

01. ANGMO (Nilza)
Factors Influencing the Reproductive Behavior of the Partially Radio-Sterilized Male Moth, Spodoptera Litura (Fabr) and its F1 Progeny for Pest Suppression Through Radio-Genetic' Inherited Sterility Technique.
Supervisor: Prof. Rakesh Kumar Seth
Th 27186

Abstract

Spodoptera litura also known as the tobacco caterpillar or the common cutworm is a noctuid polyphagous pest with high reproductive capacity. S litura is a major agricultural and forest pest widely distributed in the tropical and subtropical areas of Asia. The chemical pesticides are the common method to control the pest population of S. Litura but it resulted in an increased resistance towards the insecticides and also affected the human health and environment . In this context an eco-friendly bio-rational radio genetic technique of pest control commonly known as sterile insect technique could be an option for pest management which involves mass rearing sterilization and release of male moths in the infected area where sterile males must mate with wild females and prevent them from reproducing by transferring inviable sperm and a sufficient ejaculate including accessory gland fluid knipling 1955 Robinson 2005. In Lepidoptera the use of a high dose of gamma radiation to induce full sterility in male moths may diminish competitiveness and ejaculate quality in irradiated moths. Therefore an alternate strategy known as or inherited sterility technique as a modified SIT was proposed to overcome the drawbacks of SIT by releasing sub sterile males with the ability to cause greater sterility in their FI generation to be used in pest suppression.

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02. BHARTI(Meghali)
Deciphering the Structure and Function of Gut Microbiome of Cyprinus Carpio (Linnaeus, 1758) and Oreochromis Niloticus (Linnaeus, 1757).
Supervisor: Prof. Ram Krishan Negi
Th 27187

Abstract

This study reflects that anthropogenic stress can modulate the fish gut microbiomes by influencing not only the microbial diversity but also their potential functional as well. Water pollution considerably transformed the gut microbiome structure and enhanced the discrepancy of microbial composition of same fish species from two different sites. On one side the host retains the stable multifunctional bacterial consortia while on the other side microbial diversity become specialized due to anthropogenic stress and section pressure. A remarkable intra specific variation was observed at phylum genus and species level among the two groups. Anthropogenic activities and pollution shaped the microbial communities and functional repertoire of common carp from the polluted site whereas as microbial consortia of gut samples from less polluted site showed incidence of members negatively correlated with pollution.

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03. BISWAS (Largee)
To Evaluate Osteogenic Effects of Resveratrol Encapsulated Nanostructured Lipid Carriers (ResNLC) & Role of Lipid Nanoparticles Containing miR-214a (LNP-miR-212a) in Regulating bone Resorption to Attain bone Remodeling in Osteoporosis.
Supervisor: Prof. Anita Kamra Verma
Th 26947

Abstract

Past few decades have indicated an increase in the mean life expectancy, resulting in enhanced impact on skeletal diseases. Healthy adults have a continuous process of renewal of bone called as bone remodeling. Mature and old bone is constantly being substituted by newly formed bone in a fine-tuned cascade of events, wherein resorption of bone is being replenished with new bone formation. A young adult skeleton has an equal amount of bone formation after bone resorption (Kanis et al., 2008). But, if bone resorption exceeds bone formation, generally in the case of post-menopausal women and elderly people, decrease in bone mass is observed causing deterioration of bone microarchitecture, that eventually leads an imbalance causing osteoporosis (Moshiri et al., 2017). Osteoporosis is a bone disorder characterized by low bone density, impaired bone microarchitectures and disruption of bone tissue that leads to weakening of bone and high risk of bone fracture (Mohamad et al., 2019). It affects both sexes and prevalence of this disease increases as population ages. Often it is referred to as a silent disease, as it is not perceived until bone fractures occur, which causes secondary health problems and eventually death (Marcucci et al., 2015). Osteoporosis does not necessarily lead to fractures, but its unfortunate consequence may be fractures (Zamani et al., 2018, Irani et al., 2013). It represents a major public health issue especially in women,

men and old-aged people. Keeping in view of the increased age of people, the impact of socioeconomic and medical facility of this disease is expected to rise soon.

Contents

1. Introduction 2. Review of literature 3. Materials and methods. 4. Synthesis and characterization of nanostructured lipid carriers. 5. In-vitro release kinetics pattern. 6. In-vitro cell culture studies: osteoblastogenesis and osteoclastogenesis. 7. Anti-osteoporotic activities of resNLC in in-vitro osteoporotic model. 8. Ex-vivo biocompatibility, pharmacokinetics & bio-distribution of nanostructured lipid carriers. 9. In-vivo anti-osteoporotic activities of resNLC in VCD- induced osteoporotic mice model. 10. In-vivo anti-oxidat activities of resNLC in VCD- induced osteoporotic mice model. 11. Role of LNP-miR-214a for downregulation of osteoclastogenesis. Discussion. Summary. References. List of Publications and posters presented.

04. CHAHAL (Nidhi)
Investigations of Molecular Defects in Metabolism of Granulosa Cells and Identification of Infertility Markers in Pcos.
Supervisor: Prof. Rita Singh
Th 27264

Abstract

Polycystic ovarian syndrome is a heterogeneous endocrine disorder with symptoms like cystic appearance of the ovary oligo/anovulation and disrupted endocrinal profile in affected the women. The pathophysiology of PCQs represented by ovarian dysfunction hyperinsulinemia and hyperandrogenism leading to impaired follicular development type II diabetes and cardiovascular diseases. The disrupted hormones like LH, FSH, estrogen androgens testosterone cause abnormal menstrual cycle which lead to oligomenorrhoea amenorrhea like irregularitics. According to the world health organization assessment more than 116 million about 3.4% of women worldwide are suffering from PCOS PCOS is diagnosed with hyperandrogenism menstrual irregularities and varyig size of cysis in overies although substantial differences exist between individuals. This multifactorial condition initially develops in adolescents who are at substantial risk for the emergence of several comorbidities including obesity type II diabetes infertility endometrial dysplasia cardiovascular disorders and psychotic disorders. As thousands of women diagnosed with FCOS undergo the procedure of IVF most of them fail to conceive even undergoing said procedurs.

