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Review Article

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Impact of Metabolic Regulation in Understanding the Status of Human Health and Diseases: A Review

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Abstract: The concept of metabolic regulations deals with the varied and innumerable metabolic pathways that are present in the human body. A combination of such metabolic reactions paves the way for the proper functioning of different physiological and biological functions. Dealing with the adversities of a disease, engineering of novel metabolic pathways showcase the potential of metabolic engineering and its applications in the therapeutic treatment of diseases. A proper and deeper understanding of the metabolic functions in the human body can be known from gut-microflora and simulated yeast models. At molecular level, the metabolic regulation works mainly by modulation of the activities of the enzyme. This gives a brief understanding about the interactions between the molecular set of metabolomes and its complexity. The idea of model simulation can help us to draw some possible hypotheses regarding how different the components of a certain pathway are connected. Introduction of engineered microorganisms into the gut might bring about the required variation in the microbiota, thereby inducing them to express certain biomarkers specific to certain microbial groups forming a basis for disease diagnosis and pathogenesis. Since the metabolic homeostasis and observable phenotype are linked to each other, metabolism can be used as a diagnostic of the phenotype. The present review, therefore, focuses on the importance of both the gut-microbiota and yeast model in improving our understanding about the metabolic regulations involved in human health and disease.

Key Words: Metabolic Regulations, Metabolome, Yeast, Gut-Microbiota, Therapeutics

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1. INTRODUCTION

As a central hub or an area concentrated with the majority of metabolic reactions, it can be understood from the studies of the gut , that the systemic metabolism in humans is not just regulated by their genes and their personal dietary habits, but also by gut microbiota [1]. The general intestinal flora of a healthy human includes bacteroides , anaerobic gram-positive cocci such as *Peptostreptococcus* sp., *Eubacterium* sp., *Lactobacillus* sp., and *Clostridium* species etc[2]. If the gut microbiota present in the body is in a state of intestinal dysbiosis, certain microorganisms like *E. coli* can be engineered and modeled metabolically to improve the functioning and growth of the indigenous microbiome [3]. The role of microorganisms is widely being known and explored in recent years due to their exploitable recompense and hindrances that are meant to be kept in check. Apart from different cohorts and divisions of microbiota present, a decent understanding and knowledge about the gut microbiota present in the human digestive system is required to evaluate, explore and treat the different diseases related to the human intestinal tract. A proper balance in the growth and bioactivity of different intestinal flora is required for the homeostasis of the human biological system. It is also known that the transcriptomics, genomics and proteomics along with the metabolomics of the cell have a combined effect on the final phenotype of the organism. Through the analysis of natural and altered metabolic pathways along with model simulations, it is possible to quantify the changes when the environment of the cell is altered. By knowing the connecting pathways and kinetics of interactions, it is possible to generate hypotheses for new treatment strategies for many diseases like type 2 diabetes , tumors and nerve disorders by using some model organisms [4]. In this prospect, it has been reviewed that the usage of gut microflora for understanding their role in the treatment of metabolic disorders. The usage of yeast models for understanding apoptosis and cancer research has also been summarised. Through introduction of varied natural cycles, we contend that there is a serious extent of preservation in these pathways among yeast and human, and that yeast subsequently has a huge potential to fill in as a model life form for eukaryotic models that can fill in as a platform for more specific investigations in human cells. This could propel our comprehension of the mechanisms associated with complex diseases. The aim of the present study is to understand the concept of metabolic regulations that focuses on gut-microbiota and yeast model at metabolic level.

1.1 Scope and importance of metabolomics

The technicality and the rationale behind the term metabolome follow the path of central dogma of life starting from the DNA > RNA > PROTEINS (metabolites). The word metabolome, as a whole, covers the various types and categories of metabolites formed in the course of transcription and translation that occurs in a cell [5].

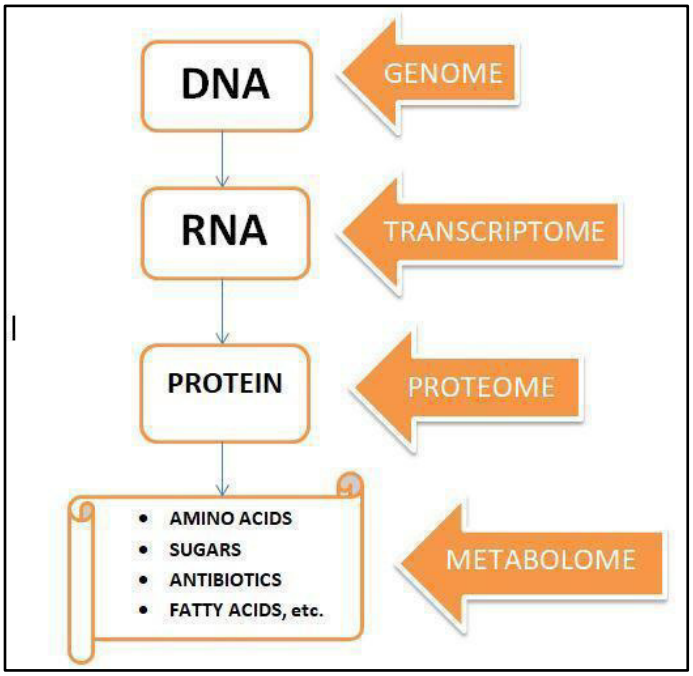

Fig 1: Schematic representation of central dogma (transcription and translation) and constituents of metabolome (amino acids, sugars, and lipids)

