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Features of Protein-Protein with Protein-RNA Interactions in Bacteria and Fungi

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Abstract

Various protein-protein and protein-RNA interactions are extant which are fundamental for the regulation of biosynthetic pathways, metabolic and cellular processes in bacteria, fungi and other microorganisms, but their role and significance must be clearly elucidated. To effectively and efficiently compete in their natural habitat or niche, bacteria, fungi, and other microorganisms utilize regulatory mechanisms in metabolic production and other cellular processes; thus controlling overproduction and excretion of the secondary metabolites of excess concentrations into the environment. The knowledge and information regarding fungal natural product biosynthesis have been retarded in comparison to the corresponding extant bacterial biosynthetic pathways due to salient externalities, constraints and challenges.

Keywords: Biosynthetic pathways; Biochemical; Cellular; Transcription; Multienzyme complexes; Environment

Introduction

This review encompasses protein factors, which participate in the biosynthetic pathways, biochemical and cellular processes of both bacteria and fungi, and current views on their mechanism of biosynthesis. Bacteria and fungi generate low molecular weight molecules having multiple biological activities. Evidence exist of specific interactions within microorganisms of disparate domains, and undergird the hypothesis that they not merely differentiate signals but have intimate physical interactions which provide the latitude for communications between microorganisms as well as induction of putative latent biosynthesis genes [1] or activation of latent gene clusters [2]. Numerous interactions are extant which are fundamental for regulation of biosynthetic pathways, metabolic and cellular processes in bacteria and fungi [3-6] as well as other microorganisms, but their role and significance need to be ardently established. The knowledge and information regarding fungal natural product biosynthesis has been retarded in comparison to the simultaneously extant bacterial biosynthetic pathways due to considerable challenges, constraints and externalities. Fungal genomes are more intricately complex than bacterial components, numerous fungi are not easily susceptible to genetic manipulation, and fungal cultivation for the production of adequate quantities of ample metabolites is rather cumbersome [7].

Multifunctionality of multienzyme complexes

Evidence indicates that several cellular reactions present in metabolic pathways are catalyzed *via* one or more membrane-associated multienzyme complexes, and not by free-floating 'soluble' enzymes. This sort of macromolecular organization has vital implications for the encompassing specificity, efficiency and regulation of presenting metabolic pathways. Several biochemical and genetic studies concerning primary and secondary metabolism have been established for this model in the provision of compelling and substantive evidence for channeling of intermediates between enzyme active sites and enzyme co-localization within a cell [8].

Multienzyme complexes are multifunctional as being capable of catalyzing two or more disparate netabolic reactions. In a vast majority of instances, such as pyruvate dehydrogenase and yeast fatty acid synthetase, the disparate catalytic functions related with the complex depict the participants in a complete or partial metabolic chain. Physically, multienzyme complexes are stable aggregates of varied polypeptide chains, as protein subunits assembled in well-defined proportions. Inasmuch as, there are no extant covalent bonds between the constituent units, the description is for the quaternary structure of multienzyme complexes that confers the inherent advantages of subunit-subunit interactions between various proteins [9]. In several instances, enzymatic activities pertaining to a common pathway have been found to be related. The association between the genetic loci coding for particular aggregates and a few complicated systems with the genetic organization are somewhat associated with a number of diverse enzymatic activities. In contradistinction to dissociated enzyme systems in which the first committed step in a pathway is usually the rate-determining reaction, it is postulated that in multi-enzyme complexes, the rate-limiting reaction is not necessarily the first committed reaction in the sequence. This postulation is best depicted by the fatty acid synthases as similar set of reactions is catalysed by a multi-enzyme complex in certain organisms and by dissociated enzymes in other organisms [10].

Fungal polyketides are natural compounds exhibiting pronounced chemical variations and expansive magnitude of biological functionality. The chemical variation emerges from specialized enzymes encoded in the biosynthetic gene cluster involved in the biosynthesis of the natural product. Fungal polyketide synthases, PKS constitute the megasynthases, which form the carbon scaffolds for the compounds. Resultant downstream tailoring enzymes, such as oxygenases augments the modification of the organic framework. Several of these enzymes have been observed tofunction itiretavely by catalyzing multiple reactions on disparate sites of the

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substrate in fungi. These iterative enzymes act in concert for the efficient biosynthesis of natural compounds, such as aurovertin E, chaetoglobosin A, cytochalasin E, and lovastatin [11].

Fatty acid synthases: Nature presents three varied models for de novo synthesis of fatty acids. Generally, eukaryotes and advanced prokaryotes employ the type I Fatty Acid Synthase System (FAS I) comprising complexes of several multifunctional enzymes. On the other hand, bacteria utilize the dissociated FAS II system that is composed of a set of distinct enzymes, each involved in a specific catalytic reaction of the fatty acid synthase cycle [12]. A third system employs membrane-bound fatty acid elongases for aliphatic chain synthesis in certain parasites [13]. Irrespective of the marked variation, each specific reaction step of fatty acid biosynthesis is fundamentally conserved in all domains of life - four essential reactions one single cycle of elongation. In the initial step, an acceptor CoA or Acyl Carrier Protein (ACP) in association with malonyl-ACP is fused to generate beta-ketobutyryl-ACP that subsequently undergoes reduction by an NADPH-dependent ketoacyl-ACP reductase. The produced beta-hydroxyacyl-ACP becomes dehydrated resulting in enoyl-ACP and ultimately reduced by an Enoyl Reductase (ER) to produce the saturated acyl-ACP that can be further elongated in a nascent cycle [14].

A description and analysis of microbial type I Fatty Acid Synthases (Fass) depicting the variety of their structural and functional significance as related to their origin and biochemical function reveals that multifunctional type I FAS proteins generate dimers or hexamers with specific organization of their catalytic domains [12]. It is likely for a single polypeptide to contain one or more sets of the eight FAS component functions. On the other hand, these functions may diverge into two disparate and mutually complementing subunits. Targeted inactivation of each yeast FAS acylation sites specifies their roles in the entire catalytic process. Their marked negative cooperativity may relate in the coordination of the FAS initiation and chain elongation processes. Expression of the unlinked genes, FAS1 and FAS2 is both partially constitutive and amenable to repression by the phospholipid precursors, inositol and choline. The regulatory proteins, Rap 1, Reb 1, Abf 1, Ino2/Ino4, opi1, Sin3 and TFIIB are influential in all catalytic reactions. Balanced concentrations of subunits alpha and beta are attained by an autoregulatory effect of FAS1 and FAS2 expression and *via* posttranslational of excess FAS subunits degradation. FAS multienzymes normally function in the presence of multiple FAS systems within the same cell. De novo synthesis of long-chain fatty acids, mitochondrial fatty acids, fatty acid elongation, acylation of some secondary metabolites and coenzymes as well as the expansive diversity of mycobacterial lipids individually emanate from distinct FAS activities. The micro compartmentalization of FAS activities in type I multienzymes presumably permits for both the controlled and combined action of multiple FAS systems within the same cell [12].

