MODULE 3

GENE EXPRESSION AND REGULATION OF GENE EXPRESSION

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What is Gene Expression & Gene Regulation?

1. **Gene Expression = translation, production of proteins, tRNA, mRNA and ribosomes**

2. **Gene regulation is the cellular control of the amount and timing of the appearance of functional gene products. The functional gene product can be RNA, protein but mostly it is the regulation of the expression of the protein coding genes (gene switching).**

3. **Gene Expression is regulated at different levels:**
   - **Chemical & structural modification of DNA or chromatin**
   - **Transcription**
   - **Translation**
   - **Post-transcriptional modification**
   - **RNA transport**
   - **mRNA degradation**
   - **Post-translational modification**
   - **Protein-protein interaction**

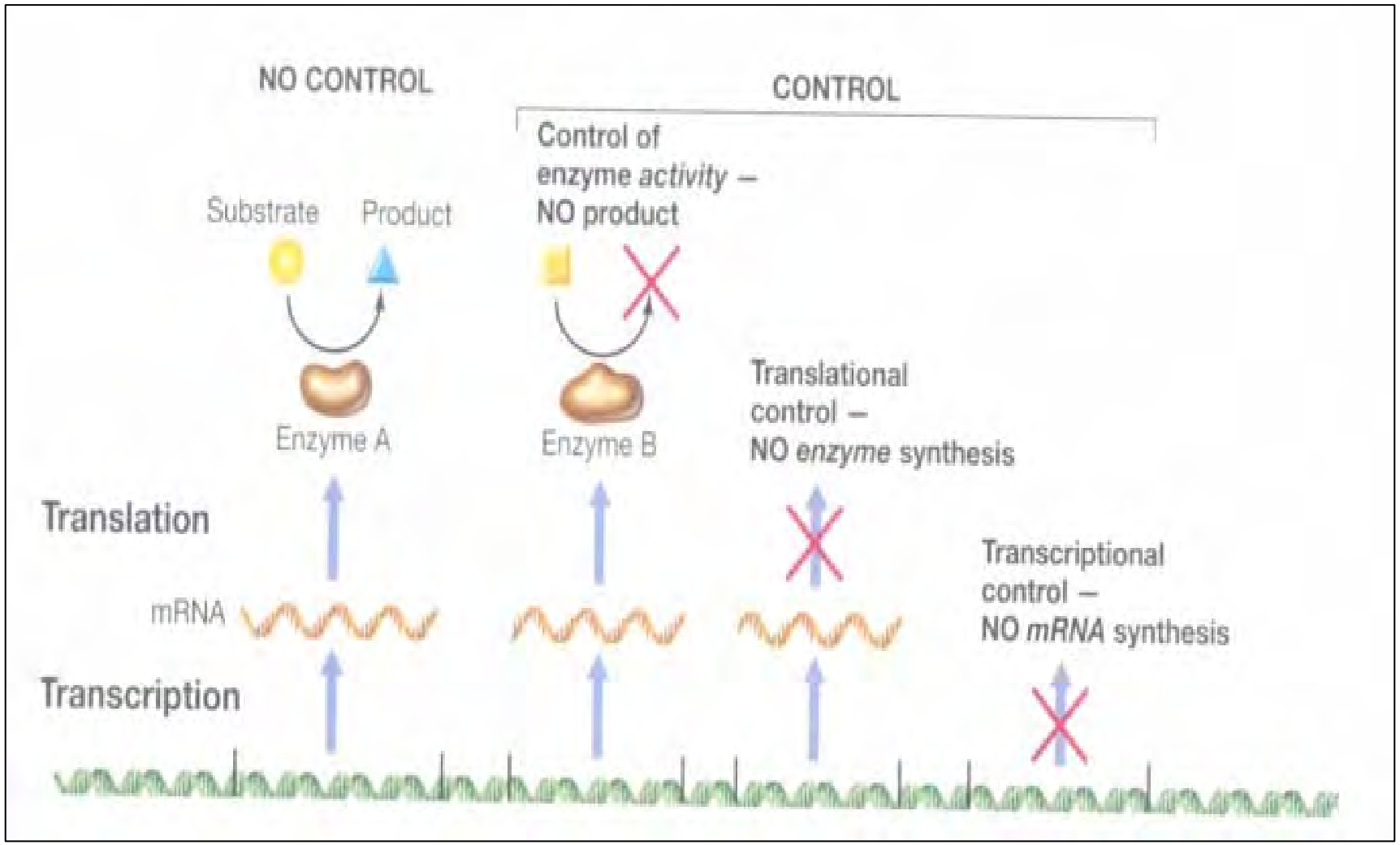
Refer to Figures 1 & 2

Gene Expression (Gene Regulation)

- **More complex in eukaryotes than prokaryotes.**

- **Major difference is due to the presence in eukaryotes of a nuclear membrane, which prevents the simultaneous transcription and translation that occurs in prokaryotes.**

- **In prokaryotes, control of transcriptional initiation is the major point of regulation, in eukaryotes the regulation of gene expression is controlled nearly equivalently from many different points**



An overview of the mechanisms that can be used in regulation.The product of gene A is an enzyme A, which in this case is synthesised constitutively and carries out its reaction. Enzyme B is also synthesised constitutively but its activity can be inhibited. The synthesis of the product of gene C can be prevented by control at the level of translation. The synthesis of the product of gene D can be prevented by control at the level of translation.