The above figure depicts the schematic representation of central dogma and constituents of a metabolome. There can be a metabolome of an organelle, a metabolome of a serum and also a metabolome of cerebrospinal fluid (CSF). Thus, the study of these metabolomes is known as metabolomics[6]. A metabolite can be anything and everything naturally produced by an organism. They may include amino acids, sugars, organic acid, antibiotics, nucleic acids, fatty acids, amines etc., which are produced naturally and chemicals like toxics and xenobiotics that are exogenously produced outside the body of an organism[7]. The metabolites, which are produced endogenously, aid in different metabolic reactions that take place in our body. These metabolites can be divided into primary and secondary based on their point of requirement. Primary metabolites are generally the ones, which are vital for an organism and directly involved in normal growth of an organism; whereas, the secondary metabolites are not directly involved in the normal growth, but are produced as a result of stress and other adverse conditions [8]. In addition to this, secondary metabolites also

i) provide characteristic properties, such as fragrance, flavour, and medicinal values to plants ii) help to attract pollinators, iii) acts as pheromone in insects etc [9]. For example, the plant pigments like capsaicin, beta-carotene, lycopene, and curcumin are secondary metabolites and produced as a result of metabolic pathways in the plant involving a specific set of primary metabolites, such as acetyl-coA, pyruvate, amino acids etc [10].

1.2 Metabolites as markers

A metabolic pathway is basic for every disease or any biological function that takes place in the body. Therefore, study about these metabolic pathways and identifying the metabolites involved in them as markers helps in easy diagnosis and treatment of different diseases, and problems faced by an organism [11]. There are various metabolites which act as markers in tracing various diseases such as anaplastic lymphoma kinase (ALK) in lung cancer, alpha-fetoprotein (AF) in liver cancer and beta-2-macroglobulin (BM2) in multiple myeloma and chronic lymphocytic leukemia [12].

1.3 Role of metabolites in precision medicine

It is known from statistics that, out of the many people who are being treated with a disease, only few of them are responding to the treatment and some are not. As an example, when it comes to the radiotherapy and immunotherapy for the treatment of different cancers, only a handful people are being cured. This is because not every individual's body responds in the same way [13]. Therefore, this is where the concept of precision medicine comes into picture. By using biomarkers, researchers are focusing on tracing disease progression and other key factors which classify patients into different subsets [14]. This may facilitate an excellent prediction of disease endings so that appropriate treatment regimes can be formulated for identifying different sub groups. In the above mentioned context, stratified medicine helped to precision medicine, where treatment is specific and predefined for each patient according to their medical history and other clinical features. In this respect, there are a set of plant derived secondary metabolites like vinblastine, peclitaxel, artemisinin, curcumin, carotenoids etc, which are of medicinal importance [10,15]. These metabolites can also be produced using GRAS (generally regarded as safe) status microbes, such as *Bacillus subtilis* and *Corynebacterium glutamicum* by modulating their respective metabolic pathways [16,17] so that they can be utilized as live therapeutics. Due to their easy culture and better adaptability to commercial fermentations, they can also be produced commercially in large amounts and aid in the treatment of different diseases.

1.4 Gut microbiota – impacting flora in human body

The fluctuation seen in the growth of different gut microbiota can be attributed to physiological status, host genotypes, diet, drugs, and living conditions of the host. The system formed as a combination of both the gut microbiota and the human system is called a "Superorganism"[18]. Based on the effects they induce, gut microbiota can be divided into 3 groups: - 1) beneficial bacteria 2) conditional pathogenic bacteria 3) pathogenic bacteria[19]. As per the growth and functioning of different classes of gut microbiota listed above, it results in the different diseases and ill effects of the gut and organs concerned to it like liver, gallbladder, colon etc. There lies a connection between gut microbiota and intestine, liver, brain and other organs through the host-microbiota co-metabolism to yield metabolic axis and thus in regulating systemic metabolism of the host [20].

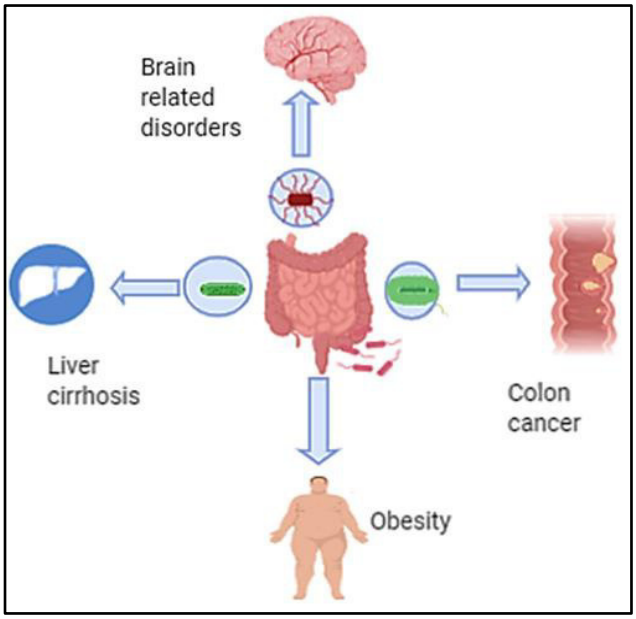

Fig 2: Tracing various metabolic disorders in liver, brain and colon using microbiota.