Contents

1. Introduction and review of literature. 2. Hypothesis and objectives. 3. Materials and methods. 4. Determination of metabolic defects in the granulose cells in PCOS women. 5. Development of customized gene array chips for the prediction of conception in infertile PCOS women. Summary and Conclusions. Supplementary Data. References. Publication.

05. CHOUBEY (Pooja)
Alasi, BVRs and FPN1 Expression in Heme Oxygenase-1 Knockout Mouse Embryos.
Supervisor: Prof. Sharmila Basu-Modak
Th 26948

Abstract

Enzymes involved in heme metabolism were expressed in mid gestation and late gestation mouse embryos. The iron transported was also expressed from 12.5 dpe onwards but the expression was low. Increase in the staining intensity for the four proteins from mid 12.5 to late gestation 18.5 indicates that their expression increases during gestation. Expression pattern of ALAS and BVRs in 16.5 and FVB embryos was similar to that in the mixed background strain indicating that the gene targeting did not affect the expression of these two proteins. Immunoreactive staining for the four proteins was highest in 16.5 dpe HET embryos and lowest in KO embryos. Significantly low immunstaining of heme metablizing enzymes in KO embryos at 16.5 dpe suggests that hmoxt deficiency probably affects heme metabolism during embryogenesis. Due to limited number of KO embryos no definite association could be made with hmox 1 deficiency and axis tilt in the heart. It will be important to take this study further for determining the relative levels of these proteins in the organs of late gestationhumox 1 KO embryos by western blotting which will be a better indicator of their effect on heme metabolism. Further a fascinating challenge will be to unravel the regulatory networks and coordinated functions of these heme metabolizing enzymes in HmoxI deficiency. For this proteomics could be another approach which will help in understanding the different proteins that are up regulated and down regulated in the absence of Hmox 1 during embryogenesis.

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06. CHUPHAL (Bhawna)

NOD-like Receptors and their Endocrine Regulation in Spotted Snakehead Channa Punctata (Bloch,1793).

Supervisors: Prof. Rina Chakrabarti, Prof. Umesh Pal and Brototi Roy

Th 26949

Abstract

Innate immunity is the first line of host defense mechanism and is particularly important in lower vertebrates in which the adaptive immune system is poorly developed. The nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are an important component of the innate immunity that recognize the conserved pathogenassociated molecular patterns (PAMPs) and mobilize the downstream signaling pathway leading to inflammation. In view of this, an effort was made to identify, characterize and study the expression of NLRs in spotted snakehead, Channa punctata. In addition, tissue-dependent expression of NLRs was analyzed and the modulation of their expression in response to bacterial infection was investigated. 3 D-modeling of LRR domain of ssNOD1, ssNLRC5 and ssNLRX1 revealed well conserved leucine rich domains that could bind with bacterial lipopolysaccharide (LPS). Further the nodosome signaling was deduced using ssNOD1 as a

reference model. It was found that the ssNOD1-CARD domain interacts with ssRIPK-CARD domain which further interacts with CASPASE-1. ssCASPASE-1 was found to interact with ssIL-1β pointing towards the possible processing of pro-IL-1β by Caspase-1 in spotted snakehead. The receptors, namely NOD1, NLRC5 and NLRX1 were found to be ubiquitously expressed in all the tissues including immune organs, spleen and head kidney and infection modulated the lymphoidic NLR expression in Channa punctata in a time-dependent manner.

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07. DINESH RAJ PANT

Expression of Genes Encoding for Gonadotropin, Thyrotropin and Deiodinases Under Natural and Artificial Photoperiods in the Catfish, Heteropneustes Fossilis (Bloch).

Supervisor: Prof. Neeta Sehgal

Th 27189

Abstract

Seasonal reproduction is an evolutionarily adaptive trait of an organism inhabiting the sub-tropical and temperate regions. Studies on reproductive timing and the influence of environmental factors are important to understand the niche of an organism. The seasonal timing is regulated by the internal clock of an organism which is also fine-tuned by several environmental factors including photoperiod temperature precipitation. The photoperiod has been considered a major cue however in several fishes the temperature also holds equal importance of photoperiod and temperature has been difficult at the physiological level so the present thesis is an attempt to identify the molecular events that are affected by photoperiod and temperature. The thyroid hormones play a crucial role in the long photoperiod stimulated seasonal reproduction of several vertebrates. The thyroid hormones are circulating biomolecules derived from the thyroid follicles and are involved in the regulation of basal metabolic rate. Their synthesis and secretion occur under the stimulation of thyroid stimulating hormone from the pituitary and are then metabolized by the deiodinase enzymes. The deiodinase enzymes are ubiquitously expressed and maintain the local thyroid level which subsequently regulates the functional activity of a tissue. Therefore in the present study we have collectively referred the genes encoding for the thyrotrophic and deiodinases as thyroid hormone regulating genes.

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08. JYOTI

Study of Immune Response in Huntington's Disease Using Transgenic Drosophila as a Model.

