

D2.2 GENE EXPRESSION

Ver. 2

Guiding Questions

How is gene expression changed in a cell?

How can patterns of gene expression be conserved through inheritance?

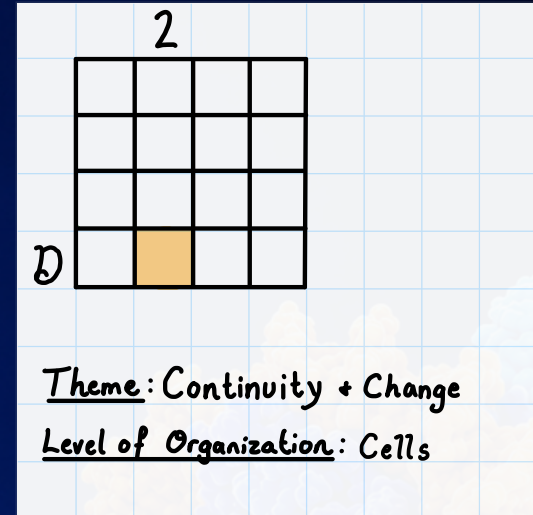
Linking Questions

What mechanisms are there for inhibition in biological systems?

In what ways does the environment stimulate diversification?

Written and drawn by:

PETER MARIER

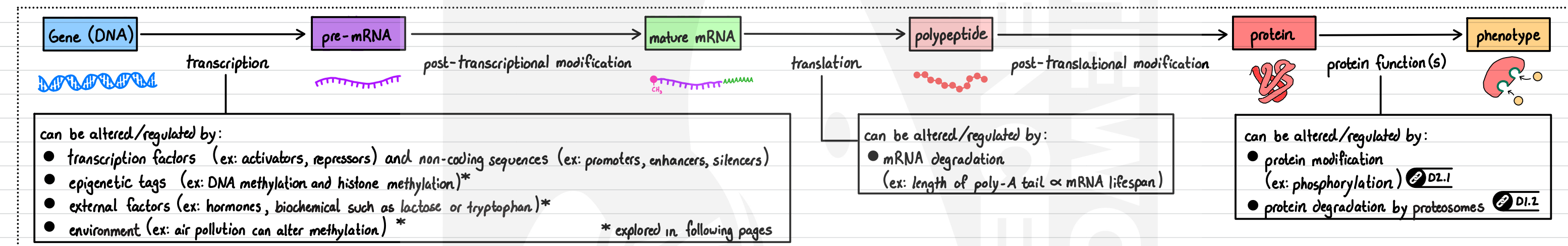
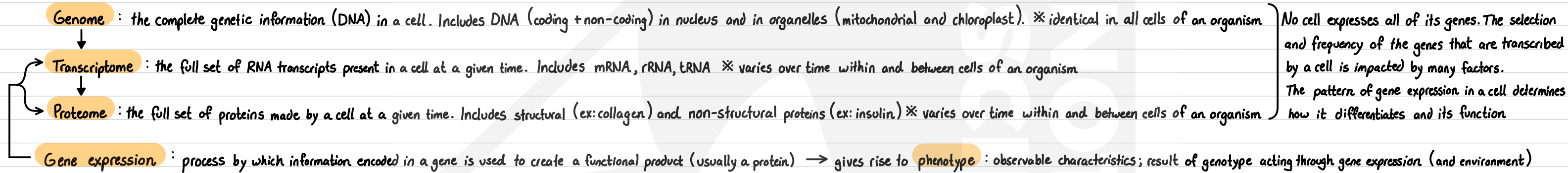