A comprehensive study on gut microbiota can give us an idea about different diseases on which they can have their effect on. Every disease has its own specific microbial marker for its targeted treatment. In this point of view, Louis et al. found that, in a weight loss problem *Firmicutes*/*Bacteroids* ratio was high in obese patients and the *Akkermansia* (an intestinal microbiota) was found in successful weight loss individuals in abundance [21]. Additionally, it was also found that the *Lactobacillus* additives maintained homeostasis and helped in reducing the body

weight to a remarkable extent [22]. Similarly, when it comes to liver diseases and liver cirrhosis, compared to healthy individuals the significant increase in the number of *Enterobacteriaceae*, and *Enterococcus* species were found in patients with liver cirrhosis [23]. At the pathogenesis of gastrointestinal diseases it was seen that the microorganisms like enteritoxigenic *Bacteroides fragilis* induced inflammatory responses in colorectal cancer (CRC) mouse models [24].

1.5 Short chain fatty acid and gut microbiota

In general, the food that enters into the digestive system is partly digested by the digestive enzymes and partly by the gut microbiota. The complex carbohydrates that enter the human gut are fermented into SCFA (small chain fatty acids) via the gut microbiota, which further promotes a process namely intestinal gluconeogenesis and thus the formation of lipids [25]. The SCFA thus produced is known to play a significant role in host organisms by improving the intestinal functioning, increasing the resistance against pathogenic microorganisms, fighting with tumours, maintaining the electrolyte balances of the host and providing energy to the host epithelial cells [25]. Another intriguing factor about the gut microbiota is found out through a study that the peroxisome proliferation receptor-ɣ (PPAR-ɣ) signal induced by them is the one responsible for maintaining homeostasis [26]. The compound that is responsible for the transduction of PPAR-ɣ is butyrate, which is mainly produced by the metabolism of *Clostridia, Faecali bacterium* and *Roseburia* [26,27]. Butyrate also decreases the production of TGF-β1 and IL-6, increases the activity of cytokines (anti-inflammatory) and enhances body immunity through anti-inflammatory effects by inducing the T cells [28]. Sometimes small indigestible compounds are also formed into small chain fatty acids (SCFAs) and they play an important role in maintaining immune response within the gut. When a diabetic patient takes insulin, it is being found that certain species like *Faecali bacterium* and *Bifido bacterium* species in humans are more dominant [27]**.** These species are important for metabolic regulation and immune function because they produce folate. Folate is also the precursor of the nucleic acids. The identified genes were submitted in databases which lead to the creation of the Human Microbiome Project which has helped in forming the microbiome database [29].

1.6 Metagenomics for gut microbiota identification and functional dysbiosis

It is now well documented that a complex and dynamic environment is established in the human gastrointestinal tract by microorganisms. The microbiota number is 10 times of the total human cells and the microbiota is referred to as an important organ [30]. However, culturing gut microbes through traditional methods is not an efficient approach for their identification and characterization. Advancement of molecular biotechnology approaches, especially metagenomic sequencing by next-generation sequencing techniques has made gut microbiota study relativity easy and more precise. By applying the metagenomics, faecal samples were analyzed and surprisingly it was found that over 100,000 bacterial species were found and metagenomics proved that 99% of the harboured microbiota are bacteria [31]. Not only has the microbial diversity been elucidated through metagenomics studies, but also the microbiome dysbiosis and its relationship with human health and disease has been studied. It was also found that millions of non-redundant genes were traced and the entire gene set was larger than that of humans indicating the significance of gut microbiota on human health. Intestinal gut microbiota dysbiosis is associated with the diseases within the host because the metabolism is not only regulated by the genes of the host, but also by its close interaction with gut microbiota [32]. Rapid development of computational approaches in recent years have helped in designing more focused studies on functional metagenomics of the human gut microbiota to increase understanding about the diseases associated with the microbiota dysbiosis [31].

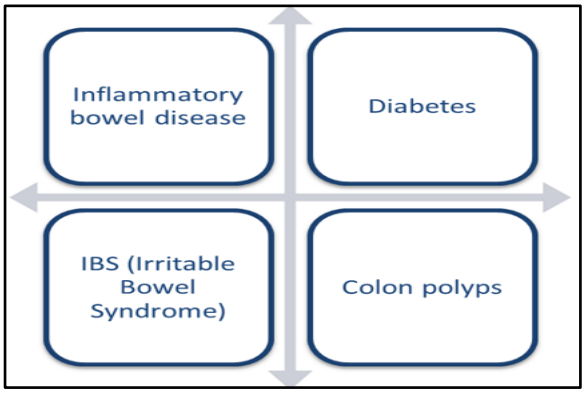

***Fig 3: Multidirectional approach of metagenomics in diagnosing complications such as diabetes, colon polyps, irritable bowel syndrome and inflammatory bowel disease*.**

Figure 3 illustrates the major metabolic diseases that were associated with the microbiota dysbiosis, however, incidences of occurrence of several diseases such as cholesterol gallstone, diarrhea, non alcoholic steatohepatitis, cardiovascular associated and neurological disorders were also prevalent [33]. The changes in microbial functions can also be understood from metagenomics. Novel plasmids were also identified in gut microbiota and these elements help in the co-evolution of host and microorganism. Based on the results of the metagenomic analysis, the chances of horizontal gene exchange between phylogenetically distant bacterial species can be investigated[34]. Majority of metagenomics studies have been carried out on identification and characterization of gut bacteria, whereas, limited studies have been carried out on eukaryotic and viruses of the gut. Further, conducting more elaborative

studies by integrating metatranscriptomics, metaproteomics and metabolomic together with metagenomics might be helpful to grasp detailed understanding of the association of gut microbiota dysbiosis and human health. In this regard, Li (2014) provided an expanded catalog that boasts to include close-to-complete sets of almost all gut microbial genes, which might be helpful to understand the variation of gut microbiota in normal health conditions and dysbiosis [35].

