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Chapter 1 : Faculty in Regulation of Gene Expression | Cell and Molecular Biology

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Chapter 2 : Molecular Mechanisms In The Control Of Gene Expression

Genetic and epigenetic control of E-cadherin expression Both reversible and irreversible loss of E-cadherin is important in the progression of cancer. Human E-cadherin (CDH1) is located on chromosome 16q, which has been reported to confer loss of heterozygosity in sporadic breast cancer [19].

A mutation in lacZaffects only b-galactosidase, not the transacetylase or other products of the operon , showing that lacZis a structural gene. A mutation in lacIaffects both enzymes, hence lacIis a regulatory gene. Both are expressed in the absence of the inducer, hence the operon is constitutively expressed the strain shows a constitutive phenotype. In a situation where the only functional lacZgene is on the same chromosome as lacI-, the functional lacI still causes repression in the absence of inducer. The lacISallele is noninducible. In a merodiploid, the lacISallele is dominant over wild-type in trans. In fact the product of the lacIgene is a repressor protein. Defects in the operator lead to constitutive expression of the operon, hence one can isolate operator constitutive mutations, abbreviated oc. Mutations in the operator are cis-acting; they only affect the expression of structural genes on the same chromosome. Thus the operator is cis-acting, and this property is referred to as cis-dominance. As in most cases of cis-regulatory sequences, these are sites on DNA that are required for regulation. In this case the operator is a binding site for the trans-acting repressor protein. Interactions between Operator and Repressor Sequence of operator The operator overlaps the start the site of transcription and the promoter. Such a dyad symmetry is commonly found within binding sites for symmetrical proteins the repressor is a homotetramer. The sequence of DNA that consititutes the operator was defined by the position of oC mutations, as well as the nucleotides protected from reaction with, e. DMS, upon binding of the repressor. Purification 1 Increase the amount of repressor in the starting material by over-expression. A wild-type cell has only about 10 molecules of the repressor tetramer. Isolation and purification of the protein was greatly aided by use of mutant strain with up-promoter mutations for lacI, so that many more copies of the protein were present in each cell. This general strategy of over-producing the protein is widely used in purification schemes. Now the gene for the protein is cloned in an expression vector, so that the host bacteria in this case makes a large amount of the protein - often a substantial fraction of the total bacterial protein. This can be monitored by the ability of the protein-DNA complex to bind to nitrocellulose whereas a radiolabeled mutant operator DNA fragement, oc, plus repressor will not bind. Electrophoretic mobility shift assays would be used now in many cases. The binding site can be synthesized as duplex oligonucleotides. These are ligated together to form multimers, which are then attached to a solid substrate in a column. The desired DNA-binding protein can then be isolated by affinity chromatography, using the binding site in DNA as the affinity ligand. The isolated, functional repressor is a tetramer; each of the four monomers is the product of the lacI gene i. The DNA-binding domainof the lac repressor folds into a helix-turn-helixdomain. We will examine this structural domain in more in Chapter III. It is one of the most common DNA-binding domains in prokaryotes, and a similar structural domain the homeodomain is found in some eukaryotic transcriptional regulators. Contact points between repressor and operator a. Investigation of the contact points between repressor and the operator utiblized the same techniques that we discussed previously for mapping the binding site of RNA polymerase on the promoter, e. Alternative schemes will allow one to identify sites at which methylation is either prevented or enhanced by the binding of the repressor. The key contact points see Figure 4. Note that the latter is a genetic definition of the operator, and it coincides with the biochemically-defined operator. The partial overlap between the operator and the promoter initially suggested a model of steric interference to explain the mechanism of repression. As long a repressor was bound to the operator, the polymerase could not bind to the promoter. But, as will be explored in the next chapter, this is notthe case. RNA polymerase canbind to the lacpromoter even when repressor is boudn to the lac operator. However, the polymerase cannot initiatetranscription when juxtaposed to the repressor. Conformational shift in repressor when inducer binds a. The repressor has two different domains, one that

binds to DNA "headpiece" containing the helix-turn-helix domain and another that binds to the inducer and other subunits called the "core. These are connected by a "hinge" region. These structural domains can be distinguished by the phenotypes of mutations that occur in them. Binding of inducer to the "core" causes an allosteric shift in the repressor so that the "headpiece" is no longer able to form a high affinity complex with the DNA, and the repressor can dissociate go to one of the many competing nonspecific sites. Even bacteria can be picky about what they eat. Glucose is the preferred source of carbon for E. Glucose leads to repression of expression of lacand some other catabolic operons. This phenomenon is called catabolite repression. Two components are needed for this form of regulation a. A high [cAMP] will relieve catabolite repression. In the lac operon, the binding site is a region of about 20 bp located just upstream from the promoter, from to For the lac operon, the binding site is a dyad with that sequence in both sides of the dyad. The lacpromoter is not a particularly strong promoter. The lacUV5 promoter is an up-promoter mutation in which the region matches the consensus. Regulatory region of lac operon, including CAP binding site 5. Direct positive interaction with RNA polymerase. This will be explored in more detail in Chapter Some generalities Repressors, activators and polymerases interact primarily with one face of the DNA double helix. Regulatory proteins, such as activators and repressors, are frequently symmetrical and bind symmetrical sequences in DNA. RNA polymerases are not symmetrical, and the promoters to which they bind also are asymmetrical. This confers directionality on transcription.

Chapter 3 : Epigenetics - Wikipedia

Section Molecular Mechanisms of Eukaryotic Transcriptional Control Transcriptional control in eukaryotic cells can be visualized as involving several levels of regulation. The concentrations and activities of activators and repressors that control transcription of many protein -coding genes are regulated during cellular differentiation and.

Hence these modifications may up or down regulate the expression of a gene. Some of these modifications that regulate gene expression are inheritable and are referred to as epigenetic regulation. Structural[edit] Transcription of DNA is dictated by its structure. In general, the density of its packing is indicative of the frequency of transcription. Octameric protein complexes called nucleosomes are responsible for the amount of supercoiling of DNA, and these complexes can be temporarily modified by processes such as phosphorylation or more permanently modified by processes such as methylation. Such modifications are considered to be responsible for more or less permanent changes in gene expression levels. DNA is typically methylated by methyltransferase enzymes on cytosine nucleotides in a CpG dinucleotide sequence also called " CpG islands " when densely clustered. Analysis of the pattern of methylation in a given region of DNA which can be a promoter can be achieved through a method called bisulfite mapping. Methylated cytosine residues are unchanged by the treatment, whereas unmethylated ones are changed to uracil. Abnormal methylation patterns are thought to be involved in oncogenesis. Often, DNA methylation and histone deacetylation work together in gene silencing. The combination of the two seems to be a signal for DNA to be packed more densely, lowering gene expression. The gene is essentially turned off. There is no lactose to inhibit the repressor, so the repressor binds to the operator, which obstructs the RNA polymerase from binding to the promoter and making lactase. The gene is turned on. Lactose is inhibiting the repressor, allowing the RNA polymerase to bind with the promoter, and express the genes, which synthesize lactase. Eventually, the lactase will digest all of the lactose, until there is none to bind to the repressor. The repressor will then bind to the operator, stopping the manufacture of lactase. Regulation of transcription thus controls when transcription occurs and how much RNA is created. Transcription of a gene by RNA polymerase can be regulated by several mechanisms. Specificity factors alter the specificity of RNA polymerase for a given promoter or set of promoters, making it more or less likely to bind to them i. The image to the right demonstrates regulation by a repressor in the lac operon. General transcription factors position RNA polymerase at the start of a protein-coding sequence and then release the polymerase to transcribe the mRNA. Activators enhance the interaction between RNA polymerase and a particular promoter , encouraging the expression of the gene. Activators do this by increasing the attraction of RNA polymerase for the promoter, through interactions with subunits of the RNA polymerase or indirectly by changing the structure of the DNA. Enhancers are sites on the DNA helix that are bound by activators in order to loop the DNA bringing a specific promoter to the initiation complex. Enhancers are much more common in eukaryotes than prokaryotes, where only a few examples exist to date. Regulation of transcription in cancer[edit] Main article: Regulation of transcription in cancer In vertebrates, the majority of gene promoters contain a CpG island with numerous CpG sites. For example, in colorectal cancers about to genes are transcriptionally silenced by CpG island methylation see regulation of transcription in cancer. Transcriptional repression in cancer can also occur by other epigenetic mechanisms, such as altered expression of microRNAs. Regulation of transcription in addiction[edit] One of the cardinal features of addiction is its persistence. The persistent behavioral changes appear to be due to long-lasting changes, resulting from epigenetic alterations affecting gene expression, within particular regions of the brain. These are 1 histone acetylations and histone methylations , 2 DNA methylation at CpG sites , and 3 epigenetic downregulation or upregulation of microRNAs. Chronic nicotine intake in mice alters brain cell epigenetic control of gene expression through acetylation of histones. This increases expression in the brain of the protein FosB, important in addiction. These CpG sites occurred in over 7, genes, or roughly a third of known human genes. The majority of the differentially methylated CpG sites returned to the level of never-smokers within