HL LEARNING OUTCOMES

D2.2.1	Gene expression as the mechanism by which information in genes has effects on the phenotype	Students should appreciate that the most common stages in this process are transcription, translation and the function of a protein product, such as an enzyme.
D2.2.2	Regulation of transcription by proteins that bind to specific base sequences in DNA	Include the role of promoters, enhancers and transcription factors.
D2.2.3	Control of the degradation of mRNA as a means of regulating translation	In human cells, mRNA may persist for time periods from minutes up to days, before being broken down by nucleases.
D2.2.4	Epigenesis as the development of patterns of differentiation in the cells of a multicellular organism	Emphasize that DNA base sequences are not altered by epigenetic changes, so phenotype but not genotype is altered.
D2.2.5	Differences between the genome, transcriptome and proteome of individual cells	No cell expresses all of its genes. The pattern of gene expression in a cell determines how it differentiates.
D2.2.6	Methylation of the promoter and histones in nucleosomes as examples of epigenetic tags	Methylation of cytosine in the DNA of a promoter represses transcription and therefore expression of the gene downstream. Methylation of amino acids in histones can cause transcription to be repressed or activated. Students are not required to know details of how this is achieved.
D2.2.7	Epigenetic inheritance through heritable changes to gene expression	Limit to the possibility of phenotypic changes in a cell or organism being passed on to daughter cells or offspring without changes in the nucleotide sequence of DNA. This can happen if epigenetic tags, such as DNA methylation or histone modification, remain in place during mitosis or meiosis.
D2.2.8	Examples of environmental effects on gene expression in cells and organisms	Include alteration of methyl tags on DNA in response to air pollution as an example.
D2.2.9	Consequences of removal of most but not all epigenetic tags from the ovum and sperm	Students can show this by outlining the epigenetic origins of phenotypic differences in tigers and ligers (lion-tiger hybrids).
D2.2.10	Monozygotic twin studies	Limit to investigating the effects of the environment on gene expression.
D2.2.11	External factors impacting the pattern of gene expression	Limit to one example of a hormone and one example of a biochemical such as lactose or tryptophan in bacteria. Students do not need to know the names or mechanisms of lac operon and/or trp operon.

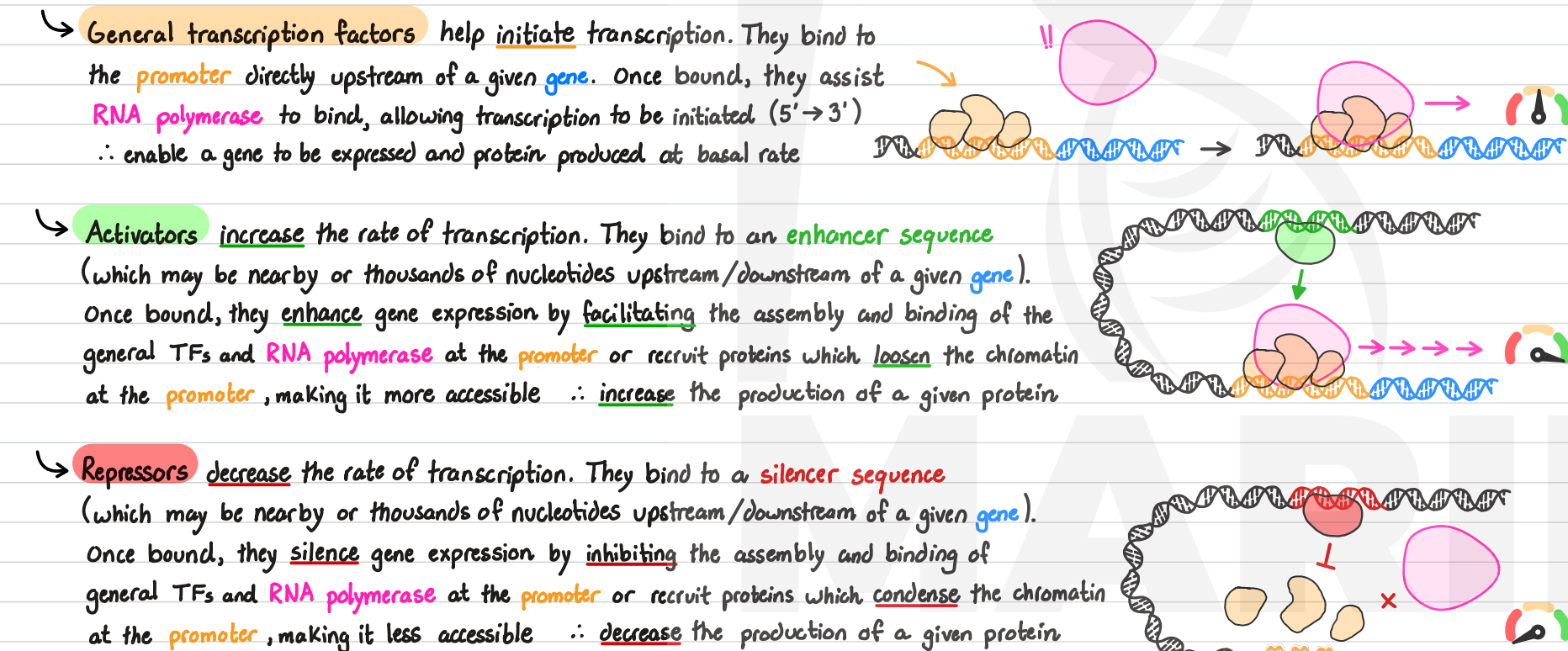
D2.2.1—Gene expression as the mechanism by which information in genes has effects on the phenotype

