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A complex network of molecular events triggered upon environmental cues which decide the fate of gene expression: a review

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Abstract: Gene expression in eukaryotes depends on a web of events which are inter-related and tightly regulated. These key events can be broadly classified into post-transcriptional and post-translational processes. In general, the post-transcriptional events include pre-mRNA processing (capping, splicing, polyadenylation), RNA stability, and translation as well as chromatin modifications through regulatory RNAs (miRNA, siRNAs and long non-coding RNAs). Protein phosphorylation, ubiquitination and sumoylation are a few post-translational events. These events are constitutive as well as provoked by specific exogenous and/or endogenous stimuli. In case of the plant system, the molecular mechanisms responsible for regulating the gene expression is diverse and yet to be fully revealed. The network of post-transcriptional and post-translational events do ensure temporal and spatial suitable patterns of downstream stress-related gene expression. The current review mainly focus on a variety of molecular events which play a pivotal role in fine tuning the gene expression in eukaryotes.

Key words: Transcription; Translation; RNA processing; P-bodies; small RNA's

Introduction

External makeup of an organism usually termed as the phenotype, is mostly determined by the functional proteins, the sequence of which are encoded as genes in its DNA. Thus, the gene expression is considered as one of the fundamental process which plays a pivot role in the transition of the genome to a physical life. This makes the gene expression a tightly regulated process whereby any misregulation at any key events may lead to deformed physical life including a wide range of genetic disease. Until now, it is very well established that the gene expression is regulated at various levels and these diverse regulatory mechanisms are well integrated as a spider's web Maniatis and Reed, (2002). Gene expression regulation can be divided into 2 main categories of (1) Post-transcriptional control and (2) post-translational control. Furthermore, upstream of these 2 processes, DNA is mostly regulated at the transcriptional level before entering into the transcription event. Transcriptional control has been extensively studied as compared to that of post-transcriptional and post-translational molecular mechanisms because of historical as well as technical aspects; it is clear that transcription is one of the fundamental and innately important steps within the cascade of gene expression regulation and techniques to study transcription and transcriptional control are well established in the scientific field. Post-transcriptional regulation mechanisms involve various processes such as mRNA processing (polyadenylation, capping and splicing), mRNA export and localization, mRNA decay, and mRNA translation (Figure 1). Despite this range of regulatory mechanisms, there is one thing in common for all of them: they ultimately control if and where a given mRNA is translated into a protein. Accordingly, translation and translational control are central to post-transcriptional gene expression regulation. Post-translational regulation mechanisms comprise Post-Translational Modification (PTM) which refers to the covalent and mainly enzymatic modification of proteins during or after protein biosynthesis. Proteins after being synthesized by ribosomes which translate mRNA into polypeptide chains, which may then undergo PTM to form the mature functional protein product. Post-translational modifications can occur on the amino-acid side chains or at the protein's C- or N-termini Pratt, (2006). Phosphorylation is a very common mechanism for regulating the activity of enzymes and is the most common post-translational modification Khoury, (2011). Many eukaryotic proteins also have carbohydrate molecules attached to them in a process called glycosylation which can induce protein folding and improve stability as well as serving regulatory

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functions. Association of lipid molecules, known as lipidation, often aims a protein or part of a protein attached to the cell membrane. Other forms of post-translational modification consist of cleaving peptide bonds, as in processing a propeptide to a mature form or removing the initiator methionine residue. The formation of disulfide bonds from cysteine residues may also be referred to as a post-translational modification Harvey Lodish, (2000). Oxidative stress also results into some types of PTM's. Dalle-Donne, (2006). Carbonylation is one example that targets the modified protein for degradation and can result in the formation of protein aggregates Specific amino acid modifications can be used as biomarkers indicating oxidative damage Grimsrud, (2008).

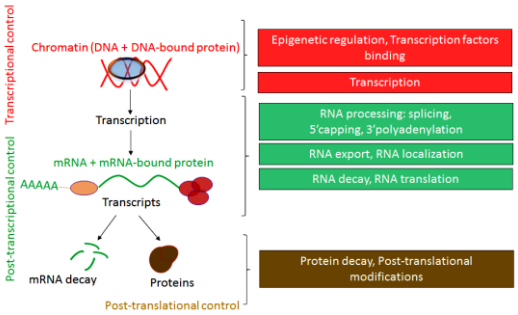

Figure 1: Schematic representation of the several layers of gene expression regulation.