five years of smoking cessation. However, 2, CpGs among genes remained differentially methylated in former versus never smokers. In rodent models, drugs of abuse, including cocaine, [12] methampheamine, [13] [14] alcohol [15] and tobacco smoke products, [16] all cause DNA damage in the brain. Cells do this by modulating the capping, splicing, addition of a Poly A Tail, the sequence-specific nuclear export rates, and, in several contexts, sequestration of the RNA transcript. These processes occur in eukaryotes but not in prokaryotes. This modulation is a result of a protein or transcript that, in turn, is regulated and may have an affinity for certain sequences. Three prime untranslated regions and microRNAs[edit] Main article: As of , the miRBase web site, [19] an archive of miRNA sequences and annotations, listed 28, entries in biologic species. Translational regulation The translation of mRNA can also be controlled by a number of mechanisms, mostly at the level of initiation. Recruitment of the small ribosomal subunit can indeed be modulated by mRNA secondary structure, antisense RNA binding, or protein binding. In both prokaryotes and eukaryotes, a large number of RNA binding proteins exist, which often are directed to their target sequence by the secondary structure of the transcript, which may change depending on certain conditions, such as temperature or presence of a ligand aptamer. Some transcripts act as ribozymes and self-regulate their expression. Examples of gene regulation[edit] Enzyme induction is a process in which a molecule e. The induction of heat shock proteins in the fruit fly Drosophila melanogaster. The Lac operon is an interesting example of how gene expression can be regulated. Viruses, despite having only a few genes, possess mechanisms to regulate their gene expression, typically into an early and late phase, using collinear systems regulated by anti-terminators lambda phage or splicing modulators HIV.

Chapter 4 : Positive and negative control of gene expression - Biology LibreTexts

Each of these steps is exquisitely regulated to control gene expression as needed. Third, proteins must be maintained in an active state, and degraded when appropriate, as aberrant protein levels and/or function can be extremely detrimental to the cell.

Project Methods The experimental approaches will include: The identification of components in the signaling circuitry of these photoreceptor systems will provide potential molecular targets and tools for engineering agronomically superior crops. What major problem or issue is being resolved and how are you resolving it summarize project aims and objectives? How serious is the problem? What does it matter? The major problem being addressed is the need to produce more food of enhanced nutritional value in an ecofriendly manner, without increasing acreage, in order to feed the expanding world population. Toward this end we are investigating the fundamental molecular mechanisms by which plants regulate their growth and development in response to the prevailing light environment. Our overall research goal is to define the molecular mechanisms by which the phytochrome family of photoreceptors perceives, interprets and transduces informational light signals from the environment to photoresponsive genes. Our specific objectives are to identify, molecularly clone, and functionally define the biological and biochemical activities of the components involved in this process using genetic, molecular and biochemical strategies. Many plant responses to light that have evolved to provide competitive advantage and survival under natural conditions are agronomically undesirable. These include the shade-avoidance response and photoperiodic control of such processes as flowering and leaf senescence. Identification of the molecular components and understanding of the biochemical and cellular mechanisms involved in light signaling to nuclear genes will provide potential targets for biotechnologically based improvement of crop plants. List the milestones indicators of progress from your Project Plan. Identify phytochrome signaling intermediates i Identify phytochrome-interacting factors PIFS ii Perform forward genetic screens for signaling intermediates b. Define phytochrome-regulated transcription networks i Perform microarray-based expression profiling ii Characterize the basic helix-loop-helix bHLH transcription factor family 3a List the milestones that were scheduled to be addressed in FY For each milestone, indicate the status: If not met, why. We will continue to screen for phytochrome-interacting factors and assess their functional relevance to phytochrome signaling using reverse-genetic disruption of the identified loci. Milestone Fully Met 2. We will continue to perform forward genetic screens for additional signaling intermediates in the phytochrome pathway by screening for abnormalities in the seedling de-etiolation process. Genes will be isolated and characterized and their protein products assessed for potential biochemical function. Milestone Fully Met 3. We will continue to map the phytochrome-regulated transcriptional networks by performing microarray expression profiling on wild-type and mutant seedlings. This will permit placement of the activity of the mutated locus in the network hierarchy. Milestone Fully Met 4. We will continue a systematic assessment of the functional role of members of the bHLH family in phytochrome signaling by reverse-genetic disruption of targets related to the phytochrome-interacting members of the family. Milestone Fully Met 3b List the milestones that you expect to address over the next 3 years FY , , and What do you expect to accomplish, year by year, over the next 3 years under each milestone? This project will expire in September Anticipated continuing milestones are: FY , , A. Define phytochrome-regulated transcription networks i Perform microarray-based expression profiling. We will continue a systematic assessment of the functional role of members of the bHLH family in phytochrome signaling by reverse- genetic disruption of targets related to the phytochrome-interacting members of the family. Year by year we expect to identify increasing numbers of signaling intermediates and phytochrome target genes and determine their biological and biochemical functions. Identification of genes encoding phytochrome signaling components. Because phytochrome is the major light receptor for plants, understanding how it functions is crucial for crop improvement. We showed that this factor negatively

regulates chlorophyll biosynthesis. PIF1 interacts specifically with the photoactivated conformer of both phytochromes A and B. This observation suggests a signaling pathway by which chlorophyll biosynthetic rates are tightly controlled during the critical initial emergence of seedlings from subterranean darkness into sunlight Huq et al. These findings demonstrate that PIF1 has a critical function in the agronomically important process of seedling establishment. Describe the major accomplishments over the life of the project, including their predicted or actual impact. The identification and cloning of the phytochrome gene family in Arabidopsis, and homologs in such crop plants as rice and corn. The identification of functionally active promoter cis elements in the phyA genes of oat, rice and corn, and the cloning of transcription factors that interact with these elements. The overexpression of phytochrome in transgenic plants leading to modified architecture due to suppression of the shade-avoidance response. Discovery of the differential functional roles of individual phytochrome family members through creation of null mutants in the photoreceptors. Genetic and molecular identification of phytochrome signaling components and definition of phytochrome-regulated transcriptional networks. What are the constraints, if known, to the adoption and durability of the technology products? The information is transferred to the research community and general public through peer-reviewed publications, presentations at international meetings and at diverse universities, and in communications aimed at the lay person. On an ongoing basis, we receive and respond to large numbers of requests for clones, mutant lines and antibodies from the scientific community throughout the U. The Plant Cell, Expression profiling of phyB mutant demonstrates substantial contribution of other phytochromes to red-light-regulated gene expression during seedling de-etiolation. Plant Journal 38 5: The phytochrome- interacting transcription factor, PIF3, acts early, selectively, and positively in light-induced chloroplast development. Proceedings of the National Academy of Sciences The photomorphogenesis-related mutant red1 is defective in CYP83b1, a red light-induced gene encoding a cytochrome P required for normal auxin homeostasis. Define phytochrome-regulated transcription networks i Perform microarray-based expression profiling ii Characterize the basic helix-loop-helix bHLH transcription factor family 3. Identify phytochrome signaling intermediates i Identify phytochrome interacting factors. We have identified and characterized two additional genes involved in phytochrome signaling, using both forward- and reverse-genetic screens, and have published this work in peer-reviewed journals. Define phytochrome-regulated transcriptional networks i Perform microarray-based expression profiling. Using Affymetrix oliognucleotide microarrays, we have defined the expression profiles induced by red light, and have identified those genes regulated by phyB, as well as those regulated by one or more other members of the phytochrome family. This work has been recently published Tepperman, et al. As part of our interest in determining whether members of the Arabidopsis family, related to phytochrome-interacting factor 3 PIF3 , might be involved in phy signaling and transcriptional regulation, we undertook a comprehensive computational analysis of this family. This was necessitated because the existing preliminary analysis based on the published Arabidopsis genome sequence was incomplete and the annotation was frequently incorrect. Our initial analysis identified members of the family Toledo-Ortiz et al. However, subsequent further analysis in collaboration with another research group, led to the identification of additional members, such that now it appears that the complete bHLH family consists of members in Arabidopsis Bailey et al. This is the first apparently complete delineation of this gene family in a plant, and indicates that this family is the second-largest transcription factor family in Arabidopsis. We have utilized the phylogenetic relationships between the genes generated by this analysis to identify targets for reverse-genetic analysis for potential involvement in photomorphogenesis. We are currently investigating knock-out mutants in several of the family members most closely related to PIF3. FY , , a i We will continue to screen for phytochrome-interacting factors and assess their functional relevance to phytochrome signaling using reverse-genetic disruption of the identified loci. What were the most significant accomplishments this past year? All aspects of plant biology hinge on their ability to perceive light, and because phytochrome is the major light receptor for plants, understanding how it functions is crucial for crop improvement. We performed molecular and genetic experiments at the PGEC to address the question of phytochrome signaling. We have