Figure 1

GENES, RNA, AND PROTEINS: FROM SIMPLICITY TO COMPLEXITY

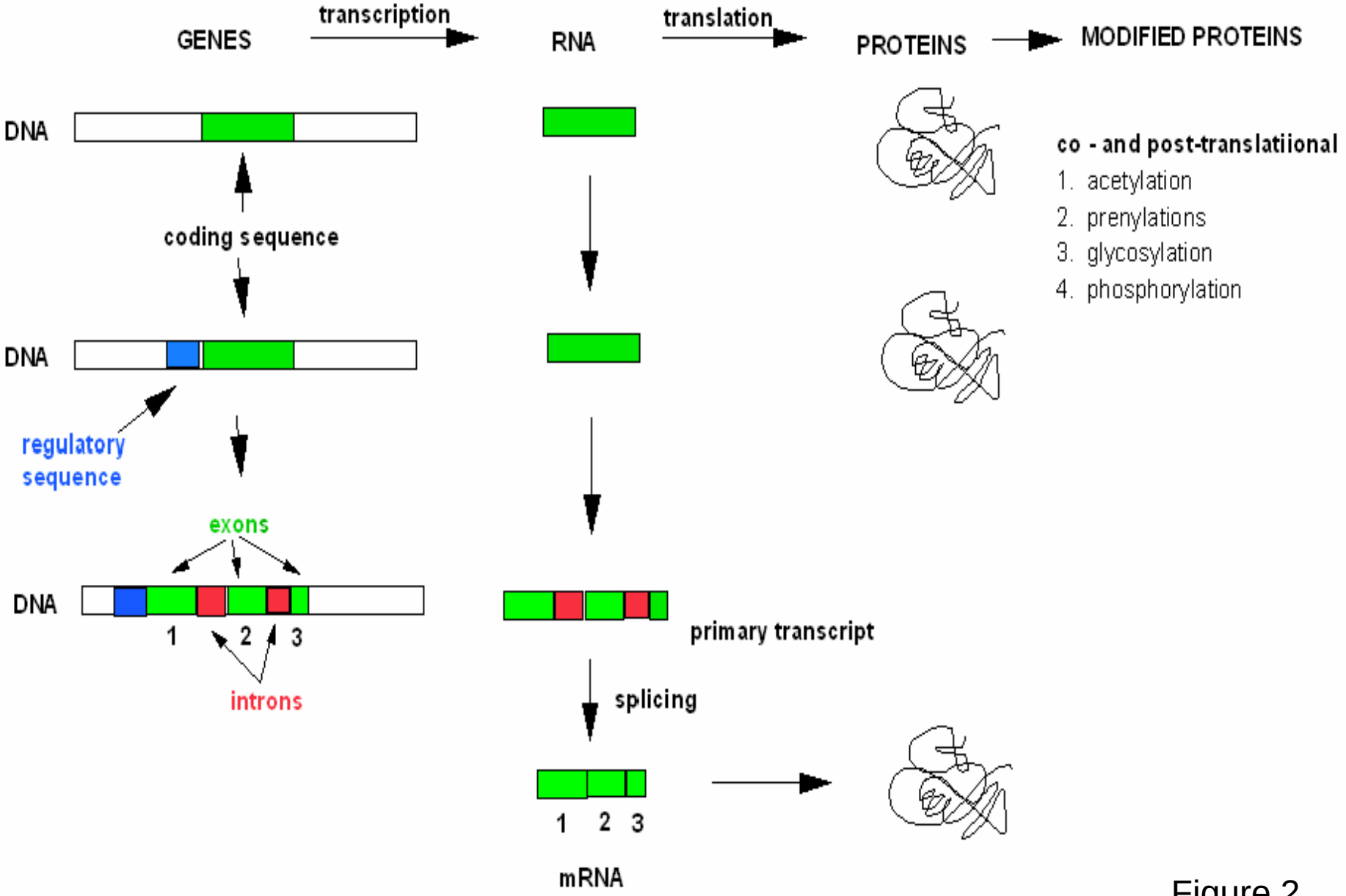


Figure 2

Why is Gene Regulation Necessary?

- The cardinal rule of existence for any organism is economy.
- By switching genes off when they are not needed, cells can prevent resources from being wasted. There should be natural selection favouring the ability to switch genes on and off.
- A typical human cell normally expresses about 3% to 5% of its genes at any given time.
- Cancer results from genes that do not turn off properly. Cancer cells have lost their ability to regulate mitosis, resulting in uncontrolled cell division.

Major Differences in Gene Organisation & Expression (Figs 2, 3, 4)

Prokaryote	Eucaryote
1. Simple regulatory process	1. Complex regulatory process; at multiple locations & levels
2. Genes are contiguous segments of DNA that are colinear with the mRNA that is translated into a protein.	2. Genes are often split- not contiguous segments of coding sequences & often interrupted by intervening sequences (introns vs exons TRANSPARENCY 6.2
3. mRNAs are often polycistronic.	3. mRNAs are monocistronic.
4. All RNA species are synthesized by a single RNA polymerase.	4. Three different RNA polymerases are responsible for the different classes of RNA molecules
5. Transcription of a gene by RNA polymerase can be regulated by at least five mechanisms: <u>Specificity Factors</u> 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.e. sigma factors used in (prokaryotic transcription). <u>Repressors</u> bind to non-coding sequences on the DNA strand that are close to or overlapping the promoter region, impeding RNA polymerase's progress along the strand, thus impeding the expression of the gene.	

Major Differences in Gene Organisation & Expression Between (cont'd)

Prokaryote	Eucaryote
Basal Factors: These 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 to by activators in order to loop the DNA bringing a specific promoter to the initiation complex.	

Major Differences in Gene Organisation & Expression Between (cont'd)

Prokaryote	Eucaryote
6. Regulation of transcription is needed for the cell to quickly adapt to the ever changing outer environment. The presence of the quantity and type of nutrients determines which genes are expressed so in order to do that genes needed to be regulated in some fashion. Repressors bind to regions called operators that are generally located downstream from and near the promoter (normally part of the transcript). Activators bind to the upstream portion of the promoter, such as the CAP region (completely upstream from the transcript). A combination of activators, repressors and rarely enhancers (in prokaryotes) determines whether a gene is transcribed.	