RNA Processing and export

Prior to the mRNA transport into the cytoplasm from nucleus in order to be available for the translational machinery, it has to undergo a series of processing steps: the mRNA acquires a cap structure at the 5' terminus, introns are spliced out from the pre-mRNA, and a specialized 3' end of the mRNA is generated, usually by polyadenylation. All these key events proceed co-transcriptionally and can influence each other Proudfoot *et al., (*2002). The first processing step is the addition of the m7G cap structure to the 5' end of the nascent mRNA and happens after 20-30 nucleotides have been synthesized In a three-step reaction, the GMP moiety from GTP is added to the first nucleotide of the pre-mRNA, and GMP is methylated at position N7. The m7G cap is important for mRNA stability and translation. In the nucleus, the m7G cap gets bound by the cap binding complex (CBC), which consists of 2 subunits and after shuttling to the cytoplasm, it gets bound by translation initiation factor 4E, which is an essential step in translation initiation. As the coding sequences (exons) of most mRNAs in higher eukaryotes are interrupted by introns, these introns must be spliced out of the pre-mRNA in order to generate a functional mRNA. Splicing requires consensus sequences on the mRNA, which mark the exon-intron boundaries, and the spliceosome, the catalytic complex which carries out the enzymatic reactions to remove the introns and ligate the flanking exons. The spliceosome consists of 5 small ribonucleoprotein particles (snRNPs: U1, U2, U4, U5 and U6), each of them made out of a small nuclear RNA (snRNA) and associated proteins, and many accesory proteins. In fact, well over a hundred proteins are thought to be splicing factors Jurica and Moore, (2003). The catalysis of the splicing reaction itself is dependent on RNA-protein, RNA-RNA, and protein-protein interactions. Furthermore, the alternative use of exons (alternative splicing) can contribute to the creation of protein variety by allowing one gene to produce multiple isoforms Matlin *et al., (*2005). Most mRNAs also bear a specific structure in the form of a poly (A) tail at their 3' end. The only known protein-coding genes lacking poly (A) tails are histone mRNAs in higher eukaryotes, but not in yeast Fahrner *et al., (*1980). Polyadenylation is achieved in two steps: the nascent mRNA is cleaved at the site where polyadenylation is meant to begin, which is followed by poly (A) synthesis. In analogy to splicing, formation of the poly (A) tail requires a multi-subunit polyadenylation complex and specific sequence-elements on the pre-mRNA. In mammalian cells, the site of cleavage lies mostly between an AAUAAA hexamer motif and a GU-rich downstream element (DSE) McLauchlan *et al., (*1985). The AAUAAA hexamer is bound by the cleavage and polyadenylation specificity factor (CPSF), and the DSE interacts with the cleavage stimulatory factor (CstF). Cleavage factor I and II (CF I; CF II) are also required. Whereas both poly (A) polymerase (PAP) and CPSF are required for cleavage of the pre-mRNA and poly (A) addition, CstF is necessary for the endonucleolytic cleavage and – together with CPSF – for the recruitment of CF I and CF II. The principles of poly (A) tail formation are the same in yeast and mammalian cells and the protein complexes involved have orthologous components, but also specific accessory factors that are only found in one of the species Furthermore, in yeast, a variable A-rich element substitutes for the AAUAAA hexamer motif and there are 3polyadenylation complexes: cleavage polyadenylation factor (CPF), which contains several factors homologous to CPSF and also the poly (A) polymerase, cleavage factor IA (CF IA) and cleavage factor IB (CF IB). The emerging poly (A) tail is bound by the poly (A)-binding protein (PAPB). PABP is thought to influence the final length of the poly (A) tail on the one hand positively by stimulating the processivity of PAP, on the other hand negatively, by interacting with the poly (A) nuclease PAN Mangus *et al., (*2003). Furthermore, PABPs are involved in nuclear export and are also important for the initiation of translation. The poly (A) tail is also crucial for several other post-transcriptional regulatory mechanisms in the cytoplasm and cytoplasmic polyadenylases can regulate the