Supervisor: Prof. Anju Shrivasatava

Th 26950

Abstract

Neurodegenerative diseases manifest insidiously in the elderly and inflict a complex debilitation which permeates every realm of the patient's life. These fatal conditions are characterized by pervasive anomalies including involuntary movements, cognitive decline and behavioural abnormalities. The devastating symptoms lead to physical and functional deterioration of individuals and untimely death. The representative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Spinocerebellar ataxias (SCAs), Amyotrophic lateral sclerosis (ALS), etc., share many abnormalities in common while yet being distinct from one another in terms of pathological ailment. The polyglutamine (polyQ) diseases represent a class of neurodegenerative disorders caused by the expansion of trinucleotide CytosineAdenine-Guanine (CAG) repeats in the translating region of the causative genes. The expanded CAG repeats translate into abnormally long polyQ track in the mutant protein. This expanded polyQ tract facilitates protein conformation changes, promote aggregation and subsequently culminate in toxic conformational transition. One such fatal disease is HD, which is characterised by a predominance of neuronal loss in the cerebral cortex and striatum. HD, which is predominantly acknowledged as a motor function disorder, manifests as a triad of motor, behavioural, and cognitive dysfunction. It results from an unstable expansion in the HD gene's Cytosine-Adenine-Guanine (CAG) repeat tract, which changes the disease-specific Huntingtin protein (HTT) into a mutant form (mHTT). Overburdening of neurons with mHTT protein and its cytotoxic fragments eventually leads to neurodegeneration. Huntington's disease research has been traditionally focused on neurological symptoms and brain pathology. However, in addition to the obvious neuronal atrophy, it is gradually becoming evident that ailments occur in peripheral system as well. Besides the hallmark neurological manifestations, a wide range of peripheral abnormalities in skeletal muscles, cardiac muscles, adipose tissues, fibroblasts, and immune cells of HD animal models and patients, advocating HD to be a multi-system disorder. Neuroinflammation is well documented in the affected brain regions of HD patients and is a major cause of concern for patients. Recent studies also observed elevated levels of pro-inflammatory mediators in the serum as well as vital peripheral organs of HD patients; However, the involvement of peripheral immune responses in disease pathology remain relatively unexplored. In this work, I aimed to investigate the possible amendment in peripheral immune homeostasis and mechanisms leading to such intense alterations in Drosophila model of HD. To answer this question, I looked into hemocytes' count and their functional activities as well as transcriptional expression of key immune mediators in HD flies with disease progression. The results of this work will take us a step forward in our understanding of the complex and multifaceted disease and may open new avenues for therapeutic targets and diagnostic biomarkers. Till date, there are no effective treatments available to alleviate the dreadful disease condition. Symptomatic treatments of HD with target-specific synthetic drugs have proved ineffective in ameliorating the relentless neuronal or physical deterioration. Moreover, synthetic treatments elicit severe side-effects which further compromise physical as well as mental health of HD patients. Identification of safe and effective therapeutic option is much needed which can

alleviate the signs of neurodegeneration along with mitigating weight loss in HD. Therefore, in present study, I aimed to test efficacy of potent immunomodulatory phytochemical curcumin in mitigating the immune derangements associated with disease by using an in vivo Drosophila model of HD. Based on my results, I propose that phytochemical curcumin can be of immense therapeutic value with least side effects for the treatment of multi-faceted HD. The present thesis entitled "A study of immune response in Huntington's disease using transgenic Drosophila as a model" is composed of 5 chapters. Chapter 1 presents an introduction to the research topic followed by proposed research objectives. Chapter 2 provides a detailed description of experimental methodologies and protocols followed to obtain results during the course of research work. The key findings of the study have been reported in chapter 3, 4 and 5. In each chapter, background concepts related to research objective, results of the experimental work, discussion of the findings and finally conclusion derived from the results are presented. At the end, summary of the thesis work and references to the text citations are provided. Parts of my thesis work have been published in peer-reviewed journals, as follows: • Dhankhar, J., Agrawal, N. and Shrivastava, A., 2022. Pan-neuronal expression of human mutant huntingtin protein in Drosophila impairs immune response of hemocytes. Journal of Neuroimmunology, 363, p.577801. doi: 10.1016/j.jneuroim.2021.577801 • Dhankhar, J., Agrawal, N. and Shrivastava, A., 2020. An interplay between immune response and neurodegenerative disease progression: an assessment using Drosophila as a model. Journal of Neuroimmunology, 346, p.577302. doi: 10.1016/j.jneuroim.2020.577302 Following research work from the thesis is presently "under review" in a peer reviewed journal: • Dhankhar, J., Agrawal, N. and Shrivastava, A. Amendment of altered immune response by curcumin in Drosophila model of Huntington's disease. Additional publications: • Kumar, A., Sharma, A., Dhankhar, J., Syeda, S., Shrivastava,

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09. KESHAVAM (Chetkar Chandra)
Identification of a Novel Nucleoid-Associated Protein from Mycobacterium Tuberculosis and study of its Physiological Relevance.
Supervisor: Prof. Sharmila Basu- Modak and Prof. Yogendra Singh
Th 26951