shown that the APRR7 gene encodes a phytochrome signaling intermediate that regulates red-light induced seedling photomorphogenesis and has an important function in phasing the central circadian oscillator of the plant biological clock Kaczorowski and Quail, This result has the potential to provide insight into the molecular mechanism by which light controls the circadian clock, an important regulator of agriculturally relevant responses, such as floral induction. Other Significant Accomplishment s , if any: Expression profiling of phyb mutant demonstrates substantial contribution of other phytochromes to red-light-regulated gene expression during seedling de-etiolation. Plant Journal, 38 5 What major problem or issue is being resolved and how are you resolving it? Why does it matter? How does it relate to the National Program s and National Program Component s to which it has been assigned? This research allows scientists to genetically engineer crop plants for improved architecture and yield in an ecofriendly manner. This result could provide insight into the molecular mechanism by which these components function. Plants sense and respond to red and far-red light using the phytochrome phy family of photoreceptors. However, the mechanism of light signal transduction is not well defined. The Arabidopsis mutants far1 and fhy3 display a phenotype of reduced responsiveness specific to far-red light and therefore specific to the phytochrome A phyA -signaling pathway. We demonstrate that the FAR1 protein is capable of activating transcription in Arabidopsis, indicating that it may define a type of transcriptional regulator. What do you expect to accomplish, year by year, over the next 3 years? Carry out Affymetrix profiling with phytochrome interacting proteins and define transcriptional networks. Determine how each of these components functions. Develop testable models for the ability of plants to perceive light. Structure, Expression, Map Position and Evolution. How does it relate to the national Program s and National Program Component s to which it has been assigned? What was your most significant accomplishment this past year? All aspects of plant biology hinge on their ability to perceive light. Phytochrome is the major light receptor for plants and thus understanding how it functions is crucial for crop improvement. We have identified a new member of the basic helix- loop-helix family of transcription factors, PIF4, that interacts specifically with the biologically active form of phytochrome B phyB , and have shown that this factor functions in phyB signaling. Using this light-driven signal, we have developed a new biotechnological switch for molecular biology. Other Significant Accomplishment s , if any Understanding the genomes of higher plants has great potential for agriculture. In collaboration with researchers at the Torrey Mesa Research Institute, we contributed to analysis of the sequence of the entire rice genome.

Chapter 5 : Control of Gene Expression

Molecular Mechanisms In The Control Of Gene Expression by Nikola This Molecular Mechanisms in the is an maintenance, as no broadcasting-style items 've to it.

Histone Methylation - Demethylation Histone Methylation Another histone modification known to affect chromatin structure is methylation. Methylation of histones can result in three distinct states, monomethylation, dimethylation, or trimethylation. However, with histone methylation there is not a direct correlation between the modification and a specific effect on transcription. Methylation of histones has been shown to occur on both lysine and arginine residues. Histone lysine K methylation at certain positions is associated with regions of transcriptionally silenced chromatin, whereas methylation at other positions is associated with transcriptionally active regions of DNA. Histone arginine R methylation has been shown to be associated with the promotion of an open chromatin structure and thereby, resulting in transcriptional activation. Methylation of lysine K residues in histone H3 specifically K9 and K27 and histone H4 K20 is associated with regions of transcriptionally silenced chromatin. However, these associations are not concrete given that H3K9 methylation has been found in transcriptionally active genes and H3K36 methylation has been shown to be associated with repression of intragenic transcription initiation. All lysine methyltransferase enzymes belong to the large family of enzymes identified as the lysine K methyltransferase KMT family. The histone lysine methyltransferases are also identified as HMTases for histone methyltransferases. Humans express a family of 27 protein lysine methyltransferase encoding genes, not all of which methylate histones. The enzymes that carry out histone lysine methylation are all members of the SET-domain-containing family of methyltransferases except for one enzyme: The SET domain is so-called as it was originally identified in three Drosophila proteins identified as Suppressor of variegation variant [Su var], Enhancer of zeste, and Trithorax. The SET domain is composed of approximately amino acids. There are four additional histone methyltransferases that belong to a different protein family identified as the PR and SET domain containing transcription factors family, identified as the PRDM family. As indicated in the preceding paragraph, several different lysine residues in histones are targets for methylation. Within histone H1 lysine 26 K26 has been shown to be methylated. Within histone H4 lysines K20 and K59 have been shown to be methylated. The products of the reaction are a methylated lysine and S-adenosylhomocysteine AdoHcy. The different histone lysine methyltransferases incorporate one monomethyl , two dimethyl , or three trimethyl methyl groups onto their target lysine. The single non-SET-domain containing histone lysine methyltransferase is encoded by the DOT1L disruptor of telomeric silencing 1 like gene. Histone arginine methylation is catalyzed by family of enzymes designated the protein arginine methyltransferase PRMT family. There are nine genes in the human genome that encode PRMT enzymes. Arginine residues in histones H2A, H3, and H4 are known to be methylated. Arginine methylation in histones can be of three distinct types: The PRMT1 encoded enzyme was the first to be shown to methylate lysine residues if histone proteins. The consequences of H4R3 methylation are enhanced transcriptional activity. Indeed, the PRMT1 protein is considered a transcriptional coactivator and it is recruited to promoters by a number of different transcription factors. Conversely, the PRMT5 encoded enzyme is a potent transcriptional repressor. The PRMT5-mediated incorporation of a methyl group into R3 of histone H4 imparts a strong transcriptional repressive action. Methylation of arginine residues in histones, and other target proteins, involves the use of AdoMet as for the histone lysine methyltransferases. The methylation of histones provides a site for the binding of other proteins which then leads to alteration of chromatin structure. Proteins that bind to methylated lysines present in histones as well as other proteins contain a domain called chromodomain. The chromodomain consists of a conserved stretch of 40â€”50 amino acids and is found in many proteins involved in chromatin remodeling complexes. Another important chromodomain-containing protein is heterochromatin protein 1 HP1. The presence of methylated H3K9 provides a binding site for HP1 which leads to transcriptional repression due to the formation of