translational state and stability of various target mRNAs via modifying the length of the respective poly (A) tails. The best studied example is probably that of translational regulation of maternal mRNAs in Xenopus oocytes, which are stock-piled in a translationally-repressed state with very short poly (A) tails, which become polyadenylated upon activation and as a consequence translated mRNA decay by exonucleolytic mechanisms is also usually preceded by a shortening of the poly (A) tail Parker and Song, (2004), and recently deadenylation of poly (A) tails has also been shown to happen in micro RNA (miRNA)-mediated expression regulation Giraldez *et al.,*; Wu *et al., (*2006). The last part in the journey from the site of transcription into the cytoplasm is the nuclear export of the mature mRNA. Export through the nuclear pore complex (NPC) happens in the context of messenger ribonuleoprotein particles (mRNPs). mRNPs comprise them RNA and associated RNA-binding proteins, which bind to the mRNA during the processing steps Aguilera, (2005). Apart from the aforementioned CBC or PABP, such RNA-binding proteins include SR (serine/arginine rich) and hnRNP (heterogeneous nuclear RNP) proteins, or the exon junction complex (EJC), which is a set of proteins loaded onto the mRNA upstream of exon-exon junctions as a consequence of pre-mRNA splicing. These factors are important for the association of the mRNP with the NPC and the shuttling into the cytoplasm, and some of them stay associated with the mRNA as it is exported, whereas others are restricted to the nucleus. Furthermore, nuclear export is an important step in quality control, as faulty or un-processed mRNAs are not only useless, but potentially harmful, if translated in the cytoplasm. Only functional mRNAs are exported into the cytoplasm and this quality control step is closely coupled to RNA processing and the mRNP composition. Again, it needs to be emphasized, that despite the introduction of mRNA transcription, capping, splicing, polyadenylation and nuclear export as sequential events, these events occur in the cell integrated with each other and not at all independently in spatial and temporal context Proudfoot *et al.,* ; Aguilera; Moore, (2005).

Significance of translational regulation

A number of plausible benefits do occur because of the well fitted translational regulation. Foremost, the translational regulation can happen as an instantaneous response without the necessity of undergoing the upstream processes of gene expression including transcription, mRNA processing or mRNA export. Furthermore, translational regulation is a reversible mechanism as it involves several reversible protein modifications such as the phosphorylation of initiation factors. Translational control is very needful for systems where transcriptional control is not possible like in reticulocytes, which lack a nucleus, oocytes or RNA viruses. Apart from these significance, another reason for the regulation of translation is spatial control of gene expression within the cell St Johnston, (2005). The need for localized protein production in neurons or during development can only be met by translational regulation, as regulation of transcription is restricted only to the nucleus of the cell Schuman *et al., (*2006). Translational regulation is a better option for the cell to regulate gene expression, is its flexibility. There are several molecular targets for translational regulation, which consequently affects translational efficiencies for many or only a few mRNAs. A last but important significance, why do cells regulate translation, is fine tuning of gene expression, as there are number like GADD45α or TNF-α of genes that are regulated at both the transcriptional and translational level Saklatvala *et al., (*2003) and Lal *et al., (*2006).

Effectors for translational regulation: initiation factors, mRNA and the ribosome

Translational control can be controlled at a global level as well as in an mRNA-specific manner Gebauer and Hentze, (2004). Global regulation affects the translational efficiency of most mRNAs through a general switch-on or switch-off of translation. mRNA-specific regulation only affects the translation of a subset of mRNA. Most translational regulation forbids or allows the association of the mRNA with the translational apparatus. A vital target in many regulatory mechanisms is the cap binding protein eIF4E that can be bound by inhibitory proteins, which results in unavailability of the mRNA. Global regulation of translation is generally mediated through such modifications of translation initiation factors.

Another target for translational regulation is the mRNA itself. The cis-regulatory elements, which can be bound by trans-acting factors (Figure 2). The cis-regulatory elements on the mRNA could be anywhere along the mRNA, but mostly for the characterized examples of translational regulation, these elements are found in the 3'UTR or 5' UTR. mRNA-specific translational regulation happens mostlyvia regulatory proteins, which bind to the cis-regulatory elements of a given mRNA.

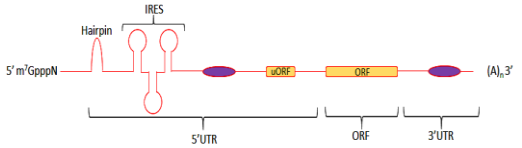

Figure 2: Cis-acting sequence elements that influence translation initiation of specific mRNAs.

The ribosome itself can also be one of the targets of translational regulation (Figure 3). Several of its protein constituents can undergo post-translational modifications. A well-known example is the the

phosphorylation of ribosomal protein S6 (RPS6) by ribosomal S6. It has been well established that the phosphorylation of RPS6 results in an increase in translation initiation. Ribosomal proteins can also undergo ubiquitination Spence *et al., (*2000) or methylation Bachand and Silver, (2004), Swiercz *et al., (*2005). An exciting hypothesis points the heterogeneity of ribosomes: the cell could construct various kinds of ribosomes, which differ in terms of paralogue composition and post-translational modifications, and "specialized" ribosomes could play a role in the regulation of translation of specific subsets of mRNAs.