Abstract

Bacteria inhabit almost every niche on the planet earth and they survive and adapt through the continuous environmental changes. Adaptations are brought about by modulating the cellular machineries at different levels. Among these modulation in the genomic architecture is universally acquired and utilized thought the eubacterial kingdom of life. Chromatin architecture modulations are utilized through the eubacterial kingdom of life. Chromatin architecture modulations are brought about by several forces out of which nucleoid associated proteins are the strongest one. NAPs are small basic eukaryotic histone counterparts in prokaryotes. Besides being a genome guardia NAPs also act as global transcriptional regulator which regulate

the expression of hundreds of genes by altering spatio lemporal organization of the genome. These proteins help packaging of genomic DNA is a confined space by bending bridging and or wrapping of the genome. The number of NAPs vary in different bacterial species. Till date only few NAPs have been identified in Mycobacterium tuberculosis the causative agent of tuberculosis in humnas which is far less than other prokaryotic model organisms of similar genome size such as coli and subtilis. Considering the importance of NAPs in bacterial physiology and survival in harsh conditions and the hostile environment where Mtb resides it is worthwhile to gain deep understandings about the NAPs of mtb and their role in Mtb life cycle. In this study we have reported the identification of HbhA as a novel NAP encoded in the mycobacterial genome possible role in the survival of Mycobacterium Tuberculosis during stress conditions and during chronic disease and phosphorylation dependent regulation of HbhA DNA binding activity.

Contents

1. Review of literature 2. Materials and methods. 3. Identification of putative NAPs from the genome of mycobacterium tuberculosis and biochemical characterization of HbhA as a novel NAP. 4. Study the physiological relevance of HbhA as NAP in the life cycle of mycobacterium tuberculosis. 5. Study of phosphorylation and its effect on DNA-binding activity of HbhA. 6. Conclusion and Future Implications.

10. MITTAL (Pooja)
Design, Development, and Biological Evaluation of Novel MCL-1 Inhibitors as Potential Cancer Therapeutics.
Supervisor: Prof. Indrakant Kumar Singh
Th 26952

Abstract

Myeloid cell leukemia 1 (MCL-1) is an anti-apoptotic protein which belongs to the BCL-2 family of proteins. The canonical role of MCL-1 is to bind BCL-2 effector proteins (majorly BAX and BAK) and inhibit their oligomerization and subsequent binding to mitochondrial outer membrane. This blocks the downstream pathway and in turn prevents the intrinsic mode of apoptosis in the cells. Cancer cells are known to possess the capacity to evade apoptosis and cell death and grow indiscriminately even in the presence of growth suppression signals. One of the molecular mechanisms that cancer cells adopt to evade apoptosis is the overexpression of anti-apoptotic proteins such as BCL-2, MCL-1, BCL-xL, etc. Thus, MCL-1 has emerged as an extensively studied and important biological target for anti-cancer treatment. The present thesis was divided into four main objectives. The first aim was to identify novel compounds that can be potential MCL-1 inhibitors using structure-based drug designing approach using the available MCL-1 protein structures in Protein Data Bank and compound structures present in PubChem database. An extensive molecular docking screening, including ensemble docking and clustering, was performed to filter compounds and molecular dynamics simulations were performed to check the stability of binding of selected compounds in the MCL-1 BH3-binding pocket. Ten clusters with different chemical scaffolds and binding affinity were obtained as potential MCL-1 inhibitors. The second aim of the present study was to evaluate the effect of repurposing dihydroergotamine mesylate (DHE), a drug used for treating migraine headaches, for treatment of pancreatic cancer. This involved performing in vitro analysis including cell viability assays, clonogenic assays, wound healing assays, apoptosis assays, real time- quantitative polymerase chain reactions (RT-qPCR), and western blotting experiments to assess the effect of different concentrations of

DHE on the pancreatic cancer cell lines, MiaPaCa-2 and PANC-1. The third aim was to characterize the association of MCL-1 expression with molecular features in colorectal cancer (CRC) using the extensive next generation sequencing and whole transcriptome sequencing data from CRC patient samples analyzed at Caris Life Sciences (USA). The study involved stratifying the MCL-1 expression data into low and high quartiles, and then analyzing its association with PD-L1 expression, tumor mutational burden, IFN score, ix T cell-inflamed signature, co-alterations and co-amplifications in cancer-related tumor-suppressor and oncogenes (TP53, PTEN, KRAS, BRAF, etc.). MCL-1 expression was also correlated with tumor immune microenvironment, immune cell infiltration, and expression of immune-oncology related markers (LAG3, PDCD1, CD80, CTLA4, etc.). Last but not the least, the fourth aim of this thesis was to study the effect of genetic variants of MCL-1 and NOXA genes on progression free survival (PFS) and overall survival (OS) in patients enrolled in three clinical trials, FIRE-3, TRIBE, and MAVERICC. The study established DHE as a potential treatment strategy for pancreatic cancer suggesting future directions for combination therapy involving DHE with other pancreatic cancer drugs for improved efficacy. The analysis for CRC demonstrated that MCL-1 is a potential biomarker in CRC and associated with tumor immune cell infiltration and clinical outcomes. Future studies are warranted to validate our findings on larger sample sizes. The analysis of SNPs showed that genetic variants in MCL-1 gene did not associate with survival or treatment outcomes in CRC patients, however, variant in NOXA gene rs8093673 did show significant genotype-specific associations with treatment outcomes in the cetuximab cohort of FIRE-3 clinical trial

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11. NEHA VIMAL

Potential Role of Radiation Hormesis in Imporving the Quality of Moths to be Employed in Inherited Sterility Technique for the Management of a Serious Lepidopteran Pest.