1.7 Shotgun sequencing – for predicting function of microbiome

The whole genome can be analyzed with this method by using continuous overlapping sequences, which are obtained from fragmented sequences and assembled from a whole, purified genome set. The reference databases like SEED, KEGG, and NCBI can be used[36]**.** The sequences can be submitted to different methods like endonucleases, nebulization for the fragmentation and alignment of sequence [37,38]. The method gives a detailed understanding of the polymorphisms that helps to know information of gut microbiota. These metagenomic studies revealed the relationship between digestion and microbiota [39]. It is now clear that metagenomics has become a powerful technology in analyzing the gut microbiota and in understanding its relationship with host [40]. However, there are some limitations. It is not an easy task to know the expression of microbial systems and it also requires higher sequence coverage. The time and cost are also considerable constraints. Among above all limitations, getting highly purified and high quality DNA samples is important because there may be 50% of human contaminants in DNA samples selected.

1.8 *Live biotherapeutic products (LBP*)

With the advent of synthetic biology and the principles of molecular biology and metabolic engineering, the members of the microbial community in the gastrointestinal tract might be used to regulate many metabolic and immune mediated diseases including obesity, malnutrition, and intestinal inflammatory disease [41,42]. The live biotherapeutic products (LBP) are defined as the designed biological components that aid in the treatment, cure and prevention of a condition or a disease in humans. The LBP's that are engineered and designed to sense and respond to existing gut environments and represent an opportunity to affect the host biology. The resultant LBP's after engineering can also incorporate bio-containment strategies, such as auxotrophs that limit bacterial replication in the absence of metabolite that is deprived. In this regard, *Escherichia coli* Nissle1917 can be a model chassis organism due to well established controllable gene expression systems for *E. coli* strains. In its native form, *Escherichia coli* Nissle1917 (EcN) has been used to treat numerous gastrointestinal disorders such as inflammatory bowel disease and irritable bowel syndrome [41,43] EcN is also believed to hinder the growth of opportunistic pathogens such as *Salmonella* species, enteropathogens by producing microcin or siderophores, which are iron scavenging proteins [44]. In addition, EcN may interact with the intestinal epithelium to stimulate anti-inflammatory activities, as well as to restore and maintain intestinal barrier function [45,46]. The LBP's are not only used in the above-mentioned gut wellbeing but also in the solid tumor analysis and as markers in different disease identifications [42,47]. The holistic study of different LBP's are utilized in diverse areas of human metabolism and disease pathology. There are a large number of LBP's that are formulated till date with the concepts of genetic engineering and system's biology showing the scope and importance of LBP's. Charbonneau et al. (2020) have to provide a detailed prospective of LBPs to treat human diseases. They also provided a specific set of considerations, which are critical before developing engineered LBPs. Briefly,

i. It is highly likely that the engineered organism might transfer antibiotic resistance cassettes/genes to other gut microbiota members [42]. To address the concern, antibiotic resistance genes can be eliminated that are used in the development of the chassis microbial host [41].
ii. Characterization of the replication or persistence ability of the engineered microbes in the host and/or the environment might be helpful for the incorporation of bio-containment strategies to restrict further replication of the developed strain within the host [41].
iii. The resident time and elimination of developed microbes is also a critical parameter that should also be determined. The clearance study of the chassis organism on non-human primates and healthy volunteers might provide better understating for such characterizations of the strains to be developed [41].
iv. Finally, it is important to study the bio-distribution of the engineered microbes other than its target site [41].

1.9 Yeast- a model organism for detailed study of complex pathways

For some human diseases, for example, malignancy, cardiovascular and neurodegenerative disorders, it is quite difficult to discover therapy techniques because of the intricacy of the complex regulatory networks. For such complex abnormalities, there are frequently used various methods that bring about a similar phenotype, and it is in this way hard to recognize the specific reason for the planning of exact treatment procedures. To discover the underlying mechanism of a disease, proficient techniques and new treatment strategies, there is need to get definite comprehension of metabolic pathways and administrative systems, which is just conceivable through utilization of model frameworks[48]. It helps in getting information at molecular or subcellular level[49]. The reductionist analysis like knowing the role of different transcription factors, enzymes and inhibitory molecules can pave the way to find out the solution for any disease. It is a well known fact that many metabolic pathways are conserved between yeast and the human system, although yeast remains phylogenetically distant [50]. Another region where yeast is a promising model life form in investigations of eukaryotic protein homeostasis, which includes controlling the focus, three-dimensional structure, co-operations and limitation of individual proteins that make up a cell. Proteostasis is impacted by the sequence of events such as transcription, translation and post-translational modifications (PTM) and the inherent science of the protein, just as by cycles of refolding, unfolding, accumulation and proteolysis [51]. All the referenced cycles are portions of various mechanisms of natural pathways that communicate and compete in biological systems. Changes in proteostasis can lead to cystic fibrosis, lysosomal affected diseases, Alzheimer's and other neurological disorders [52]. It is advantageous to use yeast as a model system because it can be easily cultivated, media is easily available and cheap, above all it allows genetic