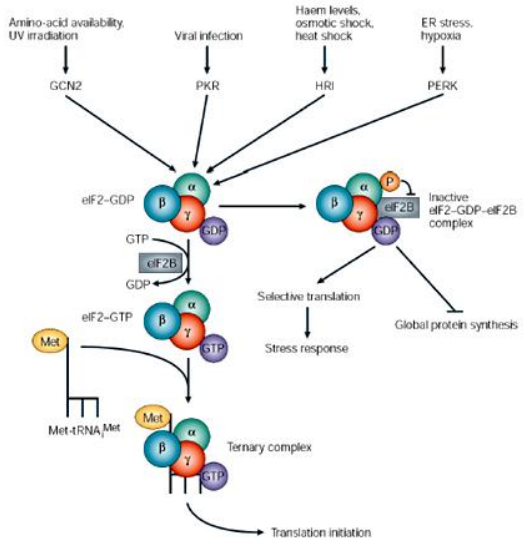

Figure 3: Inhibition of global protein synthesis in response to various stress stimuli through phosphorylation of eukaryotic initiation factor-2α. This figure is taken from Holcik *et al., (*2005).

P-bodies and micro RNAs: Novel components in translational control

Recently, two new ways to control mRNA turnover at the posttranscriptional level have engrossed a great deal of attention. The discovery of cytoplasmic processing bodies (P-bodies), which were initially described as foci within the cell with a high concentration of mRNA decay enzymes Bashkirov *et al., (*1997) was a significant outreach in the scientific field. The other discovery is that of small RNAs, which can modulate the stability and translation of target mRNAs Bartel, (2004).

P-bodies are probably a site of mRNA decay (Figure 4). P-bodies were first visualized by various groups using microscopy as factors involved in mRNA decay and accessory factors such as DCP1, DCP2, XRN1 and LSM Bashkirov *et al., (*1997). mRNA decay in eukaryotes can be controlled in different ways via endonuleolytic or exonucleolytic pathways. Exonucleolytic degradation is usually initiated by deadenylation of the poly (A) tail of the mRNA. Transcripts will then be degraded from their 5' ends by the exonuclease like XRN1, following removal of the 5' cap (decapping). Alternatively, the exosome complex can degrade transcripts from their 3' ends before decapping. Factors of the nonsense-mediated decay (NMD) pathway, which is responsible for the rapid degradation of mRNAs with a premature stop codon Conti and Izaurralde, (2005), can also be found in mammalian P-bodies. The connection between the P-bodies and mRNA turnover rate is still intriguing. The exact mechanism how mRNAs shuttle intoP-bodies and become translationally repressed is not clear at the moment.

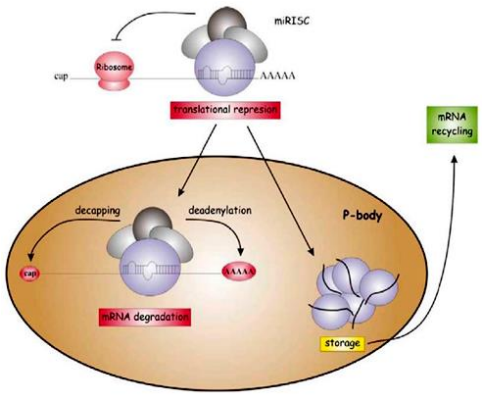

Figure 4: P bodies: The site for mRNA degradation.

Small RNAs are riboregulators that have critical roles in most eukaryotes. They repress gene expression by acting either on DNA to guide sequence elimination and chromatin remodeling, or on RNA to guide cleavage and translation expression Hervé Vaucheret, (2006). Two types of small RNA molecules have appeared as regulators of mRNA stability and translation in the last decade: micro RNAs (miRNAs) and short interfering RNAs (siRNAs). miRNAs and siRNAs are short RNAs of 21-26 nucleotides (nt) and are distinguished based on their biogenesis Kim, (2005), Jackson and Standart, (2007). miRNAs are derived from longer precursors that include a ~70 nt imperfectly based hairpin segment; siRNAs are of similar length but are derived from perfectly complementary RNA precursors (Figure 5). During RNA-interference (RNAi), exogenously introduced siRNAs target mRNAs for endonucleolytic cleavage Tomari and Zamore, (2005). In animal cells, most miRNAs are only partially complementary to their target mRNAs and the down-regulation of protein levels of the target is usually greater than the down-regulation of its mRNA abundance, which suggests regulation at the level of translation in these cases Jackson and Standart, (2007).