Glutamine synthetase: Glutamate constitutes the paramount amino group donor in anabolism that is synthesized by the synergistic effect of the glutamine synthetase, GS and the glutamine synthase, GOGAT in *Bacillus subtilis* [15]. The degradation of glutamate is exclusively conducted by glutamate dehydrogenase, GDH. GDH and GS both comprise trigger enzymes, which are functional in nitrogen metabolism and in gene expression. Feedback inhibited GS or FBI-GS regulates DNA-binding activities of the transcription factors: (i) repressor GlnR and (ii) repressor TnrA, the nitrogen metabolism universal regulator. FBI-GS binds to GlnR and activates it. The protein complex inhibits GS production and, in effect, glutamine synthesis. In addition, FBI-GS inhibits DNA-binding function of TrnA. Glutamate biosynthesis that links carbon with nitrogen metabolism is regulated by GDH, and in unison with glutamate GDH inhibits GltC, the transcription factor that triggers COGAT gene expression. Respectively, GS and GDH regulate glutamine and glutamate synthesis depending on the cells nitrogen content. B. subtilis deficiency in an active GDH depicts a deranged growth development. However, the growth impairment is suppressed va the accelerated activation of an inactive GDH. Thus, regularization with maintenance of glutamate homeostasis is relevant for cellular functionality on the intricately complex control of glutamate and glutamine metabolism in the Gram-positive B. subtilis model organism [15].

Studies showed that two protein components, P_I and P_{II}, are involved in the adenylation and deadenylation of *Escherichia coli* glutamine synthetase. P_I exclusively catalyzes both adenylation and deadenylation, but its activity is modulated by the P_{II}-protein and by glutamine, 2-oxoglutarate, ATP, and UTP [16]. The P_{II}-protein exists in two forms: one form, P_{II}-AT, stimulates P_I-catalyzed adenylation activity devoid of glutamine, and causes this activity to be very sensitive to inhibition by 2-oxoglutarate. It has no effect on deadenylation activity. The second form, P_{II}-DA, only triggers adenylation if glutamine is present, and also stimulates the deadenylation activity of P_I, that is then reliant on the presence of ATP and 2-oxoglutarate. Conversion of P_{II}-AT to P_{II}-DA is dependent on the presence of UTP, ATP, and 2-oxoglutarate. It is catalyzed by an enzyme present in P_I preparations. UTP may be directly associated in this conversion since P_{II}-DA fractions re-isolated by filtration *via* Sephadex G-100 have small amounts of a bound uridine derivative that is devoid of the γ-phosphoryl group of UTP. The activity of P_{II}-DA, but not of P_{II}-AT, is dissipated with snake-venom phosphodiesterase treatment. ATP and 2-oxoglutarate ostensibly function as allosteric effectors for the conversion of P_{II}-AT to P_I-DA [16].

Two active forms of purified ATP: glutamine synthetase adenylyl transferase from *E. coli* were observed on polyacrylamide gel electrophoresis at pH 8 [17]. The slower migrating component that is similar to the P_I-protein fraction of the glutamine synthetase deadenylylating enzyme system has S20w 5.1S and a molecular weight of circa 130,000. The faster migrating adenylyl-transferase component gives molecular weight of circa 70,000 and S20w 4.0S. On storage at 4˚C, the greater adenylyl-transferase component (P_I) becomes the lesser active unit with a concomitant dissipation of both P_I deadenyllating activity and soluble protein. The low molecular weight adenylyl transferase is a subunit of the deadenylylating Pi-protein [17].

Arginase: Arginine anabolism and catabolism are effectively isolated separately in yeast. Arginine synthesis occurs from glutamic acid *via* ornithine, with several of the participating enzymes being repressible by arginine [18]. Exogenous arginine induces the formation of arginase and ornithine transaminase responsible for the degradation of arginine. With the induction of arginine, it is perspicuous that certain control occurs in the anabolic pathway

between arginine and ornithine to prevent a futile cycle culminating in the hydrolysis of ATP [19]. With addition of arginine to the medium, the resultant impact is that ornithine transcarbamylase activity decays rapidly in "permeabilized" cells, and that protein synthesis promotes inactivation. It is obvious that the resultant inactivation is promoted through direct interaction between arginase and ornithine transcarbamylase with arginine and ornithine involved [20]. These are evident that (a) Purified arginase in association with both arginine and ornithine are inextricably linked in the inhibition of ornithine transcarbamylase activity. (b) A 1:1 complex by means of Sephadex chromatography is formed between ornithine transcarbamylase and purified arginase, with the association of ornithine and arginine. (c) Certain mutants devoid of arginine activity lack inhibitory protein, thereby indicating that arginase presents both as an enzyme and a regulatory protein impacting on another catalytic function. Perspicuously, this phenomenon is widely observable in regulation and development in higher eukaryotes. Arginine is a common substrate for both Inducible Nitric Oxide synthase (iNOS) and arginase [21]. Ornithine transcarbamoyltransferase is influenced by two principal regulatory systems in Saccharomyces cervisiae. One system is defined for the arginine biosynthetic enzymes, whereas the other system is presumably general for diverse amino acid pathways [22].

N-acetylglutamate synthetase is an enzyme that catalyses the generation of N-acetylglutamate (NAG) from glutamate and acetyl-CoA. Succinctly put, NAGS catalyses the following reaction:

Acetyl-CoA + L-glutamate CoA + N-acetyl-L-glutamate

NAGS, a member of the N-acetyltransferase family of enzymes, occurs in both eukaryotes and prokaryotes, with vastly differing role and structure depending on the species. NAG is utilizable in the formation of ornithine and arginine, or as an allosteric cofactor for Carbamoyl Phosphate Synthase (CPS1) [23]. Most prokaryotes (bacteria) and lower eukaryotes (fungi, green algae, plants, etc.) generate NAG through Ornithine Acetyltransferase (OAT) that is part of a 'cyclic' ornithine production pathway. Thus, NAGS acts in a supportive role, augmenting NAG reserves as pertinent. In certain plants and bacteria, NAGS catalyzes the first step in a 'linear' arginine production, though [24]. The protein sequences of NAGS between prokaryotes, lower eukaryotes and higher eukaryotes have demonstrated that they are not identical. Sequence similarity between prokaryotic and eukaryotic NAGS is expansively <30%) whereas sequence similarity between lower and higher eukaryotes is circa 20% [25]. Enzyme activity of NAGS is modulated by L-arginine, and acts as an inhibitor in plant and bacteria NAGS, but an effector in vertebrates [26].

The enzyme N-acetylglutamate synthase, NAGS that was associated in the first committed step in the pathway of the de novo arginine biosynthesis *via* accelerated intermediates in microorganisms occurs in a restricted number of bacterial phyla, and not present in Archaea [27]. In several bacteria, shorter proteins linked to the Gcn5-related N-acetyltransferase family ostensibly acetylate L-glutamates; a few are perspicuously identical to the C-terminal, acetyl CoA classical NAGS binding domain, whereas others are remotely related. Short NAGS are liable to be single gene products, as is evident in *Mycobacterium* spp. And *Thermus* spp., or adhered to the enzyme argininosuccinate catalyzing the ultimate step of the pathway as observed in members of the Alteromonas-Vibrio group. In selected bacteria, a bifunctional ornithine acetyltransferase effects glutamate acetylation. In several Archaea, the etiological enzyme for glutamate acetylation is not pellucid; it is, however, suggested that associations with a novel lysine biosynthetic pathway from genomic investigations is extant. In certain Proteobacteria, such as Xanthomonadaceae and Bacteroidetes, the carbamoylation step of the pathway ostensibly involves N-acetylornithine or N-succinylornithine instead of ornithine [27]. The N- acetylcitrulline product is deacetylated by an enzyme that is also connected in ornithine provision from acetylornithine. This constitutes a vital metabolic activity as ornithine serves as a source for several metabolites.