HL D2.2.2—Regulation of transcription by proteins that bind to specific base sequences in DNA D2.2.3—Control of the degradation of mRNA as a means of regulating translation D2.2.5—Differences between the genome, transcriptome and proteome of individual cells



Regulation of transcription by transcription factor proteins protein synthesis D1.2

Transcription factors (TF): regulatory proteins which control the rate of gene transcription by binding to specific non-coding DNA sequences



Regulation of translation by control of mRNA degradation protein synthesis D1.2

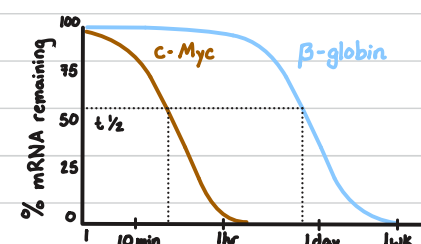
mRNA does not remain in cytoplasm indefinitely but is broken down by **nuclease enzymes** ∴ rate of degradation determines how long mRNA persists and how much it is translated/time

mature mRNA is protected from degradation by a **methylated-guanosine 'cap'** at the 5' end and a **poly-A tail** at the 3' end

nuclease enzymes first remove the **poly-A tail**, then the **5' cap**, and finally the **mRNA** is broken down into RNA nucleotides for later re-use

rate the mRNA is degraded can be controlled by:

- length of the poly-A tail added to the mRNA (longer tail = slower degradation = more protein produced)
- regulatory sequences (ex: AU rich elements in 3' UTR) bind proteins that speeds up or slows down degradation

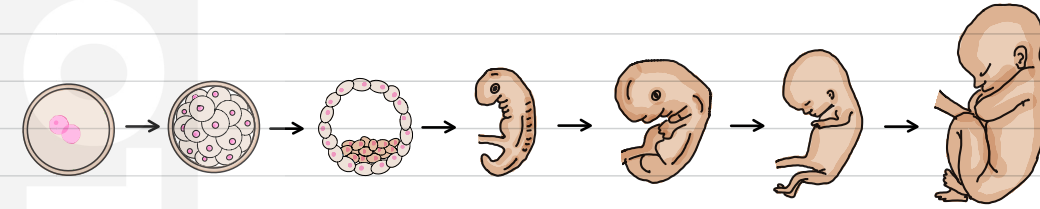


* the rate of degradation is highly variable (minutes to days), set by the mRNA sequence and cell needs ex: c-Myc mRNA has a half-life of 20min vs β -globin mRNA 16h

Epigenetics: changes in gene expression that do not involve change to the DNA nucleotide base sequence i.e. same genotype, different phenotype. Like mutations, these can be heritable but unlike mutations, may be reversible

→ these changes in gene expression are controlled by **epigenetic tags**: chemicals (such as methyl, $-CH_3$) which bind to DNA or histones → **Epigenome**: complete set of epigenetic tags in a cell or organism at a given time

→ **Epigenesis**: the development of patterns of differentiation in the cells of a multicellular organism. Through epigenetic modification, cells with identical genome can display differential gene expression and specialize. Allows undifferentiated zygotes to develop into a complex multicellular organism