heterochromatin highly compact densely staining chromatin. Processes of protein lysine methylation and demethylation. Histone protein as well as other protein lysine methylation and demethylation is catalyzed by a family of lysine methyl transferases KMT and lysine demethylases KDM. Depicted are the enzymatic steps for the generation of a trimethylated lysine residue in a peptide bond in a protein such as histone H3. Various members of the KMT family enzymes can monomethylate, dimethylate, or trimethylate their appropriate substrate lysine residue. The demethylation of lysine residues is catalyzed by members of the Jumonji C JmjC domain-containing proteins or the lysine demethylase LSD family of proteins. All these demethylases require 2-oxoglutarate as a cofactor. The LSD family of lysine demethylases only demethylate dimethyl- and monomethyllysine residues, not trimethyllysine. Histone Demethylation Histone demethylation is carried out by a distinct families of enzymes. The largest family with numerous subfamilies of histone demethylases directly reverse histone methylation. An additional family of enzymes indirectly reverses the histone methylation state. All of the histone demethylase enzymes are composed of multiple functional domains. These domains are required for recognition of the correct methylated amino acid in the target histone protein, binding of required cofactors, and carrying out the catalytic reaction. The largest subfamily of histone demethylase enzymes all contain a domain called the Jumonji C JmjC domain. The JmjC domain is responsible for cofactor binding in these enzymes. There are at least 30 human genes that encode JmjC-domain-containing proteins and these 30 proteins can be subdivided into 8 subfamilies. The JHDM enzymes can reverse all three known states of histone methylation. Another subfamily of histone demethylases was originally called the lysine specific demethylase LSD family since the founding member, a nuclear amine oxidase homolog, was called lysine specific demethylase 1 LSD1. This subfamily of histone demethylase enzymes directly reverse histone H3K4 or H3K9 methylations by an oxidative reaction that requires the vitamin-derived cofactor, FAD. The LSD family enzymes have only been shown to demethylate mono- and dimethylated histones and not the trimethylated forms. An additional family of enzymes, that is not strictly a histone demethylase family, converts methyl-arginine residues to citrulline as opposed to direct reversal of the methylation reaction. This family of enzymes was originally referred to as the peptidylarginine deiminase PADI family. PADI4 was the first enzyme in the family to be identified to catalyze demethylation of methylated arginine in histones. The catalytic activity of PADI4 functions as a histone deiminase that converts methyl-arginine to citrulline as opposed to directly reversing arginine methylation. Although PADI4 has a clear role in antagonizing methylarginine modifications, it cannot strictly be considered a histone demethylase as it produces citrulline instead of an unmodified arginine. Another enzyme shown to demethylate arginine residues in histones is a JmjC domain-containing enzyme identified as JMJD6. The primary function of the JMJD6 encoded enzyme is to hydroxylate lysine residues in target proteins. However, the enzyme has been shown to demethylate H3R2 and H4R3 residues. As a result of the large number of histone lysine demethylase enzymes and the different subfamily designations a more refined nomenclature system was adopted. All enzymes that demethylate methylated lysines in histone proteins are now identified as KDM family enzymes where KDM stands for lysine K demethylase. There are currently eight KDM subfamilies of enzymes divided based upon factors such as substrate preference, presence of certain domains, and cofactor requirements. Histone Ubiquitination Histone proteins can also be modified by addition of the small protein ubiquitin. With respect to the histones, ubiquitin is found on all of the nucleosomal histones H2A, H2B, H3, and H4 as well as on the linker histone, H1. However, the vast majority of ubiquitylated histones are H2A and H2B and these are both of the monoubiquitin form. Although monoubiquitylation of H2A and H2B predominates, polyubiquitylation is observed. Polyubiquitylation of K36 in histone H2A and the variant H2AX is associated with responses to DNA damage and this modification is required for the repair processes to be initiated. Histone H3 and H4 are also known to be polyubiquitylated but the precise biological functions of these modified histones is not fully elucidated. When ubiquitylated, H2A is associated with repression of transcription. The exact opposite effect is observed when histone H2B is ubiquitylated, leading to a stimulation of gene activity. One of the reasons that monoubiquitylated histone H2B is associated with

transcriptional activity is that this modification promotes the methylation of histone H3 at K4 and K79, which as indicated above is associated with open chromatin structure. Given that ubiquitylation of H2A is primarily associated with gene silencing it is not surprising that the H2A ubiquitin ligases are found associated with transcriptional corepressor complexes. At least seven different ubiquitin ligases have been shown to ubiquitylate the histones. The vast majority of these characterizations were carried out with studies on the monoubiquitylation of H2A and H2B. The monoubiquitylation of H2A and H2B is known to be reversible and the enzymes that catalyze the removal are peptidases identified as deubiquitylating enzymes DUB. Phosphorylation of histones occurs on Ser, Thr, and Tyr residues by the action of several kinases. The removal of the phosphorylation is catalyzed by phosphatases. Phosphorylation of histones occurs primarily, although not exclusively, in response to outside signals such as growth factor stimulation or stress inducers such as heat shock. Phosphorylated histones are localized to genes that become transcriptionally active as a consequence of these outside signals. Phosphorylation of histone proteins is also required to regulate other forms of histone modification. For example, phosphorylation of Ser 1 S1 in histone H4 prevents the acetylation of this histone. Numerous residues in the four nucleosomal histones have been shown to be phosphorylated leading to alteration of transcriptional activity. The consequences of the H2AS1 modification are transcriptional inhibition, whereas H2AT is associated with the regulation of chromatin structure during mitosis. The H2BS14 modification is involved in the induction of apoptosis. The phosphorylation of histidine residues in histone H4 is associated with the facilitation of DNA replication. In addition to the regulation of transcription as a result of histone phosphorylation, this modification is also associated with the processes of chromatin remodeling and DNA damage repair. The importance of histone phosphorylation in response to DNA damage can be demonstrated in patients with Coffin-Lowry syndrome which results from defects in the RPS6KA3 ribosomal protein S6 kinase A3; also known as ribosomal S6 kinase 2: Coffin-Lowry syndrome is a rare form of X-linked mental retardation characterized by skeletal malformations, growth retardation, hearing deficit, paroxysmal movement disorders, and cognitive impairment in affected males. Histone O-GlcNAcylation The hexosamine biosynthesis pathway HBP is a major nutrient responsive metabolic pathway whose product UDP-GlcNAc is tasked with the regulation of a wide variety cellular processes from metabolism to epigenetic control of gene expression. OGT and removal of OGA GlcNAc from nuclear and cytoplasmic proteins contribute to the maintenance of epigenetic states within the chromatin and to the etiology of epigenetic related disease states. With respect to histone modification as an epigenetic event, all four histones present in the nucleosome have been shown to be O-GlcNAcylated with histone H2B being the most highly modified. The pattern of histone O-GlcNAcylation is dynamic and has been shown to change thoughout the cell cycle. During the G1 phase the level of histone O-GlcNAcylation increases then decreases during S phase and increases again during the G2 and M phases of the cell cycle then declining again as the cells undergo cytokinesis. The ubiquitination of K in H2B is associated with transcriptional activation. The significance of this modification to the normal cellular response to DNA damage has been demonstrated with either H2B mutants that contain an Ala residue at position SA or where the OGT gene has been downregulated.

Chapter 6 : Regulation of gene expression - Wikipedia

Goals / Objectives To define molecular mechanisms by which the phytochrome (phy) family of photoreceptors perceive informational light siganls from the environment and transduce them to photoresponsive nuclear genes, thereby controlling plant growth and development.

Definitions[edit] The term epigenetics in its contemporary usage emerged in the s, but for some years has been used in somewhat variable meanings. It has been used in English since the 17th century. Waddington held that cell fates were established in development canalisation much as a marble rolls down to the point of lowest local elevation. An early version was proposed, among the founding statements in embryology , by Karl Ernst von Baer and popularized by Ernst Haeckel. A radical epigenetic view physiological epigenesis was developed by Paul Wintrebert. Another variation, probabilistic epigenesis, was presented by Gilbert Gottlieb in The developmental psychologist Erik Erikson wrote of an epigenetic principle in his book Identity: Youth and Crisis , encompassing the notion that we develop through an unfolding of our personality in predetermined stages, and that our environment and surrounding culture influence how we progress through these stages. This biological unfolding in relation to our socio-cultural settings is done in stages of psychosocial development , where "progress through each stage is in part determined by our success, or lack of success, in all the previous stages. The more recent usage of the word in science has a stricter definition. For example, Adrian Bird defined epigenetics as "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states. Such redefinitions however are not universally accepted and are still subject to dispute. The "epigenome" is a parallel to the word "genome", referring to the overall epigenetic state of a cell, and epigenomics refers to more global analyses of epigenetic changes across the entire genome. Taken to its extreme, the "epigenetic code" could represent the total state of the cell, with the position of each molecule accounted for in an epigenomic map, a diagrammatic representation of the gene expression, DNA methylation and histone modification status of a particular genomic region. More typically, the term is used in reference to systematic efforts to measure specific, relevant forms of epigenetic information such as the histone code or DNA methylation patterns. Molecular basis[edit] Epigenetic changes modify the activation of certain genes, but not the genetic code sequence of DNA. The microstructure not code of DNA itself or the associated chromatin proteins may be modified, causing activation or silencing. This mechanism enables differentiated cells in a multicellular organism to express only the genes that are necessary for their own activity. Epigenetic changes are preserved when cells divide. Moreover, if gene inactivation occurs in a sperm or egg cell that results in fertilization, this epigenetic modification may also be transferred to the next generation. These damages are largely repaired, but at the site of a DNA repair, epigenetic changes can remain. In one study, markers for oxidative stress, such as modified nucleotides that can result from DNA damage, were decreased by a 3-week diet supplemented with soy. Covalent modifications[edit] Covalent modifications of either DNA e. Therefore, the word "epigenetics" is sometimes used as a synonym for these processes. However, this can be misleading. Chromatin remodeling is not always inherited, and not all epigenetic inheritance involves chromatin remodeling. Because the phenotype of a cell or individual is affected by which of its genes are transcribed, heritable transcription states can give rise to epigenetic effects. There are several layers of regulation of gene expression. One way that genes are regulated is through the remodeling of chromatin. Chromatin is the complex of DNA and the histone proteins with which it associates. If the way that DNA is wrapped around the histones changes, gene expression can change as well. Chromatin remodeling is accomplished through two main mechanisms: The first way is post translational modification of the amino acids that make up histone proteins. Histone proteins are made up of long chains of amino acids. If the amino acids that are in the chain are changed, the shape of the histone might be modified. DNA is not completely unwound during replication. It is possible, then, that the modified histones may be carried into each new copy of the DNA. Once there, these histones may act as templates, initiating the surrounding new