Supervisor: Prof. Rakesh Kumar Seth

Th 27188

Abstract

Spodoptera litura is a polyphagous cosmopolitan leaf feeding agricultural crop pest that wreaks havoc on the variety of plants. Sterile insect technique is a unique radio genetic strategy for controlling lepidopteran populations in an afflicted field and has been used to control these moths. The use of a high dose of ionizing radiation to produce sterile insects reduces the competitiveness of the irradiated moths. As a result the sterility technique has been proposed to overcome this limitation of SIT in which moths are exposed to a much lower dose of ionizing radiation whose offspring would be entirely sterile has therefore been proposed to get around this limitation of SIT. Despite being an environment friendly and non polluting method it has sme constraints like exposing an insect to sub sterilizing dose of gamma radiation can

decrease the mating ability and reduce lifespan in comparison to wild or non-irradiated male moths and these can affect IS program.

Contents

1. General Introduction. 2. Review of literature. 3. Materials and methods. 4. Objective 1: effect of low dose of ionizing radiation (LDIR) on survival, growth, adult features and expression of genes associated with radiation hormesis in spodoptera litura (Fabr.) treated with LDIR in various ontogenic stages. 5. Objective 2: influence of radiation hormesis on the reproductive performance of irradiated, substerilised male moths,S. litua (Fabr.) having absorbed LDIR during ontogeny. 6. Summary, Conclusion and Future Directions. References.

12. NISHU

Role of Gut Microbiota-Derived Metabolite indoxyI Sulfate in in Vitro and in vivo Study and Developing Sensor for its Quantification.

Supervisor: Dr. Rajeev Singh and Dr. Anil Kumar

Th 26953

Abstract

The human microflora is the tremendous community of bacteria which perform a critical function in human life. The collection of all genes from gut microorganisms is a genetic inventory, that is many times greater as compare to human genome (1). To a certain amount, gut microbiota is also taken as “essential organ” of the human body (2). With the furthermore advancement in studies in this field, the effect of the intestinal flora on human diseases was progressively brought into light. Any alternation in intestinal microbiome (dysbiosis) has harmful impacts on the human body which will result in various metabolic disorders in particular cardiovascular disease, obesity, type 2 diabetes, malnutrition and non-alcoholic fatty liver disease (NAFLD). In-depth research has shown that intestinal microbiota and their metabolites are key factors for the maintenance of homeostasis in host intestine and can influence the progress of various diseases, like cardiovascular diseases (CVD), neurodegenerative diseases, gastrointestinal and metabolic diseases. The underlying mechanisms by which gut microbiota (GM) affects human diseases are incredibly complex. An increasing number of research have shown that intestinal microbiota and their metabolites communicate with host by various pathways to affect the advancement and appearance of cardiovascular diseases. The function of biliary acids, SCFAs and trimetlylamine oxide (TMAO) in cardiovascular diseases were confirmed in many studies that are secreted by gastrointestinal microbiota (3). Hypertension is major risk factor of cardiovascular disease. It is related with impairment of intestinal functioning, impairment of intestinal microbial community, and alteration in nervous system-intestinal interconnection. The diversity, bacterial abundance, and consistency were considerably reduced in case of hypertensive patients (4,5) while the Firmicutes/Bacteroidetes ratio was significantly enhanced (6). Alteration of the GM perform a crucial function in regulating blood pressure, and changes in intestinal microbial metabolite production can be a key mechanism. Intestinal bacterial abundance, uniformity and diversity were substantially reduced in patients suffering from high blood pressure. Gut microbiota not only affect hypertension by maintaining intestinal tract in case of hypertension but it also responsible for alternation of gut metabolite production. These observations point towards the powerful association of gut microbiota with hypertension and implying that steps towards balancing of GM can work as

an effective Introduction 2 therapy for hypertension. Recent research has identified a potential association among intestinal microbiota and CVD through demonstration of bacterial transportation upon the intestine to heart, and microbial DNA and living oral microbes has been found in atherosclerotic plaques, suggesting that GM are implicated in developing and advancing atherosclerotic disease. (7–9). Metagenome-wide relationship analysis revealed that the formulation of GM fluctuates greatly in patients with atherosclerosis. The abundance of Enterobacteria and airborne Enterobacteria is considerably increased in patients with atherosclerosis as compare to healthy controls, inhibiting the growth of healthful bacteria (10,11). In the meantime, many in vitro and in vivo researches have shown that gut bacteria dysbiosis in case of atherosclerosis can enhance the permeability of intestine, consequently increasing the amount of lipopolysaccharides absorbed into the circulation (9).

Contents

13. RANI KUMARI

Evaluation of Potent Anti-Oxidants on Lymphoma-Induced Angiogenesis in Murine Model.

Supervisor: Prof. Anju Shrivastava

Th 27190

Abstract

Tumor growth and proliferation has a cascade of event which arise from chronic exposure to extrinsic intrinsic genotoxic factors. Further for tumors to grow beyond 1-2mm in size it must recruit new blood vessels by angiogenesis. Emerging evidence suggests that oxidative stress plays a pivotal role in angiogenesis. Angiogenesis is the root cause of metastasis and recurrence of cancer. The inner mono layer of endothelial cells being highly malleable having the ability to continuously sense the micro environment play a major role in sprouting of new blood vessels. The complex process of angiogenesis involves a triad of endothelium proliferation migration and degradation of extracellular matrix regulated by growth factor transforming growth factor tumor necrosis factor angiogenin angiopoietin 1&2 and interleukins overcome the effects of anti angiogenic factors such as thrombospondin I angiostain endostatin vasostatinn interleukin 12 tissue inhibitor of metalloproteinases e-cadhein. It has been established that hypoxia induces production of pro angiogenic factors which creates an imbalance in angiogenic gene expression consequently leading to new blood vessel recruitment.