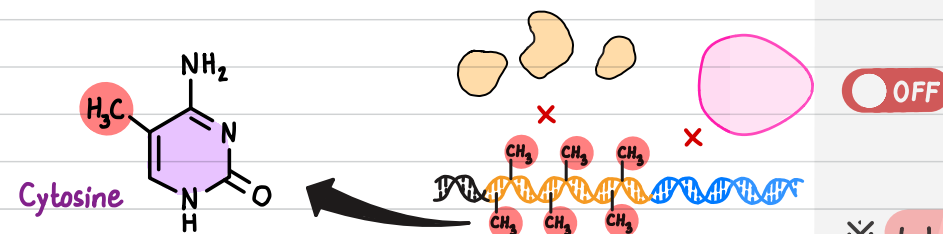


Regulation of transcription by epigenetic tags

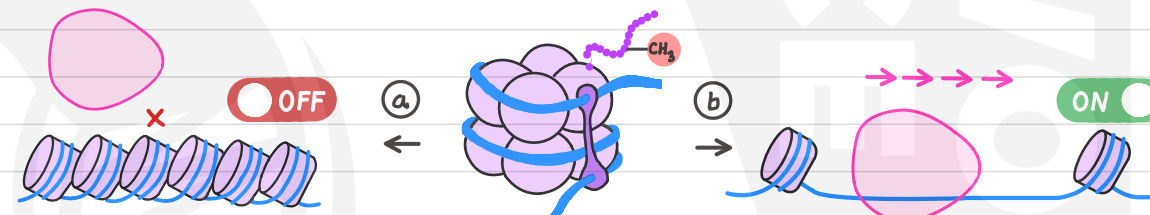
DI.3 Mutation

The addition or removal of epigenetic tags to either DNA or histones can alter how easily RNA polymerase can bind to and transcribe a particular gene, effectively switching a gene **ON** or **OFF** *extra content

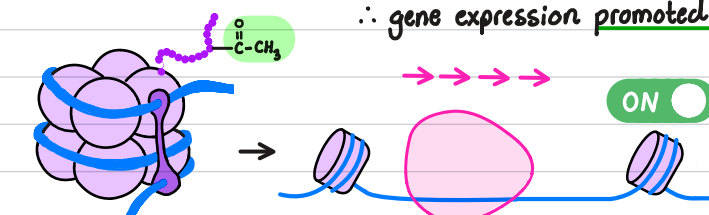
→ **DNA methylation**: the addition of **methyl** ($-CH_3$) groups to the DNA base sequence (typically **cytosine**) of the **promoter** of a **gene**. Methyl groups **prevent** transcription factors from binding and thus subsequent binding of **RNA polymerase** ∴ gene is not transcribed, gene expression **repressed**



→ **Histone methylation**: the addition of **methyl** ($-CH_3$) groups to the amino acids of **histone 'tails'** in nucleosomes. Depending on which amino acid on the histone tail is methylated, the chromatin can:
 (a) become **more condensed** and thus **inaccessible** to **RNA polymerase** ∴ gene expression **repressed**
 or (b) become **more loose** and thus **more accessible** to **RNA polymerase** ∴ gene expression **promoted**



*
 → **Histone acetylation**: the addition of **acetyl** (CH_3CO-) groups to the amino acids of **histone 'tails'** in nucleosomes. Results in looser chromatin and thus gene is **more accessible** to **RNA polymerase** ∴ gene expression **promoted**

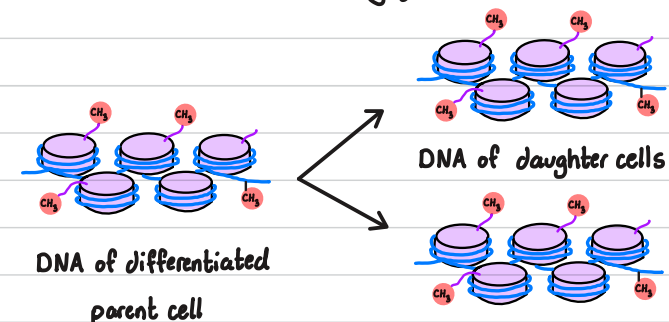


⊗ **heterochromatin**: tightly-packed (condensed) chromatin; genes here largely **not expressed** **euchromatin**: loosely-packed (decondensed) chromatin; genes here largely **expressed**

Epigenetic inheritance: the passing of epigenetic tags (on DNA and/or histones) from one cell or organism to daughter cells or offspring - without changes to the DNA base sequence