Major Differences in Gene Organisation & Expression Between (cont'd)

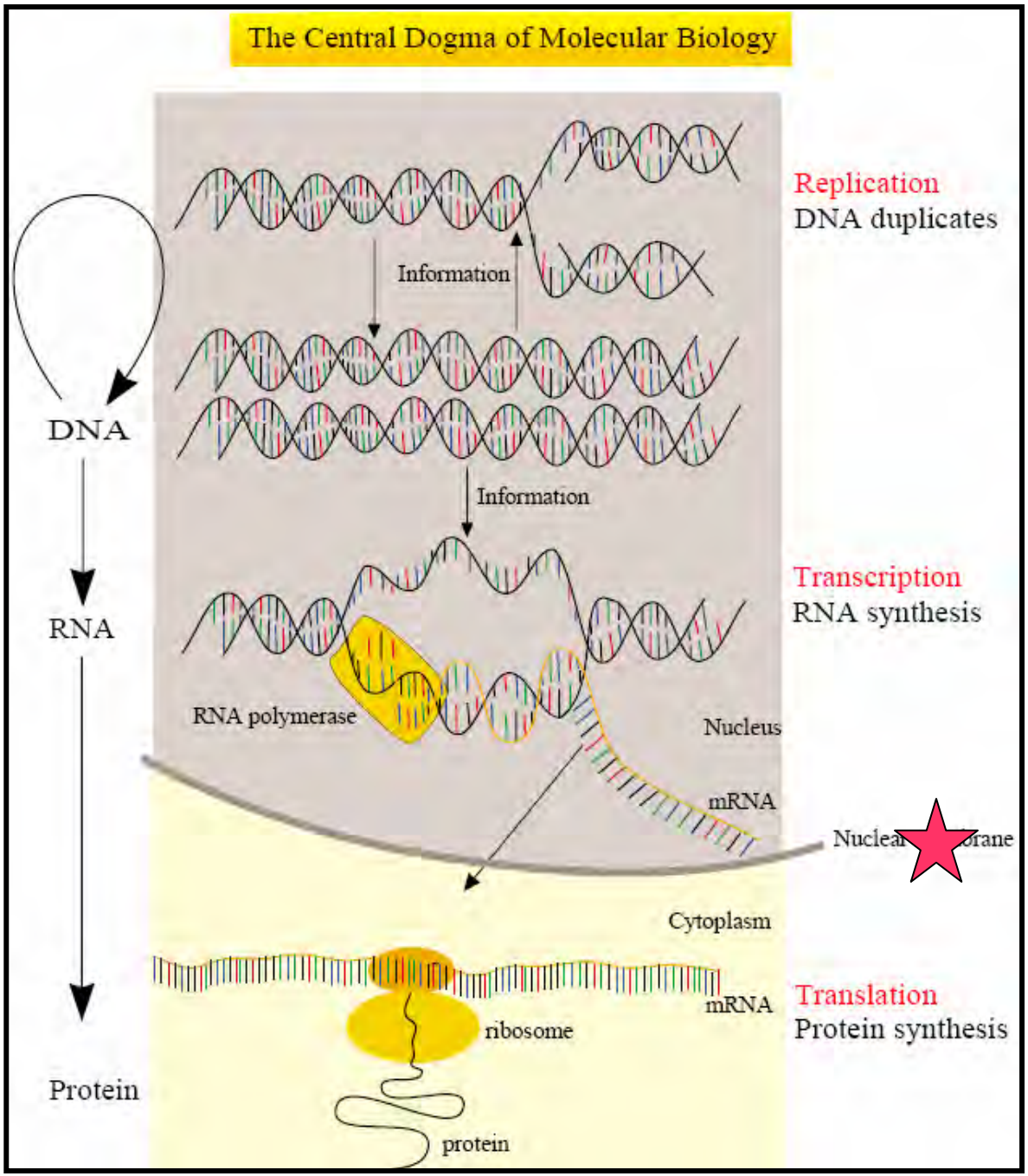
Prokaryote	Eucaryote
7. mRNA is simulataneously transcribed and translated.	7. mRNA is processed before transport to the cytoplasm where it is translated. Caps and tails are added and internal parts of the transcript are removed.
8. Operons are present- groups of genes that function to produce proteins needed by the cell. <u>Structural genes</u> code for proteins needed for the normal operation of the cell. For example, they may be proteins needed for the breakdown of sugars. The structural genes are grouped together and a single mRNA molecule is produced during their transcription. <u>Regulator genes</u> code for proteins that regulate other genes	8. Operons are absent