histones to be shaped in the new manner. By altering the shape of the histones around them, these modified histones would ensure that a lineage-specific transcription program is maintained after cell division. The second way is the addition of methyl groups to the DNA, mostly at CpG sites , to convert cytosine to 5-methylcytosine. However, some areas of the genome are methylated more heavily than others, and highly methylated areas tend to be less transcriptionally active, through a mechanism not fully understood. Methylation of cytosines can also persist from the germ line of one of the parents into the zygote, marking the chromosome as being inherited from one parent or the other genetic imprinting. Mechanisms of heritability of histone state are not well understood; however, much is known about the mechanism of heritability of DNA methylation state during cell division and differentiation. Heritability of methylation state depends on certain enzymes such as DNMT1 that have a higher affinity for 5-methylcytosine than for cytosine. If this enzyme reaches a "hemimethylated" portion of DNA where 5-methylcytosine is in only one of the two DNA strands the enzyme will methylate the other half. Although histone modifications occur throughout the entire sequence, the unstructured N-termini of histones called histone tails are particularly highly modified. These modifications include acetylation , methylation , ubiquitylation , phosphorylation , sumoylation , ribosylation and citrullination. Acetylation is the most highly studied of these modifications. For example, acetylation of the K14 and K9 lysines of the tail of histone H3 by histone acetyltransferase enzymes HATs is generally related to transcriptional competence. Because it normally has a positively charged nitrogen at its end, lysine can bind the negatively charged phosphates of the DNA backbone. The acetylation event converts the positively charged amine group on the side chain into a neutral amide linkage. This removes the positive charge, thus loosening the DNA from the histone. This is the "cis" model of epigenetic function. In other words, changes to the histone tails have a direct effect on the DNA itself. In this model, changes to the histone tails act indirectly on the DNA. For example, lysine acetylation may create a binding site for chromatin-modifying enzymes or transcription machinery as well. This chromatin remodeler can then cause changes to the state of the chromatin. It may be that acetylation acts in this and the previous way to aid in transcriptional activation. The idea that modifications act as docking modules for related factors is borne out by histone methylation as well. Methylation of lysine 9 of histone H3 has long been associated with constitutively transcriptionally silent chromatin constitutive heterochromatin. It has been determined that a chromodomain a domain that specifically binds methyl-lysine in the transcriptionally repressive protein HP1 recruits HP1 to K9 methylated regions. One example that seems to refute this biophysical model for methylation is that tri-methylation of histone H3 at lysine 4 is strongly associated with and required for full transcriptional activation. Tri-methylation in this case would introduce a fixed positive charge on the tail. This enzyme utilizes a catalytically active site called the SET domain Suppressor of variegation, Enhancer of zeste, Trithorax. The SET domain is a amino acid sequence involved in modulating gene activities. This domain has been demonstrated to bind to the histone tail and causes the methylation of the histone. Also, multiple modifications may occur at the same time, and these modifications may work together to change the behavior of the nucleosome. The idea that multiple dynamic modifications regulate gene transcription in a systematic and reproducible way is called the histone code , although the idea that histone state can be read linearly as a digital information carrier has been largely debunked. Epigenetic changes of this type thus have the potential to direct increased frequencies of permanent genetic mutation. This recently identified enzyme has a catalytically active site called the Jumonji domain JmjC. The demethylation occurs when JmjC utilizes multiple cofactors to hydroxylate the methyl group, thereby removing it. JmjC is capable of demethylating mono-, di-, and tri-methylated substrates. Epigenetic control is often associated with alternative covalent modifications of histones. Small interfering RNAs can modulate transcriptional gene expression via epigenetic modulation of targeted promoters. For example, Hnf4 and MyoD enhance the transcription of many liver- and muscle-specific genes, respectively, including their own, through the transcription factor activity of the proteins they encode. RNA signalling includes differential recruitment of a hierarchy of generic chromatin modifying complexes and DNA methyltransferases to specific loci by RNAs during differentiation and

development. Descendants of the cell in which the gene was turned on will inherit this activity, even if the original stimulus for gene-activation is no longer present. These genes are often turned on or off by signal transduction , although in some systems where syncytia or gap junctions are important, RNA may spread directly to other cells or nuclei by diffusion. A large amount of RNA and protein is contributed to the zygote by the mother during oogenesis or via nurse cells , resulting in maternal effect phenotypes. A smaller quantity of sperm RNA is transmitted from the father, but there is recent evidence that this epigenetic information can lead to visible changes in several generations of offspring. Transcription from methylated CpG islands is strongly and heritably repressed. They control gene expression including virulence genes in pathogens and are viewed as new targets in the fight against drug-resistant bacteria. Their phylogenetic analyses, for example through sRNAâ€”mRNA target interactions or protein binding properties , are used to build comprehensive databases. Fungal prions Prions are infectious forms of proteins. In general, proteins fold into discrete units that perform distinct cellular functions, but some proteins are also capable of forming an infectious conformational state known as a prion. Although often viewed in the context of infectious disease , prions are more loosely defined by their ability to catalytically convert other native state versions of the same protein to an infectious conformational state. It is in this latter sense that they can be viewed as epigenetic agents capable of inducing a phenotypic change without a modification of the genome. Structural inheritance In ciliates such as Tetrahymena and Paramecium , genetically identical cells show heritable differences in the patterns of ciliary rows on their cell surface. Experimentally altered patterns can be transmitted to daughter cells. It seems existing structures act as templates for new structures. The mechanisms of such inheritance are unclear, but reasons exist to assume that multicellular organisms also use existing cell structures to assemble new ones. Nucleosome position is not random, and determine the accessibility of DNA to regulatory proteins. This determines differences in gene expression and cell differentiation. It has been shown that at least some nucleosomes are retained in sperm cells where most but not all histones are replaced by protamines. Thus nucleosome positioning is to some degree inheritable. Recent studies have uncovered connections between nucleosome positioning and other epigenetic factors, such as DNA methylation and hydroxymethylation. Predetermined epigenesis is a unidirectional movement from structural development in DNA to the functional maturation of the protein. Probabilistic epigenesis on the other hand is a bidirectional structure-function development with experiences and external molding development. Thus, as individuals develop, morphogens activate or silence genes in an epigenetically heritable fashion, giving cells a memory.

Chapter 7 : An Introduction to Molecular Biology/Gene Expression - Wikibooks, open books for an open wo

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Figure Model for cooperative assembly of an activated transcription-initiation complex at the TTR promoter in hepatocytes. Four activators enriched in hepatocytes plus the ubiquitous AP1 factor bind to sites in the hepatocytespecific enhancer and promoter-proximal more Thus there is no single arrangement of sites that dictates hepatocytespecific gene expression. Serum albumin is expressed at far higher levels than transthyretin because the serum albumin gene is transcribed much more frequently in hepatocytes than the transthyretin gene. This difference reveals another level of control by transcription factors, regulation of the frequency of transcription initiation for those genes that are transcribed in a specific cell type. Much remains to be learned about the mechanisms that result in differential transcription-initiation frequency within a given cell type. Repressors Interfere Directly with Transcription Initiation in Several Ways A repressor is any protein that interferes with transcription initiation when it is bound to a specific site on DNA. As discussed above, some eukaryotic repressors can direct deacetylation of histones in nucleosomes near their cognate binding sites see Figure a. Histone deacetylation, in turn, inhibits the interaction of general transcription factors with their binding sites in nucleosomal DNA, thereby repressing transcription. However, the finding that a number of eukaryotic repressor proteins repress in vitro transcription in the absence of histones indicates that more direct repression mechanisms also operate. Although repression mechanisms are not well understood, different repressor proteins probably exert their effects in different ways Figure Two mechanisms involve competitive binding between a repressor and activator or general transcription factor. In both cases, binding of a repressor molecule to a specific DNA site blocks binding of proteins required to initiate transcription. In many cases, however, eukaryotic repressors inhibit transcription without interfering with the binding of an activator or general transcription factors. In such cases, the bound repressor may interact with a nearby activator, preventing its function, or with general transcription factors bound at the promoter , preventing their assembly into an initiation complex. Presumably, repression of the EGR-1 gene by WT1 protein , discussed earlier, operates by one of the latter two mechanisms, since WT1 binding does not interfere with activator binding see Figure Various eukaryotic repressors can inhibit transcription by mechanisms that do not involve histone deacetylation. In the three mechanisms shown, the repressor either inhibits activation or directly interferes with formation of the initiation complex. Regulation of Transcription-Factor Expression Contributes to Gene Control We have seen in the preceding discussion that transcription of eukaryotic genes is regulated by combinations of activators and repressors that bind to specific DNA regulatory sequences. Whether or not a specific gene in a multicellular organism is expressed in a particular cell at a particular time is largely a consequence of the binding and activity of the transcription factors that interact with the regulatory sequences of that gene. Clearly, since different proteins are expressed in different cells at different times in development , the activity of transcription factors must be controlled. An obvious critical control point for cells is transcription of the genes encoding transcription factors themselves. Hepatocyte-specific expression of transthyretin provides an example: The complete set of activators required for transcription of the TTR gene are expressed only in hepatocytes. The transcription factors expressed in a particular cell type, and the amounts produced, are a consequence of multiple regulatory interactions between transcription-factor genes that occur during the development and differentiation of a particular cell type. In Chapters 14, 20, and 23, we present examples of such regulatory interactions during development and discuss the principles of development and differentiation that have emerged from these examples. Expression of a particular gene is further controlled by regulating the activities of the factors required for its transcription. In the remainder of this section, we discuss two important mechanisms for regulating transcription-factor activity: Lipid-Soluble Hormones Control the Activities of Nuclear Receptors The activities of many transcription factors are