manipulations to be carried out. It is easy to edit or insert any gene of interest into yeast genome, the data of sequenced yeast genome and experimental data is easily available in many databases [49]. This makes it ultimately useful for bio-molecular studies. Protein and Lipid metabolism is a bit complex and cannot be studied as a whole in the organ system. Yeast can be engineered and detailed analysis at molecular level can be made that would give implications for cardiovascular diseases, neurological disorders, diabetes [53].

1.10 Yeast model system- a tool to study human apoptosis

Apoptosis is an unpredictable cycle, which is carefully regulated by many complex mechanisms. Any sort of failing in these controlling frameworks because of inadequate or inordinate apoptosis sign can conceivably prompt different kinds of diseases and neurodegenerative issues. Hence keeping this cycle firmly controlled is significant for the cell. Despite the fact that apoptosis is regularly concentrated in multicellular living beings, the revelation of yeast apoptosis in 1997 pulled in the consideration of the wide exploration network [54-56]. As in other multicellular living beings, both the inside and outer regulatory signs set off apoptosis in yeast. In yeast, the outer signs that can incorporate this mechanism are acidic environment, salts, metal particles, ethanol, osmotic pressure, lipid components, distinctive pharmacological atoms, and medications. Inward signals include ammonium, NO, reactive oxygen species (ROS) and damage of proteins, lipids, nucleic acids [57,58] . By using the yeast systems, the role of Bir1p, an anti-apoptotic protein and Stm1p, a pro-apoptotic protein, have been studied and analyzed. The yeast Boolean system gives detailed comprehensive knowledge on programmed cell death (PCD) and also insights into other inter-related diseases. It was assumed that there was only one anti-apoptotic protein Bir1p present in yeast. Later investigations revealed other proteins like TSC-22 that have the same role [59]. Certain experiments were carried out on yeast systems using acetic acid to know its outcomes. Studies showed that when acetic acid is added to media of yeast, it helps in release of mitochondrial cytochrome-C and helps in its translocation to cytosol due to which caspases are activated thereby inducing apoptosis [58] Biomarkers, such as, Stm1 are also observed in yeast model systems, whose accumulation within a cell shows that the cell is ready to undergo cell death[60]**.** Nevertheless, to bring out most similar implications to human cells humanized yeast are used for molecular studies. *In-silico* humanized yeast can make predictions and results the same as human cells because using genetic engineering techniques genes are inserted into yeast[49,59]. Protein families, which are key regulators of apoptosis, have also been studied to increase the understanding about cell cycle and apoptosis. For example, the genes that can code for Bcl-2 and valosin-containing protein were inserted for scientific studies and results were analyzed. It was observed that these genes stood as clear representatives of initiating apoptosis [58,59]. Thus, the yeast system stood useful as a predictive model to know the roles of anti-apoptotic and apoptotic proteins. [60]

1.11 Role of yeast – cancer cell research

It is well known that the growth and proliferation of cancer cells depend upon multiple factors that are acquired during tumor development [61]. The fundamental biological regulations, such as cell cycle, mitochondrial retrograde response, autophagy, protein synthesis and many more are conserved among species and dysregulation of these processes may result in cancer[62]. The yeast model system has established itself at the forefront of research studies to increase our understanding about these biological processes. This is due to easy genetic and biochemical manipulations in yeast and well-characterized omic (genomics, proteomics and metabolomics) tools. There is much similarity of tumour reprogramming between yeast and human cells. Thus, the role of oncogenes, onco-suppressors can be studied in detail using the yeast model system. Guaragnella et al. 2014[62], have reviewed the role of yeast in the expansion of cancer research and diagnosis. It is well documented that cancer cells depend on glycolysis to meet their energy requirements; it is because the mitochondria in tumour cells are abnormal. Not all the time the mitochondria are defective in cancer cells, sometimes there may be changes in electron transport chain or citric acid cycle due to mutations thereby changing the metabolic networking [62]. The p53 a nuclear phosphoprotein is a biological watchdog that helps in protecting the integrity of the genome [63]. The p53 protein is generally low under normal conditions but its expression upregulates when there are various stresses like hypoxia conditions, DNA damage and in return, the gene product of p53 gene helps and regulates in DNA repair mechanisms, genes related to cell cycle. The *S. cerevisiae* has no homologues for p53 gene and hence it could be easy for any molecular studies. Experiments showed that p53 induced apoptosis like cell death and inhibited autophagy, when expressed in yeast indicating the p53-mediated regulations are conserved through evolution.