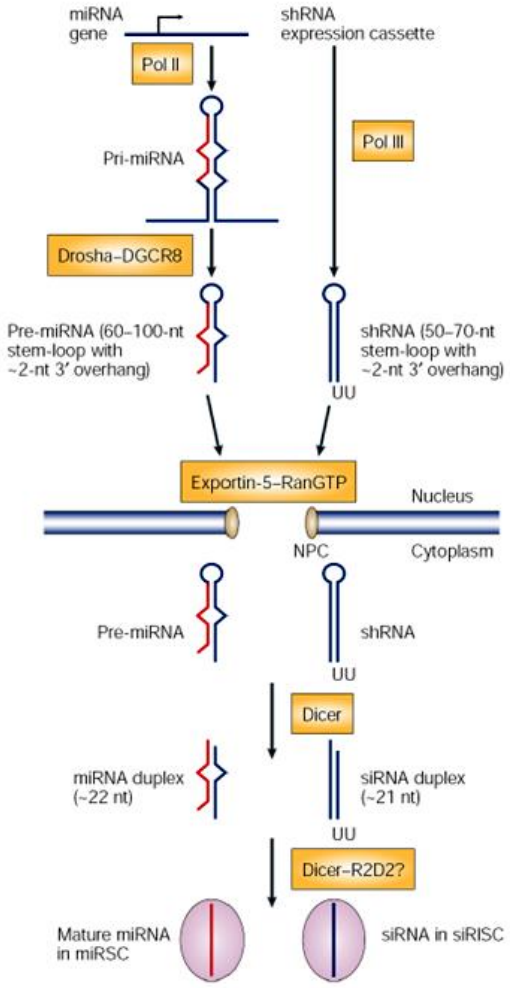

Figure 5: Biogenesis of miRNAs and siRNAs. This figure is taken from Kim *et al., (*2005).

Protein Posttranslational Modifications

Protein posttranslational modifications involve covalent alterations that occur after the translation process. The newly formed nascent proteins are then exposed to a series of specific enzyme-catalyzed manipulations on their side chains or backbones. Two broad types of protein PTM occur. The first type (Figure 6) includes all enzyme-catalyzed covalent additions of some chemical group, usually an electro philic fragment of aco-substrate, to a side chain residue in a protein. The side chain modified is usually electron rich, acting as a nucleophile in the transfer. The second category of PTM is covalent cleavage of peptide backbones in proteins either by action of proteases or less commonly, by autocatalytic cleavage. The amino acid side chains undergo a lot of diversifications, some of them are listed in Table 1**,** C. T. Walsh *et al., (*2005).

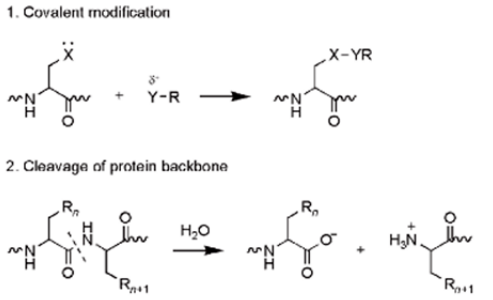

Figure 6: Two categories of posttranslational modifications of proteins:1) covalent modification of a nucleophilic amino acid side chain by an electrophilic fragment of a cosubstrate; 2) cleavage of a protein backbone at a specific peptide bond.