regulated by hormones, which function as extracellular signals in multicellular organisms Chapter Hormones are secreted from one cell type and travel through extracellular fluids to affect the function of cells at a different location in the organism. One class of hormones comprises small, lipid -soluble molecules, which can diffuse through plasma and nuclear membranes Figure As discussed earlier, these lipid-soluble hormones, including many different steroid hormones, retinoids, and thyroid hormones, bind to and regulate specific transcription factors belonging to the nuclear- receptor superfamily. Examples of lipid-soluble hormones that bind to members of the nuclear-receptor superfamily of transcription factors. Cortisol is a steroid hormone that binds to the glucocorticoid receptor GR. Like other steroid hormones, it is synthesized from cholesterol. Domain Structure of Nuclear Receptors Cloning and sequencing of the genes encoding several nuclear receptors permitted comparison of their amino acid sequences. Such studies revealed a remarkable conservation in both the amino acid sequences and different functional regions of various nuclear receptors Figure All the nuclear receptors have a unique N-terminal region of variable length â€" amino acids containing regions that function as transcription -activation domains. The DNA -binding domain maps near the center of the primary sequence and has the C4 zinc-finger motif. The hormone -binding domain lies near the C-terminal end of these receptors and contains a hormone-dependent activation domain. In some cases the hormone-binding domain functions as a repression domain in the absence of ligand. General design of transcription factors in nuclear-receptor superfamily. The centrally located DNA-binding domain exhibits considerable sequence homology among different receptors and has the C4 zinc-finger motif. The C-terminal hormone-binding domain more Nuclear-Receptor Response Elements The characteristic nucleotide sequences of the DNA sites, called response elements, that bind several major nuclear receptors have been determined. The sequences of the consensus response elements for the glucocorticoid and estrogen receptors are 6-bp inverted repeats separated by any three base pairs Figure a, b. The inverted repeats in GRE more Some nuclear- receptor response elements, such as those for the vitamin D3, thyroid hormone , and retinoic acid receptors, are direct repeats of the same sequence recognized by the estrogen receptor, separated by three to five base pairs Figure c â€" e. The receptors that bind to such direct-repeat response elements do so as heterodimers with a common nuclear-receptor monomer called RXR. The monomers composing these heterodimers interact with each other in such a way that the two DNA -binding domains lie in the same rather than inverted orientation, allowing the RXR heterodimers to bind to direct repeats of the binding site for each monomer. In contrast, the monomers in homodimeric nuclear receptors e. Mechanisms of Hormonal Control of Nuclear-Receptor Activity Hormone binding to a nuclear receptor regulates its activity as a transcription factor. This regulation differs in some respects for heterodimeric and homodimeric nuclear receptors. When heterodimeric nuclear receptors e. In the absence of hormone, these nuclear receptors direct histone deacetylation at nearby nucleosomes by the mechanism described earlier see Figure a. As we saw earlier, in the presence of hormone, the ligand-binding domain undergoes a dramatic conformational change see Figure In the ligand-bound conformation , these nuclear receptors can direct hyperacetylation of histones in nearby nucleosomes, thereby reversing the repressing effects of the free ligand-binding domain. The N-terminal activation domain in these nuclear receptors then probably interacts with additional factors, stimulating the cooperative assembly of an initiation complex, as described earlier. In contrast to heterodimeric nuclear receptors, which are located exclusively in the nucleus , homodimeric receptors are found both in the cytoplasm and nucleus, and their activity is regulated by controlling their transport from the cytoplasm to the nucleus. The hormone -dependent translocation of the homodimeric glucocorticoid receptor GR was demonstrated in the transfection experiments shown in Figure The GR hormone-binding domain alone mediates this transport. Subsequent studies showed that, in the absence of hormone, the glucocorticoid receptor is anchored in the cytoplasm as a large protein aggregate complexed with inhibitor proteins, including Hsp90, a protein related to Hsp70, the major heat-shock chaperone. In this situation, the receptor cannot interact with target genes; hence, no transcriptional activation occurs. Binding of hormone releases the glucocorticoid receptor from its cytoplasmic anchor, allowing it to enter the nucleus where it can bind to

response elements associated with target genes Figure Once the receptor with bound hormone interacts with a response element, it activates transcription by directing histone hyperacetylation and facilitating cooperative assembly of an initiation complex.

Chapter 8 : Mechanisms of Gene Expression

Regulation of gene expression includes a wide range of mechanisms that are used by cells to increase or decrease the production of specific gene products (protein or RNA), and is informally termed gene regulation.

Gene Regulation Gene Control: Transcription Factors and Mechanisms Since the elucidation of the double-helix structure of deoxyribonucleic acid DNA in , biologists have been racing to understand the details of the science of genetics. The deeper they penetrate into the workings of the DNA process, however, the more complexity emerges, challenging the early optimism that characterizing the structural mechanisms would reveal the entire picture. It now appears likely that life within an organism unfolds as a dynamic process, guided by the DNA program to be sure, yet not subject to clockwork predictability. One of the most intriguing questions involves the very first step in the process, how the DNA itself delivers its information to the organism. Eric Lander of the Whitehead Institute at the Massachusetts Institute of Technology organized the session "to give a coordinated picture of gene control in its many different manifestations, both the different biological problems to which it applies and the different methods people use for understanding it. Transcription Factors and Mechanisms. Science at the Frontier. The National Academies Press. The field of molecular biology has exploded into the forefront of the life sciences, and as its practitioners rapidly develop applications from these insights, new horizons appear continuously. The working elements of genetics, called genes, can now be duplicated and manufactured, and then reintroduced into living organisms, which generally accept them and follow their new instructions. A summary of what has been learned about DNA might serve as a useful introduction to the discussion on transcription and gene expression: The heritable genetic information for all life comes in the form of a molecule called DNA. Intrinsic to the structure of the DNA molecule are very long strings composed of so-called base pairs, of which there are four types. A gene is a segment of this string that has a particular sequence of the four base pairs, giving it a unique character. Genes are linked one after another, and the string of DNA is carried on complex structures called chromosomes, of which there are 23 pairs in humans. Researchers put the number of discrete genes in humans at about , To clarify the concept of DNA, Douglas Hanahan from the University of California, San Francisco, invoked the metaphor of a magnetic tape, "which looks the same throughout, but has within it or can have discrete songs composed of information. The general outline of this picture was known by the early s, but even the electron microscope had not revealed exactly how the DNA molecule was structured. When British biophysicist Francis Crick and American molecular biologist James Watson first proposed the double-helix structure for DNA, a thunderclap echoed throughout molecular biology and biochemistry. The structure of DNA was at once realized to be dramatically suggestive of how the molecule actually functions to store and deliver coded information. By weak chemical bonding between complementary basesâ€”adenine with thymine and cytosine with guanine, and each pair vice versaâ€”the hereditary store of information in all life forms takes shape as a coded sequence of simple signals. The signals are arranged in the double-helix structure discovered by Watson and Crick. Picture two strands of rope side by side, each with a string of chemical bases along its length Figure 5. When a base on the first rope is adenine A , the base opposite it on the other rope Figure 5. The structure repeats at intervals of 34 angstroms, which corresponds to 10 residues on each chain. Reprinted by permission from W. Page 97 Share Cite Suggested Citation: Also conversely, if thymine appears on one strand, adenine will be found opposite on the other strand. The same logic applies to analogous pairings with cytosine C and guanine G. These base pairs present the horizontal connection, as it were, by their affinity for a weak chemical bond with their complementary partner on the opposite strand. Thus the ropeâ€”call it a single strand, either the sense strand or the antisense strandâ€”of DNA can have virtually any sequence of A, C, G, and T. The other strand will necessarily have the complementary sequence. The code is simply the sequence of base pairs, usually approached by looking at one of the strands only. In their quest to explain the complexity of life, scientists next turned to deciphering the code. Once it was realized that the four nucleotide bases were the