Dehydroquinase: Two dehydroquinases are extant in Neurospors [28]. They are distinctly a constitutive biosynthetic enzyme that is part of an aggregate specified by the arom region, and an inducible catabolic enzyme that is coded for by an unlinked gene [29,30]. The arom aggregate catalyzes the latter through the sixth steps present in the polyaromatic pathway before chorismate formation. It is suggested that dehydroquinate produced within the aggregate is not available to the degradative pathway. Studies suggest that dehydroquinate bound to the aggregate is unable to induce the degradative pathway. Mutations which are destructive to the integrity of the aggregate culminate in the induction of increased concentrations of the degradative enzyme, probably as a result of the release of dehydroquinate produced biosynthetically.

A 3-dehydroquinate dehydratase catalyzes the chemical reaction 3-dehydroquinate 3-dehydroshikimate H_2O. Thus, the enzyme has one substrate, 3-dehydroquinate, and two products, 3-dehydroshikimate and H_2O. It participates in phylalanine, tyrosine and tryptophan biosynthesis. There are two classes of 3-Dehydroquinate Dehydratase which exist as type I and II. The two variants have varied amino acid sequences and secondary structures. Type I occurs in fungi, plants and certain bacteria for chromate biosynthesis. It catalyzes the cis-dehydration of 3-Dehydroquinate *via* a covalent imine intermediate. Type I is heat labile, with Km values in the low micromolar range. Type II occurs in the fungi quinate pathway and the shikimate pathway of certain bacteria [31]. It catalyzes a transhydration by means of an enolate intermediate. It is also heat labile, but has Km values one or two order of magnitude greater than those of Type I. The extensively studied type I enzyme is a homodimeric protein from *E. coli* (gene aroD) and related bacteria. In fungi, dehydroquinase constitutes a multifunctional enzyme that catalyzes five consecutive steps in the shikimate pathway, with histidine involved in the catalytic mechanism [32]. Also, 3-Dehydroquinate Dehydratase occurs in the process of quinate degradation. Both 3-Dehydroquinate and 3-Dehydroshikimate constitute intermediates in the reaction mechanism. Structural, biochemical and computational studies were used to investigate the irreversible inhibition of type I Dehydroquinase (DHQ1), the third enzyme of the shikimic acid pathway. It revealed the vital role played by His143 as a Lewis acid in this process and the necessity for a pertinent and closed active site for catalysis [33].

Tryptophan synthetase: Tryptophan is the most chemically complex and the least preponderant of the twenty of the twenty ubiquitous proteinogenic amino acids, but it is a biosynthetic precursor to numerous complex microbial natural compounds.

Several of these products portend as scaffolds for the discovery and development of drugs. The chemical attributes of tryptophan with its potential for enzymatic modifications, ostensibly in its entire atomic structure as well as in its capability for spontaneous non-enzymatic catalysis depict it as a select biological precursor for chemical complexity formation [34]. IGPS EC4:1.148 indole-3-glycerol phosphate synthase, the fourth enzyme of Trp biosynthesis catalyses the conversion of 1-(O-Carboxylphenylamine-1-deoxyribulose-5-phosphate to indole-3-glycerol phosphate [35]. Remarkably, IGPS is synthesized as a protein presenting either one or two other enzymes [36]. In plants, IGPS is detected as a monofunctional enzyme regarding its cDNA sequence and functionality of its complementation analysis [35].

Tryptophan synthetase is marked by the trp-5 region of yeast. The enzyme performs the following reactions:

Indole glycerol phosphate indole + glyceraldehydes 3-phosphate

Indole + serine + L-tryptophan

Indole glycerol phosphate serine L-tryptophan + glycerol phosphate

The reaction of considerable physiological significance is (iii). When indole presents as an intermediate in reaction (iii), it is usually enzyme-bound. The extracted tryptophan synthetase of wild-type strains is an aggregate of molecular weight 135,000 and is involved in the catalyzation of all three reactions [37]. The significance of the organization of the complex to prevent indole escape has been depicted in two strains each with a mutation that affected the complex [37,38]. Although, none of the two strains were able to catalyze reaction (iii), one possessed an enzyme capable of performing reaction (i), whereas the other performed reaction (ii); in a diploid combination, the mutant enzymes failed to aggregate but carried out indole glycerol phosphate conversion to tryptophan by coupling the two half-reactions (i, ii). Even though, the strain had the capability to make tryptophan, the growth was poor, with excretion of abundant concentrations of indole into the medium. Cultures initiated with little inocula presented an extended lag period of up to 40 hr, which was extinguished merely following the augmentation of exogenous indole levels. A hybrid produced from another pair of mutant strains which were unable to catalyze reaction (iii) formed a functional complex constituting the two mutant enzymes. This strain did not present a growth lag, probably due to complemented enzyme not been able to convert indole glycerol phosphate to tryptophan without indole release. Therefore, the capability of indole to remain bound culminates in a perspicuous biological benefit. Also, evaluation of findings in relation to the three-dimensional structure of the tryptophan synthetase enzyme complex of *Salmonella typhimurium*, and the results of mutational analyses with *E. coli* suggest that tryptophan synthetase evolved *via* an alpha-beta rather than a beta-alpha fusion, since in beta-alpha fusions the amino-terminal helix of the alpha chain is incapable of assuming the conformation required for optimal enzymatic activity [39].

Anthranilate synthetase-phosphoribosyltransferase: Studies regarding the physical characteristics of the anthranilate synthetase-phosphoribosyltransferase complex of *salmonella typhimurium* [40,41] and *Escherichia coli* [42,43] depict that these enzymes do function *in vivo* as an enzyme complex. The complex is constituted by two disparate polypeptide chains, namely component I (coI) and component II (coII), being respectively, the products of both structural genes in the trp operon. Molecular weight analyses indicate that the wild-type complex is (coI)2 (coII)2. Purified coI alone cannot perform the catalyzation to convert chorismate and glutamine to anthranilate; although, it catalyzes the conversion of chorismate and ammonia to anthranilate, and this latter reaction is tryptophan inhibited. coI must undergo activation by coII for the glutamate-dependent reaction. Both coII and anthranilate synthetase complex catalyze the phosphoribosyl transferase reaction, being the second in the reaction sequence in the biosynthesis of tryptophan.

The anthranilate synthase-anthranilate 5-phosphoribosylpyrophosphate phosphoribosyl transferase enzyme complex (chorismate pyruvatelyase (amino-accepting), (N-(5'-phosphoribosyl)-anthranilate: pyrophosphate phosphoribosyl transferase), from *Salmonella typhimurium* was purified with high yields to homogeneity [44]. Sodium dodecyl sulfate gel electrophoresis of the purified enzyme complex demonstrated a single major band containing 96% of the protein. The final yield of enzyme complex activity ranged from 30 to 60%. The principal enzyme complex band appeared to be the native tetramer, with a molecular weight of 280 000, and containing ammonia- and glutamine-dependent anthranilate synthase activity. Three other bands were molecular weight isomers of the major enzyme complex band. Two forms of molecular weight isomers were observed: dimers and an aggregate of the native enzyme complex. The molecular weight isomers of the enzyme complex are suggestively, forms generated by aggregation and denaturation of the native enzyme complex. The method is formulated on the distinctiveness in extinction coefficients between anthranilate and N-(5'-phosphoribosyl) anthranilate [44].