Residue	Reaction	Example
Asp	phosphorylation	protein tyrosine phosphatases; response regulators in two-component systems
	isomerization to isoAsp	
Glu	methylation	chemotaxis receptor proteins
	carboxylation	Gla residues in blood coagulation
	polyglycination	tubulin
	polyglutamylation	tubulin
Ser	phosphorylation	protein serine kinases and phosphatases
	O-glycosylation	notch O-glycosylation
	phosphopantetheinylation	fatty acid synthase
	autocleavages	pyruvamidyl enzyme formation
Thr	phosphorylation	protein threonine kinases/phosphatases
	O-glycosylation	
Tyr	phosphorylation	tyrosine kinases/phosphatases
	sulfation	CCR5 receptor maturation
	ortho-nitration	inflammatory responses
	TOPA quinone	amine oxidase maturation
His	phosphorylation	sensor protein kinases in two-component regulatory systems
	aminocarboxypropylation	diphthamide formation
	N-methylation	methyl CoM reductase
Lys	N-methylation	histone methylation
	N-acylation by acetyl, biotinyl, lipoyl, ubiquityl groups	histone acetylation; swinging-arm prosthetic groups; ubiquitin; SUMO (small ubiquitin-like modifier) tagging of proteins
	C-hydroxylation	collagen maturation
Cys	S-hydroxylation (S-OH)	sulfenate intermediates
	disulfide bond formation	protein in oxidizing environments
	phosphorylation	PTPases
	S-acylation	Ras
	S-prenylation	Ras
	protein splicing	intein excisions
Met	oxidation to sulfoxide	Met sulfoxide reductase
Arg	N-methylation	histones
	N-ADP-ribosylation	$G_{s\alpha}$
Asn	N-glycosylation	N-glycoproteins
	N-ADP-ribosylation	eEF-2
	protein splicing	intein excision step
Gln	transglutamination	protein cross-linking
Trp	C-mannosylation	plasma-membrane proteins
Pro	C-hydroxylation	collagen; HIF-1α
Gly	C-hydroxylation	C-terminal amide formation

Table 1: Posttranslational protein modifications at the side chains.

Covalent addition of Proteins

The five most common types of covalent additions to proteins are phosphorylation, acylation, alkylation, glycosylation, and oxidation, which are catalyzed by dedicated PTM enzymes (Figure 7). The protein products obtained in this manner make up subsets of the proteome of an organism: the phosphoproteome, the acyl proteome, the alkyl proteome, the glycoproteome, and the oxidized proteome. In turn, each of these subproteomes contribute to substantial diversity C. T. Walsh *et al., (*2005).

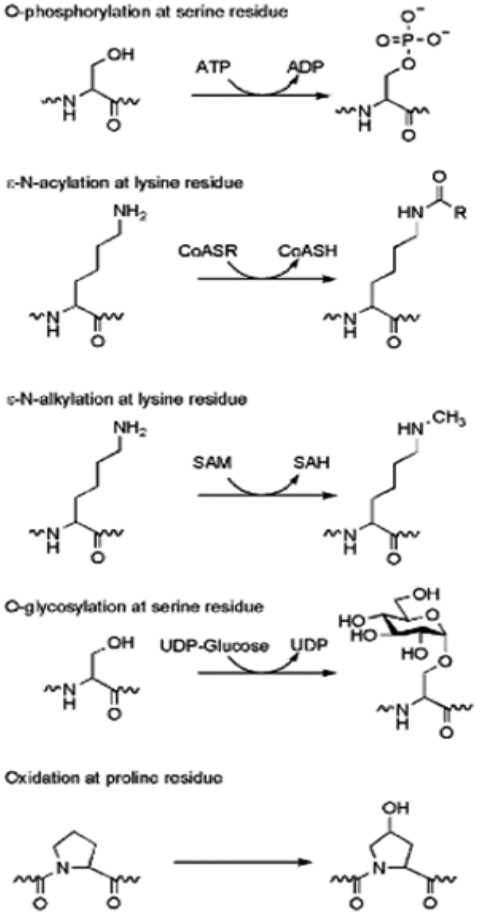

Figure 7: Five major types of covalent additions to protein side chains: phosphorylation, acylation, alkylation, glycosylation, oxidation.

Reversible and Irreversible Posttranslational Modification

Based on the cellular demand of a particular covalent modification of a protein, reversibility or irreversibility of a protein modification do depend. The archetype of reversible modification is protein phosphorylation, consistent with its evolution to the dominant role in protein-based signaling in eukaryotes. Of the five major categories of PTMs, all excluding alkylation have dedicated enzymes, often large enzyme families, which catalyze the removal of the covalent modifications. The enzymes that reverse phosphorylation, acylation, and glycosylation are, by and large, specific hydrolases, whereas disulfide bonds are cleaved by reductases C. T. Walsh *et al., (*2005).

Conclusion

The self-fidelity and reliable post-transcriptional and post-translational events ensures a safe track for the genetic makeup that is DNA of an organism and carry out the vital transition of DNA to functional protein resulting into an healthy cellular environment. The interdependence and interrelationship of these molecular events like that of a spider's web provides the base for an error less "Central Dogma" of molecular life.

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