1.12 Similarities between Cancer cell and yeast cell with respect to genetics and metabolism

According to Warburg's Theory, it was known that even in normal oxygen conditions the tumor cells show higher levels of glycolysis cycle and mostly glucose is converted to L-Lactate. This was thought to be due to the defective mitochondria within them. According to studies made by Son and his team, the cancer cells make use of the glycolysis cycle and later the lactic acid fermentation because of increased use of glutamine amino acid. Some cancer cells have functional mitochondria but with non-functional enzymes in mitochondria and this may be due to the mutations [64]. *S. cerevisiae* is well known for adjusting its metabolic pathways with respect to ecological conditions. At the point when glucose is high, yeast utilizes fermentation as its fundamental metabolic pathway notwithstanding the presence of oxygen (Crabtree effect). In glucose-limited conditions, it can shift metabolism to oxidative phosphorylation. With respect to energy metabolism, it was suggested the glucose-induced repression of oxidative metabolism of yeast possesses similarities with metabolic reprogramming of the tumor cells [65]. Moreover, the oxidative metabolism under glucose- induced repression conditions in yeast were found to be regulated by Ras and Sch9p, which are oncogene homologues in yeast [62] The DNA repair systems are basic for keeping up the DNA integrity, and their losses were correlated with cancer predisposition syndromes. In this regard, *S. cerevisiae* has contributed significantly to decipher the highly conserved mechanisms promoting genome stability in eukaryotes and

provided an excellent platform to recapitulate the key regulations leading to development and progression of cancer [66,67] Similarly, the mitochondrial retrograde dependent pathway that help cells under mitochondrial dysfunctions by activating an evolutionarily conserved retrograde (RTG) response is also assumed to be conserved in mammals and yeast [62,68]. In this case, the yeast's RTG-dependent signaling pathway is said to be conserved with the NF-κB pathway in mammalian, which are the essential part of the cellular response to ensure survival and adaptation under stress condition [68] Since, the proteins of DNA repair mechanisms play an important role in development of tumor and their involvement has also been found in attaining resistance to some therapeutics drugs by cancer cells [62]. Due to similarities of the well understood DNA repair system of *S. cerevisiae* with the mammalian counterpart, the former one could be a potential target to discover and validate novel drug candidates against cancer.

1.13 Gut Microbiota in ASD

In recent years, evidence of microbial dysbiosis in ASD has increased There is some evidence that changing the microbiota in ASD can improve behaviours, in addition to immunological and GI issues that may be connected to dysbiosis. The first investigations on the topic were conducted in the 1960s increased antibiotic use led to an overgrowth of spore-forming bacteria in children with ASD, according to a study of the microbiota and children with ASD[69]. Clostridium, which researchers believe is exposing young infants to excessive levels of microbial compounds that are harmful to their health were harmful to the nervous system[70]. 11 children with a regressive form of ASD who experienced GI symptoms of diarrhoea were treated with oral vancomycin for 8 weeks followed by 4 weeks of probiotics in a short pilot research.The deficiencies in social behaviour and communication of eight of these children (73%) were greatly improved[71].These gains, however, did not last, with most children reverting to their pre-treatment behavioural abnormalities after the medication was stopped . The microbiota of enterochromaffin (EC) cells revealed increased Clostridia (indicating the theory) as well as overgrowth of other spore-forming anerobes,tryptophan hydroxylase (Tph)1. A decent awareness and knowledge of the gut microbiota present in the human digestive system is essential to evaluate, study, and treat the various disorders associated to the human intestinal tract, in addition to the distinct cohorts and divisions of microbiota present[72]. The human biological system's homeostasis requires a correct balance in the growth and bioactivity of various intestinal flora. It is also known that the cell's transcriptomics, genomes, and proteomics, as well as its metabolomics, have a combined effect on the organism's ultimate phenotype[73]. It is possible to quantify natural and altered metabolic pathways using model simulations and analysis of natural and altered metabolic pathways. Clostridia clusters I/IX (46-fold increase) and Clostridia bolteae (46-fold increase) .These preliminary findings, as well as the significant numbers,of ASD youngsters with gastrointestinal issues and immune system problems.In ASD, the microbiome was consistently changed. Parracho et al. verified increased Clostridia in stool samples using fluorescence in situ hybridization (FISH) techniques. Its presence was highly connected with GI Dysbiosis and poor intestinal barrier function.As observed in an MIA (Maternal Immune Activation) autism model,Following therapy with Bacteriodes fragilis, there were improvements in ASD-related behaviour[74].

1.14 Microbiota in IBD

IBD, which includes Crohn's disease and ulcerative colitis, affects 3.1 million individuals in the United States and is on the rise globally[75]. IBD is defined by persistent immune-mediated intestinal inflammation triggered by genetic predisposition as well as environmental factors such diet, antibiotic use, and socioeconomic status. The gut microbiota has long been thought to play a role in the pathogenesis of IBD, but establishing solid cause–effect mechanistic linkages outside of animal models has proven difficult. Dybiosis, defined as a decrease in gut microbial diversity due to a shift in the balance between commensal and potentially pathogenic microorganisms has been linked to IBD in particular. Indeed, the fact that IBD can respond to antibiotic treatment supports the theory that intestinal bacteria play a role in the inflammatory response. The predisposition of inflammation for anatomical regions with relative faecal stasis (terminal ileum and rectum), the effectiveness of faecal diversion as a treatment for Crohn's disease, and the rapidly increasing incidence of IBD globally associated with industrialization and accompanying changes in diet and environmental exposures are all evidence that the gut microbiota plays a role in IBD. Although these findings support the idea that the gut microbiota plays a role in IBD pathogenesis, the precise role of dysbiosis is less apparent[76,77]. Studies seeking to ascertain whether dysbiosis is genuinely causal or simply a result of inflammation have had mixed results. Several studies have found variations in the gut microbiota composition between IBD patients and healthy people, particularly in terms of microbial diversity and relative abundance of specific bacterial taxa[78]. There have been reports of potential pathogen spread as well as global changes in composition (i.e., increased or decreased abundance of indicator species). For example, the phylum Firmicutes, notably Faecailbacterium prausnitzii, is frequently found in lower proportions in the stool of Crohn's disease patients7, while investigations using mucosal biopsies have cast doubt on this link. In contrast, members of the Proteobacteria phylum, such as Enterobacteriaceae, including Escherichia coli, are frequently elevated in IBD patients compared to healthy people. Even within members of the same family (including twins) who are discordant for IBD31, differences in the makeup of the gut microbiota have been identified, showing that dysbiosis is predominantly connected with disease state rather than environmental or hereditary variables[79-81].