In Serratia marcescens, AS is the initial branch node enzyme that catalytically converts chorismate to anthranilate in the elevatd energy-consuming tryptophan biosynthetic pathway. AS in conjunction with an allosterically bound inhibitor, tryptophan depicts overwhelming inhibition in its catalytic activity, although, the inhibitor-bound is closely identical to the substrate-bound AS [45]. Inasmuch as the reaction of numerous chorismate utilizing enzymes is perspicuous, the unfamiliar structure-function association in catalysis and allosteric AS inhibition by tryptophan presenting on infinitesimal structural alteration, is yet undecipherable. It is argued that this sort of regulatory mechanism devoid of significant structural alteration, but depicting functional alteration in catalysis is conducive for a branch point enzyme positioned for rapid flux dissemination regarding disparate metabolic conditions of the organism [45]. In this study, network modeling and molecular dynamic experimentation elucidated the deranged communication pathways as allosteric inhibition mechanism in anthranilate synthase.

The biosynthetic pathway in bacteria for the hydroxymethyl pyrimidine moiety of thiamine employs metabolic intermediates in common with purine biosynthesis, and the two pathways branch after the product aminoimidazole ribotide [46]. The initial ubiquitous metabolite, phosphoribosyl amine, PRA is generated without the first enzyme in purine biosynthesis, PurF. PurF-independent PRA synthesis depends on both strain background and growth status. Standard genetic strategies have not unraveled any gene product solely

implicated in PurF-independent PRA production. It is adduced that multiple enzymes are involved in PRA synthesis due to resultant side products of their defined reactions. A mutation capable of reinstituting PRA synthesis in a PurF gnd strain was established to map in the gene coding, for the TrpD subunit pertaining to the Anthranilate Synthase-Phosphoribosyl Transferase (AS-PRT) complex. Genetic analyses suggested that wild type AS-PRT generated PRA *in vivo*, and that the TrpD P362L mutant augmented the synthesis. *In vitro* functionality assays demonstrated that the mutant AS generated PRA from ammonia and phosphoribosyl pyrophosphate [46].

In the bacterium, Thermus thermophilus, the enzyme homocitratesynthase, HCS catalyzes the initial reaction of lysine biosynthesis *via* α-aminoadipic acid, homocitrate synthesis from 2-oxoglutamate and acetyl-CoA. HCS is potently inhibited by lysine, suggesting that the biosynthesis is controlled by the endproduct at the first step of the pathway. Also, HCS catalyses the reaction by substituting oxaloacetate for 2-oxoglutamate as a substrate identical to citrate synthase in the TCA cycle [47]. In riboflavin-prototrophic bacteria, riboflavin transporters might be a module for riboflavin availability for specific, not yet decipherable processes, instead of substituting for the endogenous riboflavin biosynthetic pathway or the utilization of importer proteins as commonly presented [48].

Complex loci gene clusters and enzyme aggregates

Biochemical and genetic evidence relates that two basic types of gene clusters are present in eucalypts. The first is the multienzyme complex that encodes an enzyme aggregate. In several instances, these gene clusters are cluster-genes, that is, single genes which encode multifunctional polypeptide chains, and in association as homopolymeric aggregates [49]. Also, there exists a channeling role for these enzyme aggregates, as they serve to sequester intermediates in a specific biochemical pathway, and to preclude competition between two potential competitive pathways. The other less frequent sort of gene cluster in eukaryotes is a true cluster of contiguous but disparate genes, which are not involved in the coding of an enzyme aggregate. Some of these clusters ostensibly present operon-like features. For the production of polycistronic mRNA, any one of these clusters, as in the qa cluster in Neurospora may be sustained by natural selection since it possesses a gene that encodes a regulatory protein which is primarily cis acting [49].

Prokaryotic gene clusters: Gene clusters may be identical to an operon in which genes are controlled by an individual operator and promoter with all genes being transcribed simultaneously. With regard to bacterial operons, the genes are transcribed as a polycistronic mRNA. Operon-like gene clusters are basically, but not distinctively formed through horizontal gene transfer in prokaryotes, as depicted in *E. coli* [50]. The lac operon of *E. coli* is controlled by one promoter and one operator, and it encodes three enzymes which are necessary for lactose metabolism. The three genes are transcribed to produce a polycistronic mature mRNA that forms three distinct polypeptides for an individual gene in the operon. A polycistronic mRNA is transcribed and forms multiple polypeptide chains from a single mRNA. Invariably, a translation event culminates in three polypeptide chains, depicting one for each gene of the lac operon [51].

Eukaryotic gene clusters: A variety of established gene clusters, such as DAL and GAL are discernible in yeast [52]. Filamentous gene clusters are essentially involved in the biosynthesis of primary and secondary metabolites [53]. Gene clusters of metabolic pathways vary expansively from the structure of operon-like gene clusters [52]. Generally, eukaryotic and prokaryotic gene clusters vastly differ from each other. Whereas prokaryotic gene clusters form due to horizontal gene transfer, this mechanism is not possible in eukaryotes. Although there are isolated observations of fungal gene clusters emanating due to horizontal gene transfer, the mRNA of eukaryotic gene clusters undergoes transcription as an independent, or monocistronic mRNA [53]. In all perspectives, the ilv 1 gene of Saccharomyces cerevisiae exhibits functions linked with both regulatory and structural genes, and is thus related as a multifunctional gene. The product of the ilv 1 gene catalyzes the initial step in isoleucine biosynthesis, and is integrated in the isoleucine-valine pathway repression [54]. Genetic maps of certain fungi indicate that gene clustering of related function is well-nigh impossible. Varied potential gene clusters in fungi have been distinguished and analyzed. These genetic regions have characteristics found in the bacterial operon, with distinct properties [55]. A peculiarity is that the specified enzymatic activities of the complex loci are inextricably linked physically. This association complicates itself, if these genetic regions depict a single multifunctional protein or several proteins embedded as an aggregate.

In eukaryotes, the first steps in the de novo synthesis of pyrimidines are conducted by multienzyme complexes composed of the first two enzymes in fungi. In Neurospora, evidence exists that this complex enhances channeling of the carbamyl phosphate formed by pyrimidine-specific Carbamyl Phosphate Synthetase (CPSase) in the second enzyme, aspartate transcarbamylase (ATCase)3. These enzyme aggregations in fungi are associated in close linkage of the structural genes for both CPSase and ATCase, which appear to be cotranscribed and translated. The third pyrimidine pathway enzyme, Dihydroorotase (DHOase) is encoded by unlinked genes in fungi. Thus, there is a close relationship between enzyme aggregation and gene clustering in such a system in fungi [56].

The arom region in *N. crassa* is involved in the encoding of a vast multifunctional protein that catalyzes the second through the sixth cascade in the polyaromatic pathway [29]. These five activities exist with a structure of relative molecular mass 230,000 in complete 750-fold purification [57], but its defined physical structure is unknown. It may be a homopolymer comprising a single polypeptide or a heteropolymer of diverse polypeptides. Dehydroquinate synthetase activity was restored when extracts of two arom mutants each devoid of dehydroquinate synthetase activity were mixed. The active hybrid molecule had a molecular weight of 230,000 as the normal complex, thus indicating that the aggregate has at least two subunits, which can easily dissociate and re-associate [58], but it is difficult to ascertain whether these subunits are identical.