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14. SENRUNG (Anna)
Targeting Neoangiogenesis in Globlastoma.
Supervisor: Prof. Alok Chandra Bharti
Th 26954

Abstract

Glioblastoma (GBM) is the most common aggressive malignant form of brain cancer arising from supportive glial cells. It is characterized by a high degree of cellular and molecular heterogeneity with the ability to disseminate throughout the brain parenchyma and thrive in specific or poorly accessible sensitive areas making complete resection impossible. GBM as a rapidly dividing solid tumor is coupled with marked angiogenesis for gases and nutrient supply essentially required for growth. To date, there is no cure for GBM. Present study was aimed to screen all reported anti-angiogenic phytochemicals using in silico approach to evaluate their ability to cross BBB for their utility in GBM therapy. Screening of 100 phytochemicals reported to have anti-angiogenic property having well-defined structures published in PubChem revealed, 35 of the phytochemicals with BBB permeability with an acceptable probability score >0.8. Docking of these phytochemicals with VEGFR-2 ECD2-3 and TKD showed 30 phytochemicals (out of 35 BBB permeable leads) achieved/crossed the benchmark binding affinity <-6.4 kcal/mol of TKD with the native ligand ATP alone. From 30 of these phytochemicals, trans-chalcone (TC) and piperine (PPR) were taken for further study. Using in vitro 2D and 3D U87 GBM models, the non-cytotoxic dose of TC and PPR was determined to be ≤11µM for in vivo CAM study. In the next part of the investigation, in vivo evaluation of the anti-angiogenic activity of TC and PPR at 1 and 10µM in CAM directly as a standalone model showed antiangiogenic activity including decreased vascular density as well as reduced VEGF and VEGFR-2 transcript level. This was further confirmed by decreased vascular density as well as reduced VEGF and VEGFR-2 transcript levels in CAM U87 xenografts. Taken together, the data suggests the lead phytochemicals TC and PPR have the potential to inhibit angiogenesis in GBM through VEGFR-2 inhibition.

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15. SHUKLA (Vikas)
Exploiting Macrophages Targeted therapeutics using Dual-Functional Folate Decorated Berberine-Loaded Glycol Chitosan Nanoparticles to Combat Inflammatory Arthritis in AIA Rat Model and CVD Risk via LPA Mediated ATX-LPA Signaling by Polarized Macrophages.
Supervisors: Prof. Anita Kamra Verma
Th 26955

Abstract

Rheumatoid arthritis (RA) is a multifaceted, multifactorial, autoimmune, inflammatory disorder affecting joints, with an unidentified etiology that is accompanied with increased cardiovascular risk. It is characterised by prolonged synovitis that frequently causes tissue dysfunction, localized impairment to articular cartilage, destruction of tendon, bone and ligament damage and ultimately loss of function (Shrivastava and Pandey, 2013). In RA, several joints are affected making it polyarticular where tiny joints including hands, cervical

spine and feet are particularly affected. Larger joints such as the shoulders and knees are frequently affected as well; the pattern of joint involvement may vary from patient to patient (Majithia and Geraci, 2007). The most common reason for functional disability in RA patients is bone deterioration, which includes localised bone erosion and widespread bone hollowing. Progressive bone destructions are common in patients with RA at initial stages of the disease. As a result, a timely treatment programme based on an initial diagnosis is likely to delay the disease progression, thereby preventing irreparable damage (Kourilovitch et al., 2014).

Contents

16. SINGH (Nisha)
A Study of Sleep and Mood Related Behaviours in Female Students.
Supervisors: Prof. Anju Shrivastava and Prof. Vinod Kumar
Th 26956

Abstract

Using a battery of questionnaires, we sought to examine the effect of social environmental effects on chronotype distribution sleep wake pattern and mood behaviour between school going female adolescents from urban and rural. Briefly we collected socio demographic details of all consented participants and recorded their chronotype and sleep wake pattern fatigue mood and internet addicition over school days vs freedays. We particularly assessed different sleep variables sleep latency inertia sleep onset sleep offset and sleep duration total time in bed social jet lag daytime sleepiness and sleep quality social jet lag fatigue depression anxiety and stress symptoms and addiction to the internet. The prevalence of the morning type was found in the rural cohort and the evening type in the urban cohort. There were also greater sleep latency late sleep onsets and offsets greater sleep inertia shorter sleep duration and total time spent in bed as well as greater social jet lag in the urban cohort. There were also differences in several of these parameters between school days and free days indicating the impact of the social schedule. The urban students also reported a higher daytime sleepiness higher fatigue and poor sleep quality as well as higher anxiety. The addiction to internet was also prevalent among urban adolescents. These results show an overall impact of the environmental setting on sleep and mood related behaviours among school students of the adolescence age.

Contents

17. SIMRAN

Bio-Efficacy of Entompathogenic Nematode, Steinernema Thermophilum on Lepidopteran Pest, Spodoptera Litura (Fabr.) vis-à-vis Ionizing Radiation.

Supervisor: Prof. Rakesh Kumar Seth, Prof. Yogendra Singh and Prof. Rajana Seth

Th 27191

Abstract

Food production is an essential requirement for India to hold on to the growth of its ascending population. The tropical climate of the country is favourable for the insect population to flourish. Therefore it is very important to protect the agricultural yield from insect pests and most of the pest management is done by using chemical insecticides. Lepidopteran pests are among the most catastrophic pests of various economically important crops in the Indian subcontinent. The escalated use of insecticides and pesticides to control these pests is not only an addition to the cultivation expenditure but also creates turmoil in the environment. Considering this it is an important aspect of research to study the biology of these pests and explore the sustainable mode of pest management. Spodoptera Litura is a polyphagous pest of many economicaly important crops. The larvae of are voracious feeders and heavily damage the leafy plants resulting in the deterioration of the quality and yield of crops. Chemical insecticides have been use over many years for the management of pests has established resistance against many insecticides like organochlorines carbamates.