1.15 Yeast Systems Biology

The goal of systems biology is to perform a quantitative study and reconstruction of biological processes using an in silico model. A mathematical model, such as an interaction graph, neural network, or stoichiometric model, is frequently used as the in silico representation. Alternatively, mathematical modelling could be used to extract information from the biological system in order to enrich the data's information content[82]. There is no need to choose between the two; in fact, the basis of systems biology is that mathematical modelling and experimental investigation go hand in hand. This collaboration highlights our approach to systems biology: using a combination of mathematical modelling and experimental biology to gain new insights into

the molecular mechanisms that occur in living cells or sub systems of living cells[83,84,85]. Although systems biology does not always need the use of global data, mathematical models have proven to be particularly effective in circumstances where integrated analysis of high throughput experimental data, such as transcriptome, proteome, or metabolome data, is desired. This is due to the difficulty of extracting information on molecular processes without models, such as scaffolds or hypothesis-driven analysis, due to the complexity and integration of constituents in biological systems. The use of genome scale metabolic models as a scaffold for the investigation of co-regulated modules (or sub-networks) within metabolism is one example of the use of mathematical models for integrated data analysis[86,87]. This method uses the highly annotated interaction network offered by genome-scale metabolic models as a framework for identifying co-regulated modules, and it follows the same principles as when data from protein–protein interaction studies is utilised as a scaffold. The discovery of co-regulated modules can provide useful information while also reducing dimensionality, which is significant when working with very big datasets. As demonstrated in a study of DNA-damage repair, these co-regulated modules frequently provide direct biological information and could thus lead to the rebuilding of important pathways[88]. The transcriptional response to DNA damage could be linked to the binding of a specific transcription factor, according to a genome-wide investigation of the binding of 30 transcription factors related with DNA-damage repair pathways. As previously mentioned, transcriptome data were analysed in the context of an interaction model based on protein–DNA interactions, and active modules were found. The generated model can be used to reconstruct an orthologous network in human cells directly[89]. Despite the fact that this method has yet to be used to whole networks, there are numerous examples of individual components in conserved pathways being identified using this method, such as the entire RAD-complex for DNA repair. study of the conserved Snf1 pathway is an example of top-down systems biology combined with integrated analysis of many -omes (R. Usaite et al., unpublished). Transcriptome, proteome, and metabolome studies were combined in this study to recreate the Snf1 protein kinase's worldwide regulatory network[90]. The human ortholog of Snf1 is AMP-activated kinase (AMPK), which is involved in the control of energy metabolism by activating b-oxidation and inactivating lipid biosynthesis. Based on a global reconstruction (R. Usaite et al., unpublished), it was discovered that Snf1 is engaged in far more pathways than previously thought. As a result, it's possible to conclude that the Snf1 pathway in yeast is highly similar to the AMPK pathway in human cells, and that additional research on this key protein kinase will benefit from a more thorough examination of the yeast model system[91,92].

1.16 Age-related changes in microbiota dynamics

The bacterial phyla dominate the human gut microbiota. Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria are the four groups of bacteria phyla. Other microbes, such as viruses and fungi, are also present, although their presence has not been well investigated[93]. While some species are thought to be present in the majority of healthy people, the substantial inter-individual diversity in microbiota composition has sparked discussion about whether or not common community structures exist. Despite efforts to classify microbiota profiles into enterotypes, current research suggests that each microbiota profile may be uniquely located along a continuous gradient of taxonomic abundances[94]. Food-borne microorganisms, in addition to the resident gut microbiota, provide a transitory microbial population that has the potential to affect host health. While the gut microbial community in healthy people appears to be rather constant over months, ageing causes significant changes in community structure. According to the research, changes in taxonomic composition with age include shifts in the Bacteriodetes:Firmicutes ratio and Clostridium groups, as well as increased carriage of Proteobacteria members, especially the Gamma proteobacteria[95]. Notably, rather than chronological age, the most significant changes in microbiota composition are linked to health condition. Diet, domicile status, health, degrees of inflammation, and measures of frailty have all been linked to age-related changes. While the ageing intestinal microbiota generally exhibits the dysbiosis characteristics listed above, such as lower diversity and a loss of beneficial taxa, this is exacerbated by significant differences in lifestyle, nutrition, and health[96]. Significantly, a lack of diversity is linked to frailty and poor cognitive function, rather than chronological age. In contrast, increased microbiota diversity, particularly the Clostridiales subpopulation, is linked to the risk of malnutrition in the elderly. Surprisingly, this demographic is also related with fragility and long-term residential care. When compared to young, healthy controls, inter-individual variability is higher, and this variability complicates attempts to define age-related dysbiosis signals. Aging affects the makeup of the microbiota in mice[97]. However, because to the small sample size, it is unclear if these changes are related to frailty.