Some Examples

1. When *E. coli* are subjected to heat stress, the σ32 subunit of its RNA polymerase changes such that the enzyme binds to a specialized set of promoters that precede genes for heat-shock response proteins.

2. When a cell contains a surplus amount of the amino acid tryptophan, the acid binds to a specialized repressor protein (tryptophan repressor). The binding changes the structural conformity of the repressor such that it binds to the operator region for the operon that synthesizes tryptophan, preventing their expression and thus suspending production. This is a form of negative feedback.

3. In bacteria, the lac repressor protein blocks the synthesis of enzymes that digest lactose when there is no lactose to feed on. When lactose is present, it binds to the repressor, causing it to detach from the DNA strand.



Central Dogma

The Raw Facts (Far Left)

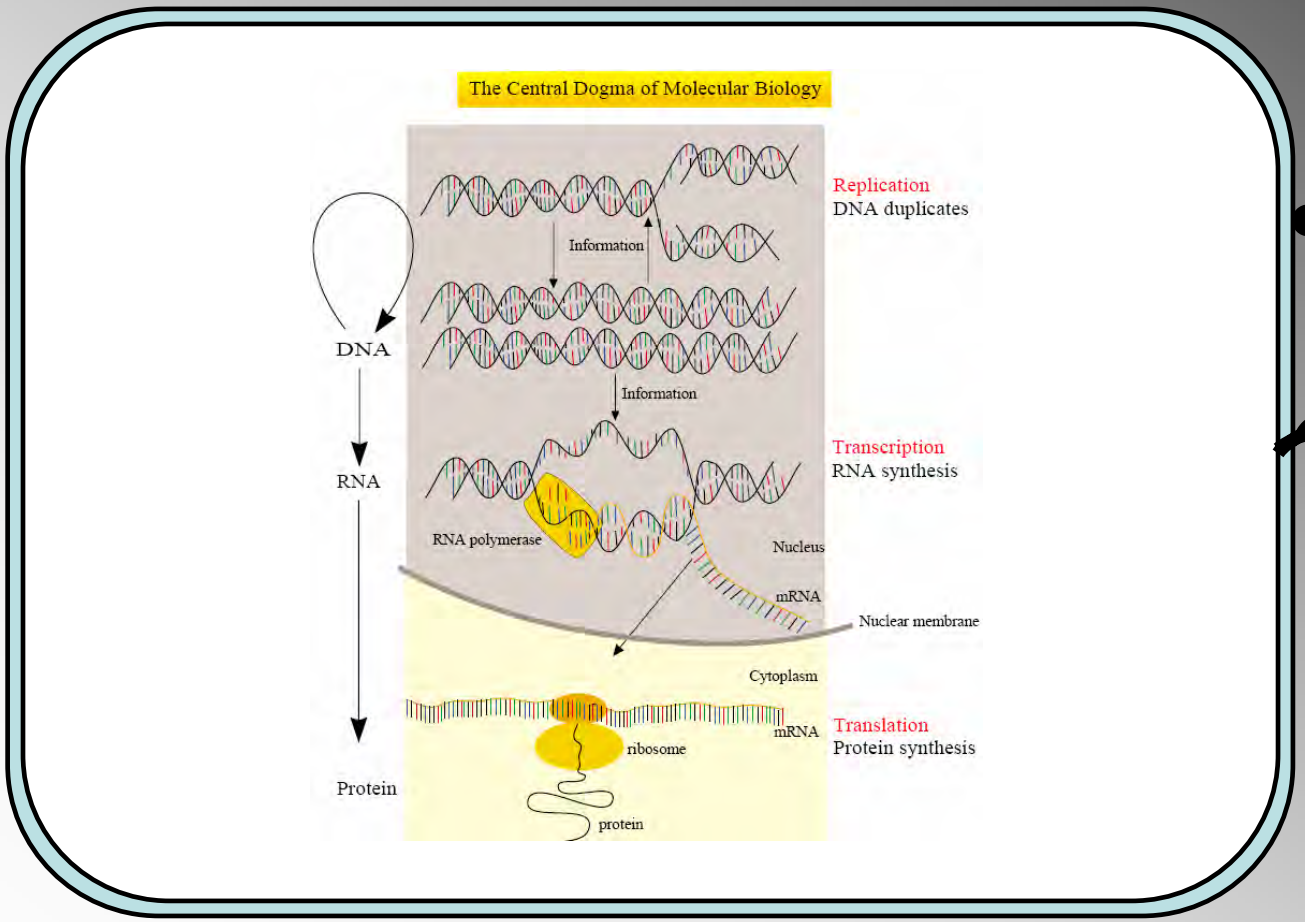
Overlay with facts on replication, transcription and translation (far right)