basic letters of the genetic alphabet, the question became, How do they form the words? The answer was known within a decade: Fitting the 64 "word commands" to the 20 outcomes showed that a number of the amino acids could be commanded by more than one three-letter "word sequence," or nucleotide triplet, known as a codon Figure 5. The explanation remains an interesting question, and so far the best guess seems to be the redundancy-as-error-protection theory: The vehicle for the transmission of information is RNA. Once the messenger transcript is made, its translation eventually results in the production polymerization of a series of amino acids that are strung together with peptide bonds into long, linear chains that in turn fold into interesting, often globular molecular shapes due to weak chemical affinities between and among various amino acids. Page 98 Share Cite Suggested Citation: Several ribosomes may be attached to one mRNA molecule at one time; the entire assembly is called a polyribosome. B Transcription and translation. Each group of three is a codon that is complementary to a group of three nucleotides in the anti-codon region of a specific transfer tRNA molecule. When base pairing occurs, an amino acid carried at the other end of the tRNA molecule is added to the growing protein chain. Reprinted with permission from Watson et al. Page 99 Share Cite Suggested Citation: Transcription Factors and Mechanisms," touched on much of the above background and presented some of the basic issues scientists are exploring as they probe the mRNA process. His colleagues in the session on gene regulation each described intriguing findings based on their studies of regulation in various organisms: They explained their work to the symposium and suggested how its implications may help to clarify human genetics and fill in the larger picture of how life operates. Scientists cannot say for certain whether the majority of noncoding genes that do not seem to say simply "make this string of amino acids," are saying anything at all. Tjian has heard a lot of speculation on this question: But far be it for me to say that all that intervening sequence is entirely unimportant. Why do amphibians have so much more DNA than we do? Actually, a lot of people wonder about whether those sequences are perhaps there for more subtle differencesâ€”differences between you and me that at our present stage of sophistication may be too difficult to discern. How would you get rid of it? It takes work by way of natural selection to get rid of things, and if it is not a problem, why would you junk it? That is really the way life is probably looking at it. Or more likely, a number of functions. Now that the questions being posed by scientists mapping the genome are starting to become more refined and subtle, the very definition of a gene is starting to wobble. It is often convenient to conceptualize genes as a string of discrete pearlsâ€”or an intertwined string following the double-helix metaphorâ€”that are collected on a given chromosome. But Tjian reinforces the significance of the discovery that much less than half of the base sequences are actually coding for the creation of a protein. He is searching for the messages contained in the larger by a factor of three or four "noncoding" portion of the human genome. Mapping is one thing: For Tjian, however, that will only be like the gathering of a big pile of puzzle pieces. He is looking to the next stage, trying to put the puzzle together, but from this early point in the process it is difficult to say for certain even what the size and shape of the individual pieces look like. He knows the title of the assembled picture: Life is a process, calling for infinitely many and infinitely subtle reactions and responses to the conditions that unfold. The formal way of clarifying this is to refer to the actual generic sequence of bases in an organism as its genotype, and the actual physical life form that genotype evolves into as the phenotype. Tjian and his colleagues strongly suspect that, on the cellular levelâ€”which is the level where molecular biologists quest and where DNA eventually produces its effectsâ€”the instructions are not merely laid down and then run out like a permanently and deterministically wound-up clock. Most of the noninstinctiveâ€”that is, other than biochemically exigent and predictableâ€”functions performed within the cell must have a guiding intelligence, and that intelligence must be coded in the DNA. The Central Dogma of Biology Not long after Crick and Watson made their celebrated discovery, they pursued their separate researches, and Crick was among those given the most credit for helping to unravel the code itself. Crick was responsible for what came to be called the central dogma of biologyâ€”the sequence of steps involved in the flow of information from the DNA master plan through to the final manufacture of the proteins that power the life process Figure 5. Molecular biologists and biochemists have uncovered a number of fascinating and

unexpected phenomena at each of these distinct steps. But the transcript made at the first step is understandably critical, because somehow the proper part of the enormous DNA master planâ€”the correct gene or sequence of genesâ€”must be accessed, consulted, and translated for transmission to the next step. A cell has many jobs to do and seems to be programmed to do them. Moreover, the cell must react to its environment and thus is constantly sensing phenomena at its cell membrane with receptors designed for the task, and then transmitting a chemically coded signal to the nucleus. Processing this information, to continue the metaphor, requires a software program, and undoubtedly the program is located in the genes. It is the job of the transcription machinery to find the proper part of the genome where the needed information is located. The arrows indicate the directions proposed for the transfer of genetic information. Correspondingly, all proteins are determined by "translated on" RNA templates. Most importantly, the last two arrows were presented as unidirectional; that is, RNA sequences are never determined by protein templates, nor was DNA then imagined ever to be made on RNA templates. Bottom Transcription and translation are closely coupled in procaryotes A , whereas they are spatially and temporally separate in eucaryotes B. In procaryotes, the primary transcript serves as mRNA and is used immediately as the template for protein synthesis. In eucaryotes, mRNA precursors are processed and spliced in the nucleus before being transported to the cytosol. Page Share Cite Suggested Citation: One could be thought of as preprogrammed; for example, when a cell begins to die its natural death, it must be replaced, and a full new set of DNA must be created for the progeny cell. Such a DNA replication event is biologically predictable, and thus it could conceivably be anticipated within the program itself. But a different sort of signal is probably far the more numerous sort: With this latter sort of signal, the RNA-transcribing enzyme, RNA polymerase, is somehow able to search out the proper part of the DNA library where the needed information is stored, copy it down by transcription, and then deliver the transcript to the next step in the process, which will move it outside the nucleus to the ribosomes. Again, the central dogma. Since the chemical rules by which RNA polymerase operates are fairly well understood, he is looking for more subtle answers, related to how the protein finds the proper part or parts of the genomeâ€”that is, the gene or genes that need to be consulted at the moment. His research indicates that the answer most likely will involve at least several phenomena, but his target at the moment is a collection of proteins called transcription factors. Since timing is also a crucial component of the transcription process, geneticists are trying to understand how the rapid-fire creation of proteins is coordinated: This long string, when conceived as the product of a program, can be seen as the sequential order in which the proteins are called for and assembled, because they are strung together one after another by chemical bonding in a long chain in one direction only. The ribosomal cell factories pump out proteins at the rate of over 30 per second. An only slightly fanciful example: Thanks to the electron microscope, Tjian was able to provide moving pictures of the transcription process in action.

Chapter 9 : New study finds molecular mechanisms that control Rb2/p gene expression in lung cancer

Most importantly, eukaryotes use epigenetic mechanisms primarily to regulate gene expression which bacteria rarely do. However, bacteria make widespread use of postreplicative DNA methylation for the epigenetic control of DNA-protein interactions.