1.17 Advances in yeast technology

The yeast genome was the first eukaryotic genome sequence to be published. As a consequence of a collaborative effort in functional analysis, a variety of genome-wide information has been accessible since the release of this sequence in 1996. Saccharomyces cerevisiae has become one of the most used eukaryotic model organisms for the development of genomic technologies[98]. Genome-wide mutational investigations to explore gene expression and function are part of the area of yeast genomics, among other things. To this, genome-wide libraries of haploid and diploid yeast deletion strains have been created. These strain collections have played a significant role in the reintroduction of yeast into medical screening procedures (discussed later). The worldwide examination of synthetic lethality is the subject of a revolutionary genome-wide technique. Synthetic lethality arises when mutations in two distinct genes are viable individually but not when combined[99]. As a result, the relevant genes are most likely functionally linked. Crossing 132 chosen yeast mutants with w4700 viable mutant strains has just begun the building of a global genetic interaction network [SGA (synthetic genetic array)] based on synthetic lethality. In the ensuing double mutants, our research led to the discovery of 1000 synthetic fatal interactions. In addition, a large number of microarray investigations have been carried out to investigate transcript patterns under diverse environmental situations[100]. These included genome-wide assessments of the effects of exogenous medications on transcript levels, which allowed for the identification of potential therapeutic targets. Furthermore, genome-wide

mapping approaches have provided significant protein–protein interaction, protein expression, and protein localization data, and systematic analyses of the yeast proteome's organisation have provided insight into how proteins are assembled into functional multiprotein complexes[101]. Furthermore, these studies revealed a remarkable degree of conservation from yeast to humans.

1.18 Yeast as an experimental tool

1.19 Protein–protein interactions

Yeast cells serve as a 'toolbox' for studying protein–protein interactions. The two-hybrid analysis, as well as its derivatives, the one-hybrid and three-hybrid screens, are extensively used tools. It is now feasible to look for molecular partners of a large number of eukaryotic (including human) proteins of interest using two-hybrid studies in yeast[102]. For example, the three-hybrid technique has been used to search the proteome for kinase inhibitor targets.

1.20 High-throughput screening

To find chemical inhibitors of human proteins in yeast, many high-throughput techniques have been developed. The majority of these approaches rely on sensitive (liquid) growth tests. In brief, the expression of a human protein in yeast generates a growth deficiency that may be controlled by drug-induced inhibition of the protein or the development of a second human protein that acts as an inhibitor of the first[103]. The fact that yeast has effective efflux pumps, which allow small-molecule medicines (lead compounds) to be extruded from the cell, was once seen as a disadvantage in the chemical compound screening technique. However, yeast strains lacking the key efflux pumps Pdr5p and Snq2p, as well as strains with higher membrane permeability (ERG6 deletion) and the absence of multidrug resistance regulators (PDR1 and PDR3 deletion), are now available[104].

1.21 Genome-wide screening

Several genome-wide screenings have been performed using collections of yeast deletion mutants. A test to find genes that impact UV irradiation sensitivity, for example, discovered numerous unique genes that impart UV sensitivity, some of which have human orthologs linked to cancer. Other phenotypes caused by treatment with pharmaceutical chemicals or hazardous agents that target pathways or processes that are comparable in yeast and mammalian cells can also be screened using this technique[105]. Yeast deletion collections have also been utilised to undertake genome-wide transformation-based tests with great success.

2. CONCLUSIONS

From this review, we can understand the role and importance of gut microbiota present in the gastrointestinal tract of the host. A brief insight into how different microbiota are involved and are specific for different diseases can help us to draw some necessary conclusions and use the same knowledge for further applications in curing the disease. Metagenomics studies uncover more up to date qualities, pathways of digestion and dysbiosis and gives an unmistakable connection between gut microbiome and sicknesses. The microbiota can go about as microbial demonstrative markers that help in finding numerous ailments like diabetes, inflammatory bowel disease and illnesses identified with colon. To defeat the metagenomic restrictions the strategies for DNA extraction and computational point of view must be created. Understanding the requirements of growing patient populations, clinical development can be done using development of LBPs evolved from gut microflora. As there exist similarities between the yeast system and human cells, the majority of the mammalian pathways can be studied and well understood by using the yeast model. The oncogenes and suppressor genes can also be analyzed using the yeast model systems. Thus, the microbial community might open a new gateway for the development of non-antibiotic and non-chemical therapies for the treatment of the ailments associated with metabolic dysfunctions.

3. AUTHOR CONTRIBUTION STATEMENT

Nadeem Siddiqui has given the idea and edited the review. Potluri Bhavana and Vemuri Sarvani have prepared the draft which was edited by Sriraman Gurumanchi, Sibin Nambidi and Sai Madhav, Siva Reddy, Koteswara Reddy, Koteswara Rao have helped in reference works and collecting suitable images.

4. CONFLICTS OF INTEREST

Authors declare no conflict of interest

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