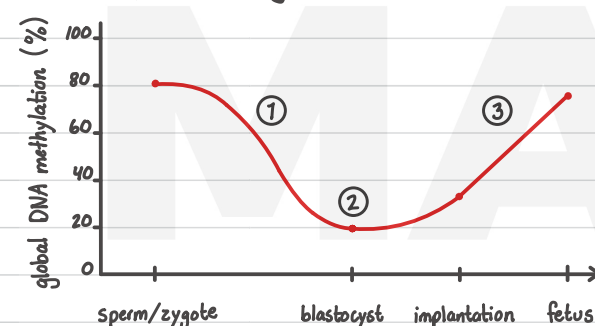
Cell → cell epigenetic inheritance (mitosis)

When a cell specializes, it accumulates epigenetic tags which characterize their gene expression. When this cell undergoes DNA replication prior to mitosis, tags are copied to the new daughter strands ∴ daughter cells inherit tags and pattern of gene expression
 → allows specialized cells to maintain differentiation (i.e. their 'identity') during growth



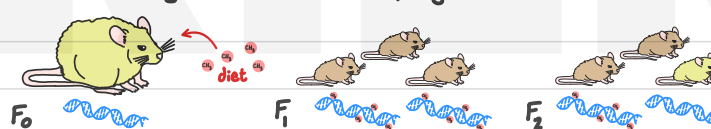
Reprogramming (gamete and zygote formation)

① First during meiosis and then shortly after fertilization, most pre-existing epigenetic tags are removed from the DNA of the sperm and ovum. ② This returns the early embryo to a mostly undifferentiated 'blank slate' → allows the embryo to ③ form new epigenetic tags and differentiate into all the new specialized cells required during embryonic development



Parent → offspring epigenetic inheritance (meiosis)

A small proportion of epigenetic tags are not removed from the sperm/ovum during reprogramming. Retained tags stay in gametes through meiosis and fertilization.
 → allows for possible transgenerational epigenetic inheritance where phenotypic changes in an organism are passed on to their offspring
 ex: in Agouti mice, an unmethylated **agouti gene** → **yellow, obese** but methylated → **brown, healthy**. When yellow mother fed **methyl-rich diet** in pregnancy, methyl tags are added to **agouti gene** in offspring → pups brown, healthy despite identical DNA to her.
 In later generations some offspring inherit these tags



Example of genomic imprinting in ligers and tigers

Genomic imprinting: a gene is expressed from only one parental copy. Set by epigenetic tags in the gametes that survive reprogramming.

- lions produce sperm with imprinted **genes** that **promote growth**
- lionesses produce ova with imprinted **genes** that **repress growth**
- ∴ growth promotion and repression cancel each other out } offspring same size as parents
- tigers do not imprint either growth genes

Liger = male lion + female tiger

Lion sperm is imprinted for **increased growth** and tiger ovum is non-imprinted
 → very large offspring

Tigon = male tiger + female lion

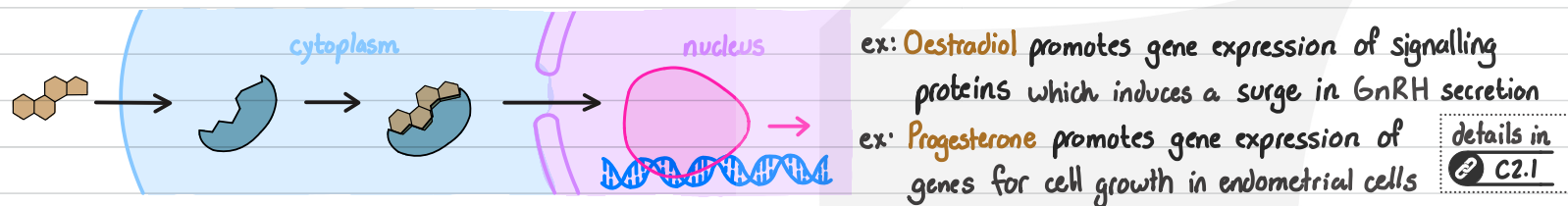
Tiger sperm is non-imprinted and lion ovum is imprinted for **reduced growth**
 → small offspring

Gene expression can be regulated and impacted by **external factors** i.e. environmental or bodily signals ex: hormones, biochemicals, pollutants, diet, etc.