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18. SHARMA(Shagun)

Elucidating the Role of Canonical Wnt Signaling Pathway in Aeromonas Hydrophila induced Pathogenesis in Danio Rerio.

Supervisor: Prof. Rina Chakrabarti and Prof. Shibnath Mazumder

Th 27192

Abstract

The ubiquitous presence of opportunistic pathogens in the environment poses a threat to the survival of organisms in their natural habitat. There is always an on going tug-of-war between a host's immune defense system and the pathogen's capacity to avert and invalidate the host responses. This fight for survival leads to co evolution of both host and pathogen causing the evolutionary success form bacteria to primates. Immune system is a complex network of biological proteins cells and organs that detect foreign entity and deploys many different types of responses to maintain the status quo of a pathogen free internal environment. The receptors associated with the immune system are generally concerned with interrogating the environment for evidence of danger infection or abnormal cell death. The present study is aimed at deciphering the role of canonical wnt signalling at A. hydrophila ZKM interface. Furthermore the key cellular and molecular events controlled by

canonical Wnt signalling in regulating. A. hydrophila pathogenesis is explored in this study. Altogether we believe that our findings will pave way for better understanding this disease and designing effective control strategies.

Contents

19. SUMIT KUMAR

Transcriptomic and Proteomic Analysis of Midgut and Malpighian Tubules of Spodoptera Litura Larvbae Fed on Maize Leaves.

Supervisors: Prof. Indrakant Kumar Singh

Th 26957

Abstract

Spodoptera litura which is recognized as a highly adaptable polyphagous peast failed to cope with the dietary challenges posed by the African tall grass. This vicious moth has spoilt various economically crucial crops throughout different territories such as Asia, Africa, Australia, Japan and New Zealand, Morcover the increased usage of insecticides has built up resistance in insect species. The reduced efficiency of modern pest control techniques has given motivation to researchers to analyze the detained effects of insecticide resistance by S. Litura. Studies have been performed regarding molecular responses behaviour and physiology to understand the escape mechanisms of the insect from environmental toxins. These previous researches have given stimulus to our work. Henceforth our study is a detailed analysis of the insect defense response of S. litura against maize. Identification of defense related responses in S.Litura following the insect diet gave information on specific metabolites and defensive pathways in the insect. The analysis of insect counter defensive response to plant toxins will help in designing methods targeting the defensive pathways of insect pests to make them mare vulnerable to insecticides.

Contents

20. SYEDA (Saima)

Investigating the Role of Lymphoma-Derived Exosomes in Macrophage Polarization and its Regulation by Melatonin.

Supervisors: Prof. Anju Shrivastava

Th 26958

Abstract

Background: Cancer is a complex disease wherein dynamic and mutual cross-talk occur within the tumor microenvironment. The tumor microenvironment is constituted by multiple

stromal cells, which include fibroblasts, endothelial cells as well as immune cells, wherein the intercellular interaction influences the tumor occurrence as well as its further growth. Importantly, the tumor-immune crosstalk has potential implications in cancer development. Previous studies have demonstrated that such interactions occur either via direct contact or by the secreted signaling molecules. Later, the discovery of exosomes opened up a new perspective of tumor-immune cell cross-talk. Exosomes are among the various secreted vesicles which perform diverse functions, governed by their enveloped cargoes. Of note, cancer cells show increased exosome biogenesis, which are released out and consequently leading to its high level in the circulation. Accumulating evidence has shown that exosomes play pivotal roles in tumor initiation and its metastatic progression. Importantly, the immunosuppressive tumor microenvironment is known to be mediated by tumor-derived exosomes. Within tumor microenvironment, among various immunological effector cells present, macrophages are known to be the crucial players. Macrophages are the differentiated immune cells of myeloid lineage which respond to local signals released in their niche to carry out their specific functions. Broadly, they can be divided into classically activated M1 and alternatively activated M2 macrophages. They display a high degree of plasticity and thus change their activation states in presence of different stimuli and often can coexist. The tumor microenvironment mediates activation of pro-tumoral macrophages which usually show M2 polarized state. In turn, they orchestrate tumor growth and metastasis by releasing pro-tumoral cytokines, pro-angiogenic and immunosuppressive factors. Importantly, increased infiltration of these tumor-associated macrophages (TAMs) at tumor site is correlated with poor clinical outcomes in various malignancies, including lymphoma. Now, it is evident that tumor-derived exosomes are readily taken up by macrophages which show altered functional response, depending upon the molecular constituents of exosomes. Also, it has been established that tumor-derived exosomes promote xi activation of TAMs. Although substantial studies have shown that exosomes could induce M2 macrophage polarization in tumor condition, others revealed activation of M1 or mixed phenotype. In view of the important role of TAMs in tumor development, there is an urgent need to understand the exosome-mediated cross-talk between tumor cells and macrophages. Question: In light of this, we aimed to decipher whether there is any impact of tumor burden on systemic exosome level in tumor-bearing host or not. Also, are there any immunomodulatory proteins present within the exosomes, if yes, then whether and how do they affect macrophage polarization. Further, if exosomes are mediating pro-tumoral change in macrophages, then whether this cross-talk could be targeted using potent immunomodulatory agents, such as melatonin, or not. If targeted, it could pave the way towards cancer immunotherapy. The present study was conducted in a murine tumor model of Dalton's lymphoma (DL). DL originates spontaneously in the thymus of the murine host and resembles a condition more similar to human neoplasia than experimentally induced tumors. Importantly, DL growth is fatal for hosts and known to be associated with impaired immune response of the host. However, whether this immune regulation, particularly the macrophage function, is mediated by exosomes or not need to be investigated. So, to answer these questions, we framed following objectives: 1. Evaluation of exosome load in murine model of lymphoma 2. Investigating the effect of lymphoma-derived exosomes on macrophage polarization 3. Studying the impact of melatonin in regulating lymphoma-derived exosomeinduced macrophage polarization Methods: To evaluate the exosome load in the murine tumor model of DL, we checked the exosome level in tumor cells, serum as well as in the peripheral blood leukocytes. Next, we analysed the exosome level in different tissues of tumor-bearing hosts by immunohistochemistry. Following this, we did the

