CHAPTER 5

BIOPHYSICS

Doctoral Theses

01. ASWAL (Manisha)
Discerning the Role of Bacterial Intrinsic Chromosomal Genes in Imparting Specific Phenotype Through - Omics Analysis.
Supervisor: Dr. Manish Kumar
Th 27353

Abstract

Typically, a bacterial genome consists of a single circular chromosome. Genes that are encoded by the chromosome are called intrinsic genes and are inherited vertically from one generation to another generation. The majority of genetic information that is essential for the survival and reproduction of bacteria is present on the chromosomal DNA. The repertoire of intrinsic genes also helps in the adaptation of microbes to a particular niche that in turn may lead to pathogenicity or commensality. In addition to the chromosome, sometimes bacteria may also contain extrachromosomal small, circular DNA known as plasmids. Plasmids along with, Genomic Islands (GIs), Prophages (Φ) and Insertion Elements (IS) can move within the genome thereby contributing to the genetic diversity and facilitating the acquisition of new traits by bacteria, considered as mobile DNA. Genes that are encoded by mobile DNA are generally known as acquired genes and are transferred from one generation to another via horizontal transfer and carry genes that confer antibiotic resistance properties, virulence factor etc. The role of acquired genes in shaping bacterial genotype and phenotype has been studied extensively. However, a moderate effort has been made to study the role of intrinsic genes in shaping the microbial phenotype. In this work, we tried to study the role of intrinsic genes in conferring specific phenotypes to a few microbes using -omics approaches (genomics, transcriptomics and proteomics). For example immune evasion in Yersinia pseudotuberculosis, hypocholesterolaemic attributes in Enterococcus faecium and antimicrobial resistance in Escherichia coli. Through our work, we identified intrinsic genes and pathways that are involved in immune evasion in Yersinia pseudotuberculosis contributing to its pathogenicity. Further, we identified intrinsic genes of Enterococcus faecium (strain LR13) involved in cholesterol reduction such as SCFAs production, bile salt hydrolases genes etc. In addition, we identified genes/proteins of trans-translation pathways as a part of the intrinsic resistome of multi-drug resistant (MDR) Escherichia coli isolated from river water. We proposed proteins of the trans-translation pathway as a novel drug target against MDR Escherichia coli. Lastly, All the works described in this thesis are based on multi -omics dataset(s). To analyse the data, we also developed analysis pipelines. The analysis pipelines, developed during this work, can also be used for other works. For example, we developed a genome assembly pipeline for prokaryotes named De-novo reference-based guided genome assembly. This pipeline can be used as a general-purpose prokaryotic genome assembly using an already assembled genome as a template. In summary, our work not only advances our understanding of intrinsic genes and their influence on microbial phenotypes but also holds promise

for novel therapeutic interventions and targeted strategies against bacterial pathogens.

Contents

1. Introduction 2. Review of Literature 3. Comparative in-silico analysis to discern the potential role of Yersinia pseudotuberculosis intrinsic genes/proteins in granuloma formation 4. Comprehensive genomic analysis of hypo-cholesterolemic probiotic Enterococcus faecium LR13 reveals unique intrinsic genes in cholesterol assimilation 5. Integrative proteo-transcriptomic analysis reveals trans-translation intrinsic pathway protein (smpB) as a novel drug target against multidrug resistant E. coli 6. Genomic analysis of phylogroup D Escherichia coli strains using novel de-novo reference-based guided assembly 7. Summary and Future Prospect. Bibliography.

02. SHARMA (Bhanu)
Modelling the Role of Nitric Oxide in Synaptic Plasticity: Study in Neuronal Coupling.
Supervisors: Dr. Manish Kumar and Prof. Subhendu Ghosh
Th 27354

Abstract

Synaptic plasticity, fundamental to learning and memory, represents the brain`s remarkable adaptability in response to experiences. This phenomenon involves modifying the strength and connections between neurons triggered by stimuli. Understanding these mechanisms offers insights into neurological disorders and potential therapeutic approaches for modulating synaptic function. Neuronal and glial interactions during brain processing involve intricate collaborations. Activation of neurons induces calcium oscillations in astrocytes, influencing neuronal activity. Astrocytes play a multifaceted role by modulating synaptic strength, neuronal excitability, and providing essential metabolic and chemical support for neurons. They also contribute to synapse formation, elimination, and network-level coordination, influencing the balance between excitatory and inhibitory signaling. In exploring neuronal coupling and interactions mediated by molecules like glutamate, GABA, and Acetylcholine, our focus turned to nitric oxide (NO). Functioning as a potent signaling molecule, NO diffuses among neurons and astrocytes, impacting neuronal activity and synaptic efficacy. Our computational model revealed the dynamics of postsynaptic components, emphasizing the role of Ca2+ oscillations in maintaining homeostasis and NO`s modulation of NMDA receptors through negative feedback mechanisms. We investigated if NO released from astrocytes aids in the long-range propagation of information efficiently. Our model of 1,000 astrocyte-neuron units demonstrated various stable patterns in astrocyte behavior, suggesting that NO release by astrocytes contributes to energy-efficient information propagation in large networks. Synchronized calcium oscillations resembling `glissandi` potentially enhance synaptic transmission by reducing energy demand. Expanding our study to tripartite synapses, which enable bidirectional communication between neurons and astrocytes, uncovered the complex role of NO. Within this intricate network, NO was found to induce both neuroprotection and neurotoxicity. Notably, NO contributed to long-term depression in distantly connected neurons, highlighting its role in neuroprotection and prompting hypotheses about its involvement in regulating neurotoxicity.

Contents

1. Introduction 2. Role of nitric oxide in the modulation of NMDA receptor and dynamics of post-synaptic components via feedback mechanism 3. Emergence of synchronized astrocytic calcium oscillations mediated by nitric oxide in a coupled astrocyte-neuronal network 4. Modelling the role of nitric oxide in neuroprotection and neurodegeneration in an ensemble of tripartite synapses 5. Summary and Future Prospects 6. References.