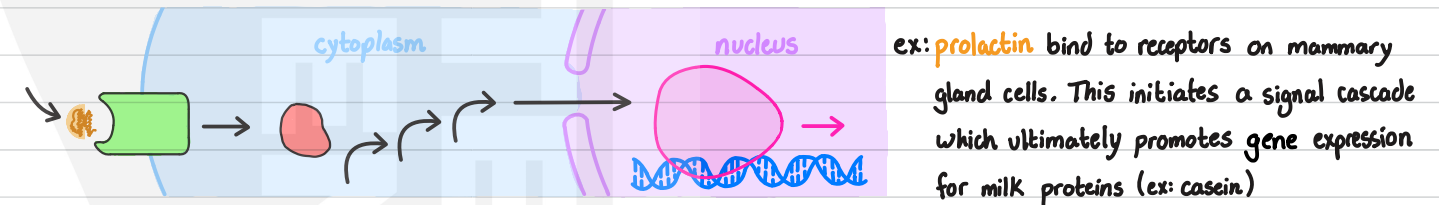


↳ **hormone**: Chemical messenger (signalling molecule) that is secreted by an endocrine gland (or specialized cell) into the bloodstream where it is transported around the organism. Hormones bind to specific receptors in order to induce a response. The hormone's mechanism of action is dependent on its chemical properties:

- **Hydrophobic hormones** (typically steroids) freely pass into target cells and bind to a specific **intracellular receptor**. The receptor-hormone complex binds to **DNA** at a specific region, acting as a transcription factor to alter gene expression



- **Hydrophilic hormones** (typically peptides/proteins) bind to **transmembrane receptors** on target cells. The binding activates intracellular **second messengers** which via signal transduction can alter gene expression



↳ the concentration of certain biochemicals (in the environment or the cell) can impact gene expression as a means of metabolic regulation - switching genes on/off to match the cell's needs. Both examples occur in the bacterium *E. coli*.

- **lactose** (a sugar) is a food source, but *E. coli* must produce lactose-digesting enzymes to utilize it metabolically. The necessary genes are clustered together (the **lac operon**)



∴ the mechanism is **inducible** - substance (lactose) switches its breakdown genes **ON** - made only when needed

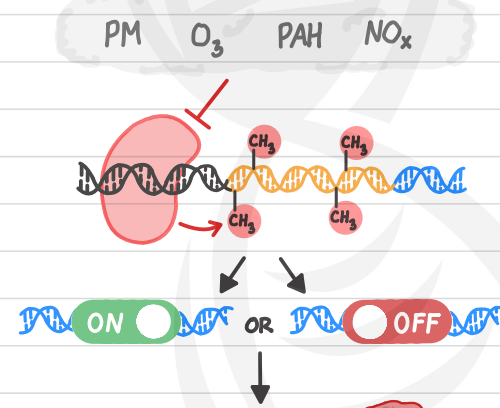
- **tryptophan** (amino acid) can be made by *E. coli* using tryptophan-synthesizing enzymes to utilize it metabolically. The necessary genes are clustered together (the **trp operon**)



∴ mechanism is **repressible** - product (tryptophan) switches its synthesis genes **OFF** - stopped when not needed

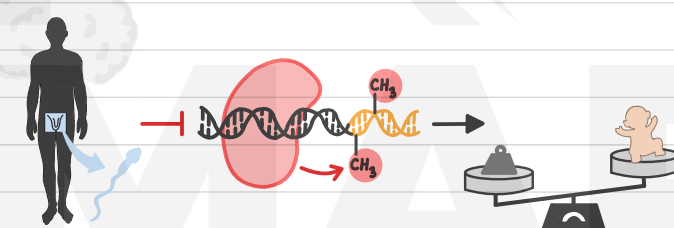
Exposure to air pollution can alter gene expression by altering methyl tags on DNA

- ↳ Particulate matter, ozone, nitrogen oxides, polycyclic aromatic hydrocarbons - PAH can alter the activity of the enzyme **DNMT (DNA methyltransferase)** which alters DNA methylation ∴ pattern of gene expression is impacted



- ↳ In general, methylation is decreased across the genome (although some areas increase), specifically in immunoregulatory genes. This leads to an increase in inflammation and altered immune response which can result in cardiopulmonary complications such as high blood pressure and asthma.