Genetic analysis shows that the arom region is divisible into five nonoverlapping segments [28,29]. Missense mutations in any of these result in the dissipation of any of the five activities related to the aggregate. Nonsense mutations in the initial region of the arom cluster are devoid of all five activities. The presence of these polar mutations constitutes the pertinent available evidence of the transcription of the arom region into a single RNA molecule. Certain missense mutations ostensibly affect the aggregation status of the complex with the production of gross alterations in the subunit activity. A peculiar

class, mapping at an extremity of the locus, forms a smaller particle presenting activity for the enzyme, EPSP synthetase but devoid of three other activities [59,60]. Coupled with the genetic presentation, this result shows that areas of the complex have certain magnitude of functional autonomy. Expansive genetic and biochemical studies have been conducted with revertants and secondary arom-2 mutants induced in two separate primary non-complementing mutants mapping within the *Neurospora crassa* arom gene cluster [61]. The recovery of secondary arom-2 mutants as revertants of non-complementing arom mutants significantly indicated that non-complementing arom mutants are localized in the arom-2 structural gene of the arom gene cluster. Also, the presence and features of these secondary arom-2 mutants regardless of the outcome with nonsense suppressors that the arom gene cluster is transcribed starting with the arom-2 gene as a single polycistronic mRNA that becomes translated into the arom multienzyme complex [61].

The nucleotide sequence of the Saccharomyces cerevisiae ARO1 gene which encodes the arom multifunctional enzyme has been determined. The protein sequence deduced for the pentafunctional arom polypeptide is 1588 amino acids in length and has a calculated Mr of 174555. Functional regions within the polypeptide chain have been identified by comparison with the sequences of the five monofunctional *Escherichia coli* enzymes whose activities correspond with those of the arom multifunctional enzyme. The observed homologies demonstrate that the arom polypeptide is a mosaic of functional domains and are consistent with the hypothesis that the ARO1 gene evolved by the linking of ancestral *E. coli*-like genes [62].

The his4 region of a fungal gene cluster that specifies the second, third, and tenth steps in the biosynthetic pathway leading to histidine has been well investigated [63]. The genes which specify the other seven yeast histidine biosynthetic enzymes lack contiguity with the his4 cluster or with one another. There are pertinent missense mutations in the his4 region map in three distinguishable groups with each group devoid of one of the three activities [64]. The array of the genetic and complementation maps of these mutations in the region depict that the region is comprised of three contiguous genes A, B and C which respectively influence the catalytic reactions of 3, 2 and 10. Nonsense mutations in the his4A region present a full complement polarity; while strains bearing such mutations are devoid of any detectable activity of the gene products for B and C. The nonsense mutations in C have no influence on the functions of A and B. It is suggested that if the his4 region is an operon, and that the direction of translation as A to C is established by the given data [64].

As is obtainable in the arom system, the activities specified by the his4 region are linked in a single complex. The purified complex has a molecular weight by sedimentation equilibrium of 80,000-90,000. The particle remains intact in the presence of dissociating agents, such as sodium dodecylsulphate; but with both dissociating and reducing agents present, the complex degrades into two subunits of molecular weight unified by disulphide bonds. It is not clear whether these subunits are similar. An analysis of the molecular weight of the residual A and B activities in his4C nonsense mutants result in a partial complex of molecular weight of 40,000-50,000 with A activity, thus, indicating that the subunits are not identical. It may be that the his4 region specifies two polypeptides of molecular weight 40,000-50,000 bound by disulphide bonds. Thus, the fragment of the his4C chain formed in C nonsense mutations are not amenable to complex with the 40,000-50,000 molecular weight unit that are involved in the catalytic reactions of A and B [64].

Although, aggregates are crucial in several instances, it does not explicate why genes encoding them are clustered. A perspicuous explication for the genetic proximity of regions encoding disparate activities is because these regions constitute part of the same gene. The distinct enzyme reactions would all be performed by an aggregate composed of numerous copies of a single polypeptide chain or homopolymer, as observed in aspartokinase-homoserine dehydrogenase complex of *E. coli*. Expansive physico-chemical studies indicate that aspartokinase I and homoserine dehydrogenase activities invariably reside on the same polypeptide chain, with the native chain comprising six identical subunits of relative molecular mass of 60,000 [65]. Presenting in its simplest form, the homopolymer model does not explicate the remarkable characteristics of the fungal gene clusters; that is, the information linkage between genetic map position and function. Every mutation that has the same functional defectiveness invariably map together. This information relatedness is commonplace in an operon structure where several disparate genes are inextricably linked. Portions of this protein present significant autonomy that the product of a complex genetic locus is one multifunctional polypeptide. Inchoate chains produced by nonsense mutations are active in certain catalytic reactions of the complete protein. In contrast, where these aggregates comprise distinct polypeptide chains, which are specified by the same mRNA, it then means that aspects of protein synthesis influence the aggregation. A distinct possibility is that the nascent polypeptides aggregate during their formation on the polysome, even as they are able to associate on polysomes [66]. Another feature is that the transcription of a mRNA into a single polypeptide chain results in the subsequent cleaving to several chains by polypeptide activity. It is suggested that in eukaryotes, the synthesis of polypeptide chains is initiated just once on a single mRNA, culminating in the first instance in a single polypeptide per mRNA [67]. The appropriate alignment and formation of disulphide bridges necessitates the initial formation of a single polypeptide chain as amenable for insulin synthesis [68].

In two rigorously studied aggregates, it was found that mutational alteration of yeast tryptophan synthetase and the arom-specific aggregate of Neurospora resulted in abnormalities in the flow of intermediates through the pathway. The implications of disruptions of these two aggregates suggest the importance of the intact complex in the sequestration of intermediates and their prevention from being forced out of the cell or access to adversarial degradative cycles. This substrate compartmentalization is referred to as channeling [64].

A quantitative model was used demonstrate that co-clustering of multiple enzymes into compact agglomerates enhances the processing of intermediates, resulting in the same efficiency advantages as direct channeling. It is suggested that the model predicts the separation and size of coclusters, which maximize metabolic efficiency. A metabolic branch point in *Escherichia coli* was experimentally used to confirm the model prediction that enzyme agglomerates accelerates the processing of a shared intermediate by one branch, and thus the regulation of a steady-state flux division. The studies

suggest a quantitative framework to understand coclustering-mediated metabolic channeling and its application to both efficiency enhancement and the regulation of metabolism [69].

The importance for the inextricable physical linkage for full and proper feedback regulation of each compartment is expansively described regarding anthranilate synthetase-phosphoribosyltransferase complex as described above. Related complexes which are similar but not studied in detail include carbamyl-phosphate synthetase-aspartate transcarbamylase in yeast [70] and Neurospora [71] and the chorismate mutase-prephenate dehydrogenase complex in Aerobacter aerogenes [72,73]. Speculations are rife as to the advantage of a control mechanism that presents diverse activities which are inhibited simultaneously. As generally presented, endproduct inhibition is associated with the inhibition of only the initial enzyme of a pathway. Accelerated depletion of the resultant intermediates by being converted to the endproduct are liable to be debilitative as other enzymes in the pathway undergo subsequent stabilization by their substrates as evident in the leucine pathway [74]. The simultaneous feedback inhibition of all enzyme aggregates would portend instantaneous enzyme freezing with their substrates, thus precluding intermediate conversion to end product.