RNA sugar-phosphate backbone forms. The RNA is further processed and then moves through the small nuclear pores to the cytoplasm. Transcription is the first step leading to gene expression. If the gene transcribed encodes a protein, the result of transcription is messenger RNA mRNA , which will then be used to create that protein via the process of translation. A DNA transcription unit encoding for a protein contains not only the sequence that will eventually be directly translated into the protein the coding sequence but also regulatory sequences that direct and regulate the synthesis of that protein. Transcription has some proofreading mechanisms, but they are fewer and less effective than the controls for copying DNA; therefore, transcription has a lower copying fidelity than DNA replication. Although DNA is arranged as two antiparallel strands in a double helix, only one of the two DNA strands, called the template strand, is used for transcription. The other DNA strand is called the coding strand, because its sequence is the same as the newly created RNA transcript except for the substitution of uracil for thymine. Transcription is divided into 5 stages: One gene-one enzyme hypothesis[edit] The one gene-one enzyme hypothesis is the idea that genes act through the production of enzymes, with each gene responsible for producing a single enzyme that in turn affects a single step in a metabolic pathway. The concept was proposed by George Beadle and Edward Tatum in an influential paper on genetic mutations in the mold Neurospora crassa, [3] and subsequently was dubbed the "one gene-one enzyme hypothesis" by their collaborator Norman Horowitz. It is often considered the first significant result in what came to be called molecular biology. Although it has been extremely influential, the hypothesis was recognized soon after its proposal to be an oversimplification. Even the subsequent reformulation of the "one gene-one polypeptide" hypothesis is now considered too simple to describe the relationship between genes and proteins. Neurospora crassa is a type of red bread mold of the phylum Ascomycota. The genus name, meaning "nerve spore" refers to the characteristic striations on the spores. Analysis of genetic recombination is facilitated by the ordered arrangement of the products of meiosis in Neurospora ascospores. Its entire genome of seven chromosomes has been sequenced. Beadle and Tatum exposed N. They then observed failures in metabolic pathways caused by errors in specific enzymes. This led them to propose the "one gene, one enzyme" hypothesis that specific genes code for specific proteins. Their hypothesis was later elaborated to enzyme pathways by Norman Horowitz, also working on Neurospora. One gene-one polypeptide[edit] By the early s, advances in biochemical geneticsâ€”spurred in part by the original hypothesisâ€”made the one gene-one enzyme hypothesis seem very unlikely at least in its original form. Beginning in , Vernon Ingram and others showed through protein fingerprinting that genetic variations in proteins such as sickle cell hemoglobin could be limited to differences in just a single polypeptide chain in a multimeric protein, leading to a "one gene-one polypeptide" hypothesis instead. According to geneticist Rowland H. Davis, "By â€” indeed, even by â€” one gene, one enzyme was no longer a hypothesis to be resolutely defended; it was simply the name of a research program. This splicing was discovered in by Phillip Sharp and Richard J. Operon[edit] An operon is a functioning unit of genomic material containing a cluster of genes under the control of a single regulatory signal or promoter. The genes are transcribed together into an mRNA strand and either translated together in the cytoplasm, or undergo trans-splicing to create monocistronic mRNAs that are translated separately, i. The result of this is that the genes contained in the operon are either expressed together or not at all. Several genes must be both co-transcribed and co-regulated to define an operon. Originally operons were thought to exist solely in prokaryotes but since the discovery of the first operons in eukaryotes in the early s, more evidence has arisen to suggest they are more common than previously assumed. Operons occur primarily in prokaryotes but also in some eukaryotes, including nematodes such as C. An operon is made up of several

structural genes arranged under a common promoter and regulated by a common operator. It is defined as a set of adjacent structural genes, plus the adjacent regulatory signals that affect transcription of the structural genes. The regulators of a given operon, including repressors, corepressors, and activators, are not necessarily coded for by that operon. The location and condition of the regulators, promoter, operator and structural DNA sequences can determine the effects of common mutations. Operons are related to regulons, stimulons and modulons. Whereas operons contain a set of genes regulated by the same operator, regulons contain a set of genes under regulation by a single regulatory protein, and stimulons contain a set of genes under regulation by a single cell stimulus. The promoter is recognized by RNA polymerase, which then initiates transcription. In RNA synthesis, promoters indicate which genes should be used for messenger RNA creation â€" and, by extension, control which proteins the cell manufactures. Operator â€" a segment of DNA that a regulator binds to. It is classically defined in the lac operon as a segment between the promoter and the genes of the operon. In the case of a repressor, the repressor protein physically obstructs the RNA polymerase from transcribing the genes. Structural genes â€" the genes that are co-regulated by the operon. Prokaryotic promoters[edit] In prokaryotes, the promoter consists of two short sequences at and positions upstream from the transcription start site. The Pribnow box is absolutely essential to start transcription in prokaryotes. Its presence allows a very high transcription rate. Both of the above consensus sequences, while conserved on average, are not found intact in most promoters. On average only 3 of the 6 base pairs in each consensus sequence is found in any given promoter. It should be noted that the above promoter sequences are only recognized by the sigma protein that interacts with the prokaryotic RNA polymerase. Complexes of prokaryotic RNA polymerase with other sigma factors recognize totally different core promoter sequences. They typically lie upstream of the gene and can have regulatory elements several kilobases away from the transcriptional start site enhancers. In eukaryotes, the transcriptional complex can cause the DNA to bend back on itself, which allows for placement of regulatory sequences far from the actual site of transcription. The TATA box typically lies very close to the transcriptional start site often within 50 bases. Eukaryotic promoter regulatory sequences typically bind proteins called transcription factors which are involved in the formation of the transcriptional complex. Enhancer[edit] An enhancer is a short region of DNA that can be bound with proteins namely, the trans-acting factors, much like a set of transcription factors to enhance transcription levels of genes hence the name in a gene cluster. While enhancers are usually cis-acting, an enhancer does not need to be particularly close to the genes it acts on, and need not be located on the same chromosome. In eukaryotic cells the structure of the chromatin complex of DNA is folded in a way that functionally mimics the supercoiled state characteristic of prokaryotic DNA, so that although the enhancer DNA is far from the gene in regard to the number of nucleotides, it is geometrically close to the promoter and gene. An enhancer may be located upstream or downstream of the gene that it regulates. Furthermore, an enhancer does not need to be located near to the transcription initiation site to affect the transcription of a gene, as some have been found to bind several hundred thousand base pairs upstream or downstream of the start site. Enhancers do not act on the promoter region itself, but are bound by activator proteins. These activator proteins interact with the mediator complex, which recruits polymerase II and the general transcription factors which then begin transcribing the genes. Enhancers can also be found within introns. Additionally, an enhancer may be excised and inserted elsewhere in the chromosome, and still affect gene transcription. That is the reason that intron polymorphisms are checked though they are not translated. Corepressor[edit] A corepressor is a protein that decreases gene expression by binding to a transcription factor which contains a DNA binding domain. The corepressor is unable to bind DNA by itself. The corepressor can repress transcriptional initiation by recruiting histone deacetylases which catalyze the removal of acetyl groups from lysine residues. This increases the positive charge on histones which strengthens in the interaction between the histones and DNA, making the latter less accessible to transcription. Thus, an mRNA that contains a riboswitch is directly involved in regulating its own activity, in response to the concentrations of its target molecule. The discovery that modern organisms use RNA to bind small molecules, and discriminate against closely related analogs, significantly expanded the

known natural capabilities of RNA beyond its ability to code for proteins or to bind other RNA or protein macromolecules. The original definition of the term "riboswitch" specified that they directly sense small-molecule metabolite concentrations. Although this definition remains in common use, some biologists have used a broader definition that includes other cis-regulatory RNAs. However, this article will discuss only metabolite-binding riboswitches. Most known riboswitches occur in bacteria, but functional riboswitches of one type the TPP riboswitch have been discovered in plants and certain fungi. TPP riboswitches have also been predicted in archaea, but have not been experimentally tested. It consists of three adjacent structural genes , lacZ, lacY and lacA. The lac operon is regulated by several factors including the availability of glucose and of lactose. Gene regulation of the lac operon was the first complex genetic regulatory mechanism to be elucidated and is one of the foremost examples of prokaryotic gene regulation. In its natural environment, the lac operon allows for the effective digestion of lactose. However, it would be inefficient to produce enzymes when there is no lactose available, or if there is a more readily-available energy source available such as glucose. It achieves this with the lac repressor , which halts production in the absence of lactose, and the Catabolite activator protein CAP , which assists in production in the absence of glucose. This dual control mechanism causes the sequential utilization of glucose and lactose in two distinct growth phases, known as diauxie. Similar diauxic growth patterns have been observed in bacterial growth on mixtures of other sugars as well, such as mixtures of glucose and xylose , or of glucose and arabinose , etc. The genetic control mechanisms underlying such diauxic growth patterns are known as xyl operon and ara operon , etc. The three structural genes are: Only lacZ and lacY appear to be necessary for lactose catabolism. IPTG is an allolactose analog. They were also able to isolate the portion of DNA bound by the protein by using the enzyme deoxyribonuclease, which breaks down DNA. This was later confirmed. These experiments were important, as they confirmed the mechanism of the lac operon, earlier proposed by Jacques Monod and Francois Jacob. The structure of the lac repressor protein consists of three distinct regions: This can be viewed as two dimers, with each dimer being able to bind to a single lac operator. The two subunits each bind to a slightly separated major groove region of the operator. The promoter is slightly covered by the lac repressor so RNAP cannot bind to and transcribe the operon. The DNA binding region consists of a helix-turn-helix structural motif. The lac repressor LacI operates by binding to the major groove of the operator region of the lac operon. When lactose is present, allolactose binds to the lac repressor, causing an allosteric change in its shape.