proteome profile of lymphomaderived exosomes by LC-MS and analysed them for presence of any xii immunomodulatory protein. As we were interested to study the cross-talk between tumor cells and macrophages via exosomes, we studied the effect of lymphoma-derived exosomes on macrophage function, in the in vitro study using murine macrophage cell line, RAW264.7. We assayed morphological as well as functional parameters to investigate the polarized state of macrophages. Importantly, we performed the phagocytic assay, checked the reactive oxygen species (ROS) and nitrite level. Also, we assessed the expression of M1/M2 marker, (NOS2/arginase-1), cytokine profile as well as key pro-tumoral factors, such as PD-L1, VEGF and bFGF, by quantitative PCR. Next, we investigated the effect of melatonin in regulating exosome-induced alterations in macrophage function in the in vitro system. Results: In the present study we observed increased exosome biogenesis in tumor cells as well as its increased level in the blood. Also, the peripheral blood leukocytes showed increased uptake of exosomes in tumor condition. Importantly, we found high exosome levels in different tissues of tumor-bearing hosts compared to the control group. Further, LC-MS analysis of lymphoma-derived exosomes revealed the presence of immunomodulatory proteins which could either promote the recruitment of macrophages at tumor sites or impact the polarized state of macrophages. The in vitro study showed that frequent uptake of lymphoma-derived exosomes by macrophages induced a morphological change and reduced their phagocytic activity. In parallel, exosomes increased the reactive oxygen species (ROS) level while inhibited the LPSinduced nitric oxide (NO) level in macrophages. Also, the exosomes increased the expression of arginase-1 (M2-marker) while the NOS2 (M1-marker) expression did not change in macrophages. Importantly, we observed altered cytokine profiles, with high levels of IL10, TGFβ, IL1β, IL6 levels and basal levels of TNFα, IL12, in macrophages activated by exosomes. Moreover, we observed increased transcript levels of protumoral factors, such as PD-L1, VEGF, and bFGF, in macrophages activated by exosomes. Overall these results suggested that lymphoma-derived exosomes mediate a pro-tumoral change in macrophages which resembled M2 in phenotype. Next, we explored the immunomodulatory property of melatonin and observed that it impacted the lymphoma-derived exosome-induced morphological changes as well as significantly inhibited the functional alterations. Remarkably, melatonin reduced the xiii arginase-1 expression, regulated the cytokine profile and reduced the levels of protumoral factors in macrophages induced by lymphoma-derived exosomes. Conclusion: The present work gives insight into the systemic presence of exosomes in lymphoma. Importantly, our study revealed the presence of immunomodulatory proteins in lymphoma-derived exosomes which induced macrophage polarization towards pro-tumoral M2 type. This exosome-mediated cross-talk between tumor cells and macrophages provide novel avenues for designing efficient immunotherapeutic drugs against cancer. However, detailed mechanistic studies need to be conducted to better understand the impact of tumor-derived exosomes. Further, our study unraveled the immunotherapeutic efficacy of melatonin in interfering with the exosome-mediated cross-talk between tumor cells and macrophages and thus offers a strong prospect to activate the anti-tumor immune response in cancer condition.

Contents

21. THAKUR (Kulbhushan)
Investigation of Molecular Mecjamos, (S) of STAT3-Mediated Regulation of HPV Inection and Cervical Carcinogenesis.
Supervisor: Prof. Alok Chandra Bharti
Th 27193

Abstract

Cervical cancer is a leading cause of cancer related mortality among women globally persistent infection with high risk human papilliomaviruses is the etiological factor for CaCx development. The proposed study aimed to understand the mechanisms of viral pathogenesis specifically addressing the role of oncogenic host transcription factor STAT3 in regulating HPV-induced cervical carcinogenesis. In this line we first investigated the association of STAT3 with key components of JAK/STAT signalling in HPV driven CaCx using large transcript levels in HPV positive CaCx chort. Further using RT2 profiler PCR array we obtained a set of 21. Out of these genes were found upregulated in cohort. Six out of 7 genes correlated with and overall survival and held prognostic significance in HPV positive as well as overall CaCx chort. In the next part of investigation in silico assessment of genome revealed presence of potential binding motifs. However the experimental validation lack of binding on network analysis of with other host transcription factors having known binding sites on highlighted a strong physical association of with FOS and JUN. This was further confirmed upon co immunoprecipitation and co localization of star with fos and jun in and positive cells. Alteration of STAT3 expression affected the colocalization of FOS JUN and viral oncoproteins.High JUN and STAT3 expression were found correlated with poor prognosis in HPV positive and positive tumor tissues repectively.

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