Comparative analyses involving bacteria and fungi depict that the primary function of the arom aggregate is dehydroquinate channeling. In the examination of five bacterial species, the five-arom enzymes were not found to be aggregated and there was only one kind of dehydrogenase activity [75]. In six fungal species including *Neurospora crassa*, there was presence of arom aggregate, with two of these containing dehydroquinase associated with the serum aggregate as well as another dehydrogenase probably linked in the catabolism of quinate [76]. The absence of a second dehydroquinase in the other four fungal species places doubt in the channeling hypothesis, it is probable that the enzyme was present but was not decipherable by the procedure applied.

Characterization of morphological and spatial organizations

An excess of 90% of the filamentous fungus Aspergillus fumigates cell wall constitutes of polysaccharides. Polysaccharide cell wall biosynthesis is under the purview of three sorts of enzymes: transmembrane synthase, which are invariably attached to the plasma membrane and utilize nucleotide sugars as substrates, and cell wall-linked transglycosidases and glycosyl hydrolases, which are associated to remodel the de novo synthesized polysaccharides and establish the three-dimensional cell wall structure [77]. Cell wall is a live organelle that undergoes alterations in its composition and localization of the various constituted cell wall ingredients (particularly the external layers) as the fungus is sensitized to alterations in the external milieu. The cell wall is critically involved during infection as its recognition by the host is remarkable for the immune response initiation. The interactions between the diverse Pattern-Recognition Receptors (PRRS) and cell wall pathogen-linked molecular patterns position the host response for fungal mortality, growth or development with resultant disease development or survival.

Cells of rod-shaped Myxococcus xanthus cells are usually polarized with proteins which are asymmetrically localized to defined positions. The spatial organization is significant for the regulation of motility, cell division and spatiotemporal alterations. Discrete protein modules control motility devoid of cell cycle, and cell division reliant on the cell cycle. With regard to motility, a prominent lagging cell polarity is determined and undergoes inversion at cellular reversals [78]. The determination and inversion of the polarity are controlled hierarchically by interfaced protein modules, which select polarized motility proteins to the specific poles or promote their relocation between cell poles at reversals identical to a spatial toggle switch. During division, a newfangled auto-organizing protein module that incorporates a ParA ATPase places the FtsZ-mng at mid-cell [78]. Elongation Factor-P, EF-P binds to ribosomes with assistance to produce oligoprolines for EF-P to associate with retarded ribosomes, certain tRNAs with unique d-arm residue are invariably positioned in the peptidyl site, such as tRNAPro, with occurrence of peptide bond synthesis [79]. The undergirding mechanism *via* which EF-P enhances this reaction is ostensibly of entropic origins. Maximal activity of EF-P necessitates a posttranslational modification in *E. coli*, *Pseudomonas aeruginosa* and *Bacillus subtilis*. Every alteration or modification is unique, discrete and inextricably-ligated to its specific Ef-P invariably by complete convergent interactions.

Gibberellins, GAs promote stem growth in seed plants, angiosperms and gymnosperms [80,81]. The pathogenic fungus, Gibberella fujikuroi generates gibberellins, Gas which cause tremendous prolongation of infected rice plants, and these GAs have been extensively detected in fungi and bacteria [82]. The GA biosynthetic pathway in fungi is significantly distinct than that expressed in angiosperms [83]. GGDP conversion to ent-kaurene in fungi undergoes catalyzation by a lone bifunctional terpene cyclase [84] rather than two disparate enzymes, CPS and KS. The fungal KAO (a P-450 enzyme) sequence exhibits slight similarity to angiosperm KAO. Furthermore, the fungal pathway from GA12 aldehyde is unique, and merely employs P-450 enzymes in contradistinction to the 20DDS in angiosperms; thus suggesting that GA biosynthetic pathway in angiosperms and fungi evolved disparately. It was not clearly elucidated why certain fungi form Gas because strains defective in GA biosynthesis have normal growth in culture (Hedden et al., 2001). It is ostensible that GA promotes infection *via* necotrophic pathogens, such as G. fujikuroi due to the suppression of the jasmonic acid signaling pathway [85].

Biotin constitutes an essential micronutrient with task as a co-factor for biotin-reliant metabolic enzymes. In bacteria, biotin production is achievable by de novo synthesis or obtained from exogenous supplies. A variety of bacteria are capable of producing biotin *via* both mechanisms, whereas others resort to their biotin needs by de novo synthesis. The inability to meet cellular requirements of biotin usually present deleterious effects for cell virulence and cell viability [86]. The most expansively characterized protein that controls biotin uptake and biosynthesis is BirA. In some bacteria, such as *E. coli* and *S. aureus*, it is defined that BirA is a bifunctional protein that acts as a transcriptional repressor to regulate genes of biotin synthesis, including the role of a ligase in the catalyzation of the biotinylaton of reliant enzymes. BioQ and BioR are two other proteins, which regulate biotin biosynthesis and transport.

Channeling and osmosensors in the ambient

Bacteria act to sustain hydration when the osmotic pressure

with the alteration of the environment. As reduction in the external osmolality or osmotic downshift occurs, mechanosensitive channels become activated to release low molecular weight osmolytes including water from the cytoplasm. Consequent upon osmotic upshift, osmoregulatory transporters become activated to import osmolytes, and hence water. Osmoregulatory channels and transporters are sensitized and respond to osmotic stress by means of varied mechanisms [87]. Mechanosensitive channel MscL senses the rising membrane tension, and appears to gate as the lateral pressure in the acyl chain region of the lipids decreases below a threshold value. Transporters OpuA, BetP and ProP are activated when increasing external osmolality causes threshold ionic contents in excess of circa 0.05 M to be obtained in the proteoliposome lumen. The threshold activation levels for the OpuA transporter markedly depend on the fraction of anionic lipids that surround the cytoplasmic aspect of the protein. The greater the fraction of anionic lipids, the greater the threshold ionic levels. An identical trajectory was detected for the BetP transporter. The lipid reliance of osmotic activation of OpuA and BetP are suggestive that osmotic signals are transmitted to the protein by means of interactions between charged osmosensor domains and the ionic headgroups of membrane lipids [87].

The charged, C-terminal domains of BetP and ProP are significant for osmosensing. The C-terminal domain of ProP participates in homodimeric coiled-coll production, and could interact with the membrane lipids and soluble protein ProQ. The activation of ProP by lumenal, macromolecular solutes at constant ionic strength suggests that its structure and activity responds to macromolecular crowding. This excluded volume effect may circumscribe the range in which the osmosensing domain is able to electrostatically interact. In essence, the relatively high ionic levels at which osmosensors are activated at various surface charge densities compare well with the predicted reliance of 'critical' ion levels on surface charge density. The critical ion levels represent transitions in Maxwellian ionic distributions at which the surface potential of 25.7 mV for monovalent ions is obtained. The osmosensing mechanism is qualitatively established as an "ON/OFF switch" for thermally relaxed and electrostatically locked protein conformations [87].

Osmosensors are proteins that sense environmental osmotic pressure. They mediate or direct osmoregulatory responses, which permit cells to survive osmotic alterations and extremes. Bacterial osmosensing transporters sense elevated external pressure and respond *via* mediating organic osmolyte uptake, hence cellular rehydration. Extensive studies of osmosensing transporters OpuA, BetP, and ProP indicate that they sense and respond to various osmotic pressure-dependent cellular properties. These studies also indicate that each protein has a cytoplasmic osmosensory or osmoregulatory domain, but that these domains vary in structure and function. It has not been determined whether each transporter represents a specific osmosensory mechanism or whether other researchers are working on an identical mechanism through different trajectories. It is pertinent to have applications to other osmosensors, and to those that trigger signal transduction cascades in prokaryotes and eukaryotes [88].