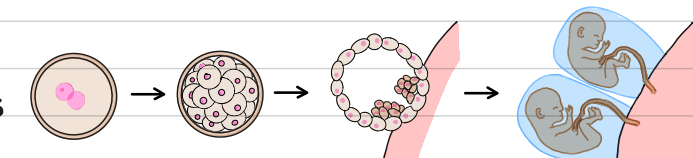
- ↳ Air pollution in men can also alter methylation in **sperm DNA** (ex: imprinted IGF2R growth gene). Study found that men exposed to air pollution had offspring with lower birthweights. ∴ environmental effect on parent can be inherited



- ↳ These changes are reversible (unlike a mutation). A diet rich in methyl donors (ex: folate, B₁₂, choline) supports normal methylation, and lifestyle factors (ex: exercise) can also influence it.

✗ other environmental factors (diet, temperature, stress, etc.) can also alter epigenome and gene expression

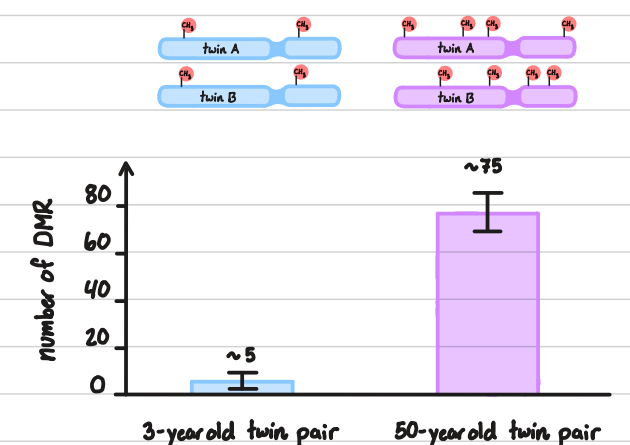
Monozygotic (MZ/"identical") twins form when an early embryo splits into two, forming natural genetic clones with identical genomes



- ↳ As MZ twins share the same genome, any differences in their phenotype (or disease susceptibility) must be caused by the environment (via epigenetics) and not their genes ∴ MZ twins are the ideal "natural experiment" to separate the effects of genes (nature) from the environment (nurture) as the genotype is controlled

- ↳ MZ twin studies identify **Differentially Methylated Regions (DMR)** between the two twins - regions in DNA where methylation levels differ between them - as these epigenetic differences (and gene expression) can only be due to differences in their environment

- Fraga et al. 2005 studied 40 pairs of MZ twins, aged 3-74. For each pair they compared the two siblings' epigenomes (ex: DNA methylation and histone tags) as well as environmental differences gathered from lifestyle questionnaires
- Twins are epigenetically almost identical early in life but older pairs showed large differences in epigenetic tags. Pairs who had lived apart or had more different lifestyles differed the most
- ∴ epigenetic differences accumulate over a lifetime because of differing environments resulting in differences in gene expression