with

Facts on Prokaryote and Eukaryote Cell Structure (middle cartoon)

Figure 3

Spatial or density dependent sensing of environmental products (nutrients, toxins etc) – regulates gene expression leading to control of **cellular metabolism**



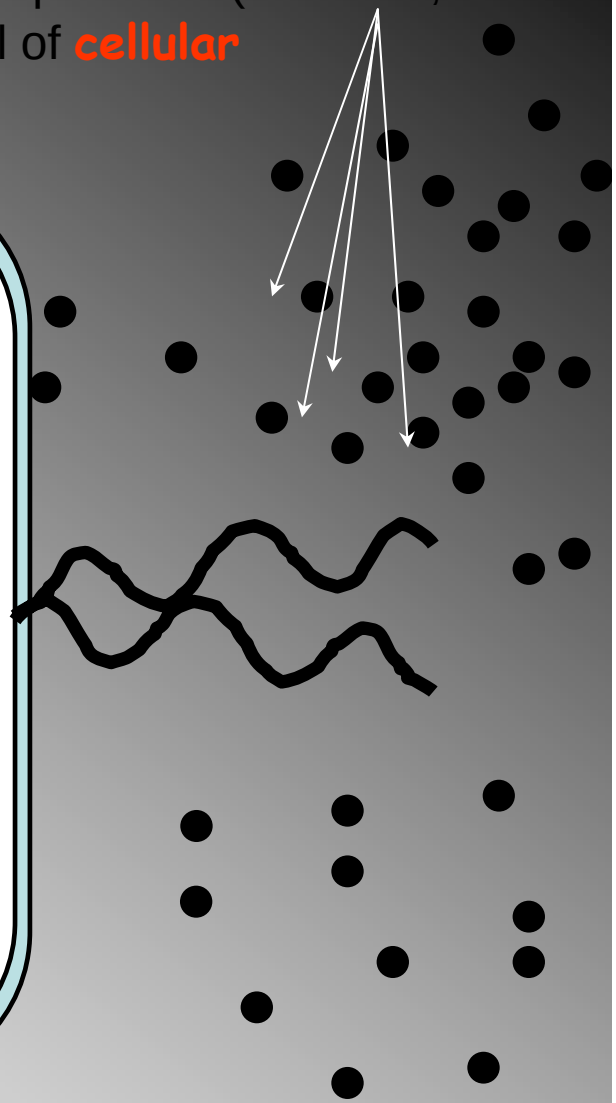


Figure 4