Secondary metabolites and perturbations in the milieu

In order to compete in their natural habitat or niche, bacteria, fungi, and other microorganisms apply regulatory mechanisms, which control metabolic production, thereby enabling the harnessing of overproduction and excretion of the secondary metabolites of excess levels into the environment. Metabolic co-regulation amongst biosynthetic pathways concerning secondary metabolites is usually in microsomal communities and depicts their importance of microbial interactions. It has been demonstrated that the intermediate in 2,4-Diacetyl-Pholoroglucinol (DAPG) and pyoluteorin, being two antimicrobial metabolites formed by the soil bacterium Pseudomonas protegens, that an intermediate in the DAPG biosynthesis, phloroglucinol undergoes transformation by a halogenase encoded in the pyoluteorin gene cluster into mono- and di-chlorinated phloroglucinols

[89]. The chlorinated phlorogluciols act as intra- and inter-cellular signals which promote or induce the expression of pyoluteorin formation, and pyoluteorin-mediated inhibition of the plant-pathogenic bacterium, Erwinia amylovora. The evidenced metabolic co-regulation strategically provides for optimum application and utilization of secondary metabolites with discrete functionalities in inextricably-linked symbiosis and competitive microbial interactions.

Filamentous fungi generate several minute bioactive compounds as constituents of their secondary metabolisms extending from ostensibly innocuous antibiotics, such as penicillin to debilitative mycotoxins, for instance, aflatoxins. Secondary metabolism may be associated with fungal developmental phases elicited by diverse abiotic or biotic extraneous influences. The velvet family of regulatory proteins is significantly involved in the coordination of secondary metabolism and differentiation, such as asexual and sexual sporulation as well as sclerotia or fruiting body production [90]. This velvet family has a common protein domain that presents portion of the fungal kingdom in an extensive portion from chytrids to bactidiomycetes. Aspergillus nidulans features where VeA, the founding entity was detected decades ago. Disparate entities of the velvet protein family interact with one another and the non-velvet protein LaeA, principally in the nucleus. LaeA is a methyltransferase domain protein with functionality of secondary metabolism and development regulator. The position that VeA has only been located in fungi, coupled with advances in the explication of the VeA mechanism, it becomes pertinent to design optimum future regulatory strategies to mitigate the deleterious consequences of fungi with concomitant promulgation of beneficial qualities [91]. The study of protein-protein interactions in Candida albicans is important to understand the control mechanism of the signal transduction network that elicits its defined pathogenic trajectory. The development of an optimized set of plasmids that provides the latitude for N- and C-terminal protein tagging allows for useful molecular interpretation and analysis of the regulation of protein functionalities [92]. Biosynthetic pathways are inextricably linked in protein-protein interaction networks. In the biosynthetic pathways of Arabidopsis, aliphatic and indole glucosinolate defence molecules are well-established and mediated *via* protein-protein interactions [93]. The yeast two-hybrid system has been employed for the characterization of numerous protein-protein interactions. An *E. coli* two-hybrid system was devised in which one-hybrid protein bound to a specific DNA site inculcates another in an adjacent proximal binding site. Reconstruction experiments involving the fos and jun leucine zippers demonstrated protein-protein interactions with homodimeric or heterodimeric leucine zippers [94].

The frequently employed β-lactam antibiotics for infectious disease therapy are penicillin and cephalosporin. The former is is produced as an endproduct by certain fungi, most remarkably by Aspergillus/Emericella nidulans and Penicillium chrysogenum. Bacteria and fungi, for instance, the fungus Acremonicum chrysogenum/cephalosporium acremonium synthesize cephalosporins [95]. The biosynthetic pathways culminating in both secondary metabolites commence from the same three amino acid precursors with common initial two enzymatic reactions. Catalysis of penicillin biosynthesis is by three enzymes encoded by acvA (pcbAB), ipnA (pcbC) and aatA (penDE) with the genes in a cluster. In A. chrysogenum, a second cluster as well as acvA and ipnA harbours the genes, which catalyze the reactions of the further phases of the cephalosporin pathway (cefEF and cefG). It has been demonstrated that the fungal β-lactam biosynthesis genes are regulated by a complex network, such as the putative amino acids, pH, and carbon sources.

An encompassing proteomics analysis identified the proteins, which interact with the eleven canonical members of the pathway, also identified by genetic studies. An immune receptor protein complex devoid of all ingredients may culminate in misrepresentation, omitting, misleading and misinterpretation of data or inferences [96]. Comparative analysis of computationally predicted protein-protein interaction networks of five closely related yeast species by the application of protein-protein Interaction Prediction Engine in the magnitude and feature of protein-protein interaction network evolution showed expansive evidence for protein-protein interaction conservation with decreased expectancy or extent of alterations in protein-protein interactions in circa 25% of the proteomes, accompanied by inadequate prediction of sequence divergence [97].

Rice blast disease caused by the fungus Magnaporthe grisea constitutes a deleterious disorder for cultivated rice, Oryza sativa as detected in protein-protein interactions between rice and fungi. Analysis of the contextual ubiquitous master regulators, Xanthomonas oryzae pv.oryzae and rice strip virus responsive to rice infection showed that the ubiquitin proteasome pathway remained the usual pathway in rice controlled by these pathogens, whereas apoptosis signaling pathway induction is by bacteria and fungi [98]. The Drosophila protective mechanism against pathogens is expansively dependent on the activities of the signaling pathways of (i) immune deficiency, IMD and (ii) Toll. The former is principally induced by Gram-negative bacteria, whereas the latter pathway is responsive mainly to Gram-positive bacteria and fungi. The activation of both pathways results in rapid formulations of several NF-kB-induced immune response genes coupled with antimicrobial peptide genes. The IMD pathway depicts marked similarities as the TNF receptor pathway. Also, it is perspicuous that the IMD pathway is activated in response to diverse non-infectious stimuli, such as inflammatory reactions [99].

Transcriptional Factors and Regulatory Mechanisms

A defined regulatory segment of a mRNA molecule is a riboswitch that binds a small molecule, culminating in alteration in production of the proteins encoded by the mRNA [100,101]. Hence, a mRNA that has a riboswitch is inextricably linked in the regulation of its own activity in response to the level of its effector molecule. The knowledge that recent organisms mobilise RNA to bind small molecules and exclude closely related analogues did broaden the established natural scope of RNA beyond its ability for protein coding, catalyze reactions or to bind other RNA or protein macromolecules. Riboswitches are present in bacteria, but functional riboswitches of one type (the TPP riboswitch) have been observed in plants and some fungi [102]. Riboswitches depict that naturally occurring RNA can bind small molecules, a feat that was associated only with proteins or artificially constructed RNAs called aptamers. The existence of riboswitches in all domains of life therefore adds some credence to the RNA global hypothesis for original life existence employing only RNA, with later advent of protein. This postulation necessitates that all vital functions conducted by proteins and small molecule binding could be undertaken by RNA. It is certain that riboswitches represent ancient regulatory systems, or even remnants of RNA world ribozymes whose domains are conserved [103].