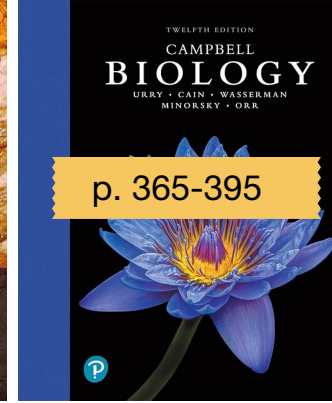
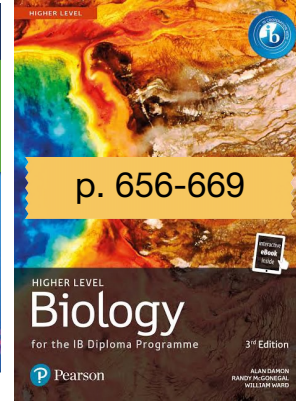
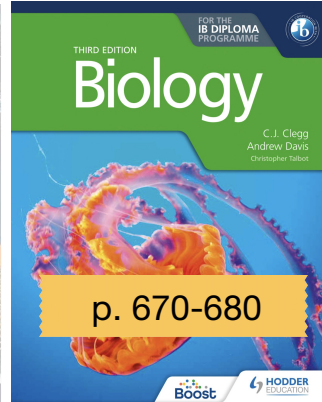
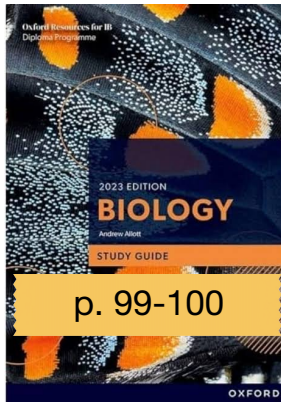
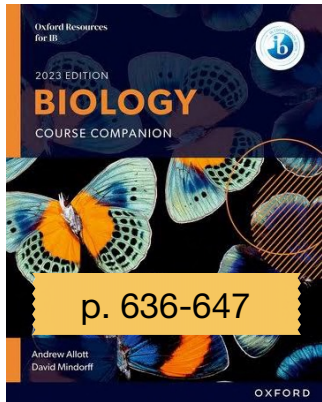


Resource Links

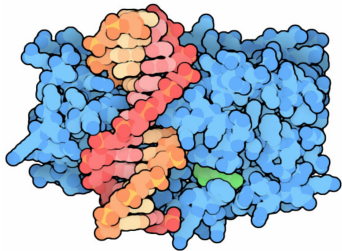
each resource is hyperlinked



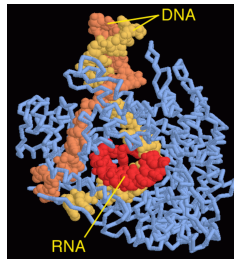
Textbooks



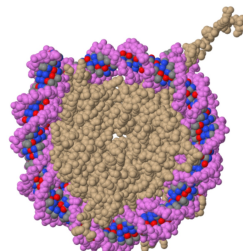
3D models



DNA Methyltransferases

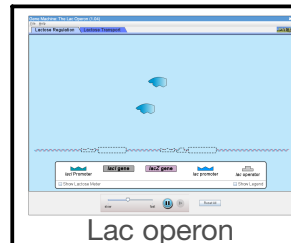
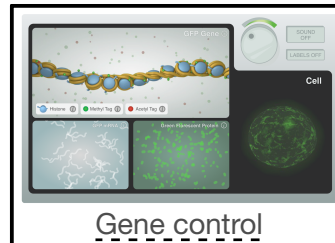
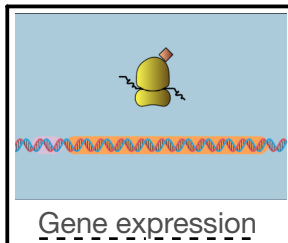
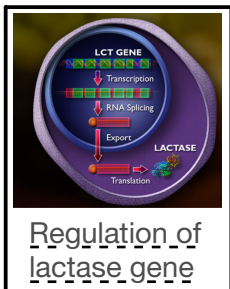


RNA polymerase



Nucleosome

Simulators / Interactives



Articles

Cheng et al. (2023). Alterations in sperm DNA methylation may as a mediator of paternal air pollution exposure and offspring birth outcomes: Insight from a birth cohort study. *Environmental Research*, 244, 117941. <https://doi.org/10.1016/j.envres.2023.117941>

Fraga, et al. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences*, 102(30), 10604–10609. <https://doi.org/10.1073/pnas.0500398102>

Micheu et al. (2020). From air pollution to cardiovascular diseases: the emerging role of epigenetics. *Molecular Biology Reports*, 47(7), 5559–5567. <https://doi.org/10.1007/s11033-020-05570-9>

Waterland, R. A., & Jirtle, R. L. (2003). Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Molecular and Cellular Biology*, 23(15), 5293–5300. <https://doi.org/10.1128/mcb.23.15.5293-5300.2003>

Weaver, I. C. G. et al. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, 7(8), 847–854. <https://doi.org/10.1038/nn1276>

Yamada, T., Nagahama, M., & Akimitsu, N. (2018). Interplay between Transcription and RNA Degradation. In *InTech eBooks*. <https://doi.org/10.5772/intechopen.71862>