Genetic studies have given only anecdotal reasoning in this regard. The number of genes in a region is determined by the number of independent functional units with the assumption that these are proportional to the number of genes. Mutations which affect one polypeptide in an enzyme aggregate may influence the physical state and enzyme activities associated in the complex; and these complicate the pleiotrophic effects of polar mutations in bacterial operons [64]. With the causation of defects in the translation or transcription of a polycistronic message, it is evident that polarity mutations, whether nonsense, promoter or regulatory mutations are able to influence gene functions in the operon simultaneously. Devoid of any chemical evidence for a polycistronic messenger, it is demonstrable that the pleiotrophic impacts of polarity mutations present as the operon identifier. Therefore, the influence of a mutation in one gene as it affects the gene function of another may be attributed either to the organization of the operon or to protein-protein interactions. Serious considerations need to be given for a complex genetic locus in a fungus such as a bacterial operon that specifies many distinct polypeptide chains translated from the same mRNA. As a result of this confusion, it is not clear how genetic analysis can explicate the number of genes when a complex genetic locus is specifying a particle presenting with multiple enzyme functions [64].

Two specific macromolecular interactions support demonstrated transcriptional stimulation of distinct sets of genes incident to the binding of varied polypeptide ligands to cells [104]. The initial polypeptide-receptor interaction is specific. The binding of specific transcription factors to well-defined DNA sites activates specific genes. A third, equally specific protein-protein interaction links the first two specific interactions and ensures the high specificity pertinent in these pathways. It is proposed that a receptor-recognition protein is necessary to recognize the bound receptor. This receptor-recognition protein is suggestively a part of a transcription factor or interacts directly with a transcription factor that is activated and translocated to the nucleus to participate in gene activation. This hypothesis relates that no global alterations in second messenger contents are necessary, and the enzymatic attributes of the receptor-recognition protein(s) need not be specified. Phosphorylations of, or by, receptor-bound proteins, hence would not be excluded. However, such modifications during ligand-mediated signal transduction may not rely on global second messenger alterations. This model is derived from studies of the proteins associated in Interferon (IFN)-

stimulated gene transcription. It was determined that Interferon-alpha (IFN alpha) activates a multisubunit transcription factor in the cell cytoplasm, and that this factor then travels to the nucleus in order to activate a set of IFN-stimulated genes [104].

The P_{II} proteins constitute one of the most expansively disseminated families of signal transduction proteins in nature. They are pivotal actors in the control of nitrogen metabolism in bacteria and archaea, and are also obtained in the plastids of plants. Significantly, P_{II} proteins control the activities of a varied range of enzymes, transcription factors and membrane transport proteins; and in all demonstrated instances, their regulatory effect is achieved by direct interaction with the target. P_{II} proteins in the Proteobacteria and the Actinobacteria are influenced through post-translational modification by uridylylation or adenylylation, respectively, whereas in some Cyanobacteria they are modifiable by phosphorylation [105]. In these instances, the protein modification status is governed by the cellular nitrogen status, and to regulate its activity. However, in several organisms no evidence exists for modification of PII proteins and the propensity of these proteins to respond to the cellular nitrogen status is essentially exclusive of post-translational modification.

Researchers reported a functional operon associated with the secondary metabolism of the fungus Glarea lozoyensis, a member of Leotiomycetes Ascomycota [106]. Two contiguous genes, glpks3 and glnrps7, which encode polyketide synthase and nonribosomal peptide synthetase, respectively, are cotranscribed into one dicistronic mRNA influenced by the same promoter, and the mRNA undergoes translated into two individual proteins, GLPKS3 and GLNRPS7. Heterologous expression in Aspergillus nidulans demonstrates that the GLPKS3-GLNRPS7 enzyme complex catalyzes the biosynthesis of a novel pyrrolidinedione-containing compound, xenoloyenone (compound 1) that suggests that the operon is functional. Inasmuch as, it is structurally identical to prokaryotic operons, the glpks3-glnrps7 operon locus depicts a monophylogenic origin from fungi in contrast to being horizontally transferred from prokaryotes. Also, two additional operons, glpks28-glnrps8 and glpks29-glnrps9, were observed at the transcriptional level in the same fungus, as the first report of protein-coding operons in a member of the fungi. Moreover, operon-like structures have been predicted in silico to be prevalent in other fungi. The ubiquity and operon-like structure in fungi provide evolutionary design and fundamental data for eukaryotic gene transcription [106].

Responses to biotic stress in bacteria and fungi result in remarkable reprogramming of the gene expression promoting or inducing stress responses to the excoriation of normal cellular functionalities. Transcription factors constitute principal regulators of gene expression at the transcriptional level, with regulation of these factors, which causes the alteration of the transcription of bacteria and fungi with concomitant metabolic and phenotypic alterations in response to stress [107]. The analytic functionality of interactions amongst transcription factors or attributes as well as certain proteins is crucial to elucidate the task of these transcriptional regulators or control mechanisms in disparate signaling cascades. Modulation of the functionality of transcription factors *via* interactions with regulatory proteins is an important process during activation or repression of signal transduction pathways. Attenuators were found which regulate operons associated with biosynthesis of branched amino acids, histidine, threonine, tryptophan, and phenylalanine in γ- and α - proteobacteria, and in certain instances in low-GC Gram-positive bacteria, Thermotogales and Bacteroidetes/Chlorobi [108].

Discussion

It is established with respect to cellular metabolic functionalities that the rates at which enzymes act must be compatible and in tandem with each other, while the appropriate quantities of enzymes must be amply spatiotemporally synthesized as required which the regulatory enzymes have evolved to perform. Proteins undergo interaction with one another or other macromolecules, and never segregated in any milieu as they mediate metabolic and signaling pathways, cellular processes and organismal systems. As a result of their pivotal task in biological functionalities, it is pellucid that protein interactions also regulate the mechanisms culminating in wholesome and impaired organismal conditions [109]. The availability of rapid and frugal genome sequencing of fungi and bacteria has exposed a milliard of biosynthetic gene clusters which encode secondary metabolite synthesized. In inordinate instances, the gene clusters are rapidly and easily annotated and identified with probable prediction of the precise structure of the encoded metabolite for any specific natural product biosynthetic gene cluster [110]. Overproduction of microbial metabolites is associated with microbial developmental stages. Effectors, inducers and inhibitors as well as diverse signal molecules are involved in disparate sorts of overproduction biosynthesis of enzymes involved in the catalyzation of metabolic reactions in microbial cells is regulated by inter alia induction, functional control mechanisms, such as carbon or nitrogen source control mechanisms and feedback regulators [111]. In order to compete in their natural habitat or niche, bacteria, fungi, and other microorganisms apply regulatory mechanisms, which control metabolic production, thereby harnessing overproduction and excretion of the secondary metabolites of excess levels into the environment.

Conclusion

As evidenced in other studies, this work reviewed here encompasses protein factors, which participate in the biosynthetic pathways of both bacteria and fungi [3-6], and current views on their mechanism of biosynthesis. In fungi and bacteria, the genes which code successive steps in a biosynthetic pathway tend to cluster on the chromosomes as biosynthetic gene clusters [112]. The control mechanisms which are associated in macromolecular interactions, and influence specific enzyme molecules [113], catalytic reactions and control function are described in this review in the regulation of biosynthetic pathways in bacteria and fungi. There is ample evidence that numerous cellular reactions extant in metabolic pathways undergo catalysis through varied membrane-associated multienzyme complexes [114]. Biochemical and genetic evidence presents two primary types of gene clusters in eucalypts. Of importance, is a complex genetic locus in a fungus, and as in a bacterial operon that specifies several polypeptide chains translated from the same mRNA. Several interactions [3-6] are extant which are fundamental for regulation, but their role and significance are required for benefits of Man and society.

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