Lecture 13 – How Genes Are Controlled

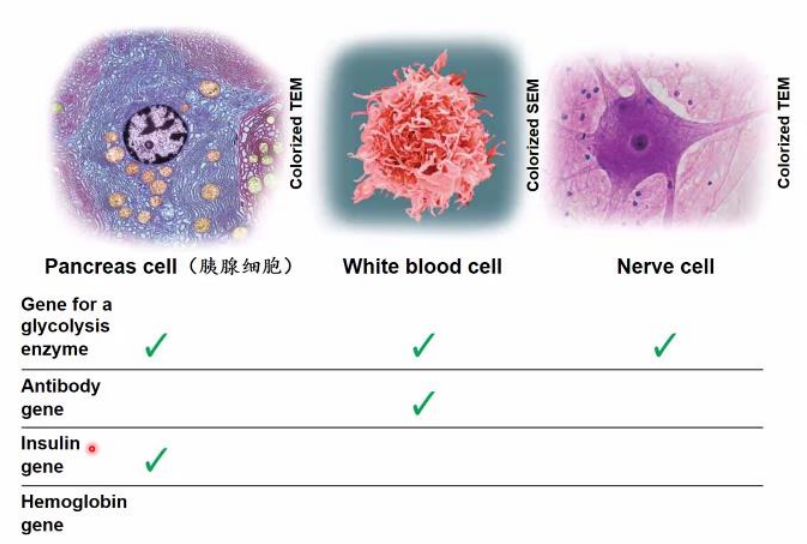
Why panda eat bamboo?

➔ From evolution, it's hard to find meat, so panda change their diet into eating bamboo. The gene umami receptor, e.g. from monosodium glutamate (MSG) are not expressed in panda (turned off).

e.g., neuron and liver cells share the same genome, but the structure is different because they express many different RNAs and proteins.

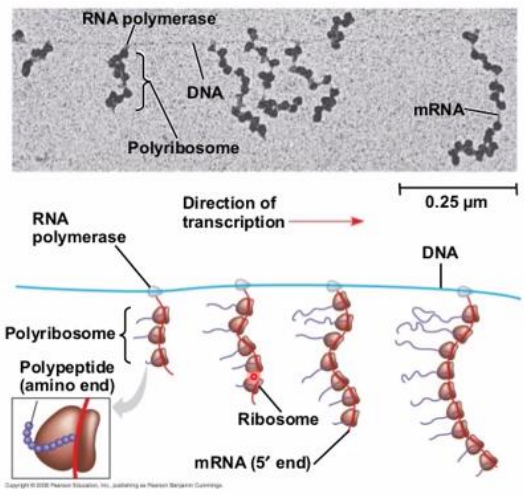
Control of gene expression

DNA – RNA – Protein (central dogma)



In prokaryotic organisms, RNA transcription and protein formation occur almost simultaneously, gene expression is regulated primarily at the transcriptional level. However, in eukaryotic cell, the gene expression is regulated at many levels (pre-transcriptional, transcriptional, post-transcriptional, translational, post-translational)

Differences in the Regulation of Gene Expression of Prokaryotic and Eukaryotic Organisms	
Prokaryotic organisms	Eukaryotic organisms
Lack nucleus	Contain nucleus
DNA is found in the cytoplasm	DNA is confined to the nuclear compartment
RNA transcription and protein formation occur almost simultaneously	RNA transcription occurs prior to protein formation, and it takes place in the nucleus. Translation of RNA to protein occurs in the cytoplasm.
Gene expression is regulated primarily at the transcriptional level	Gene expression is regulated at many levels (pretranscriptional, transcriptional, post-transcriptional, translational, and post-translational)



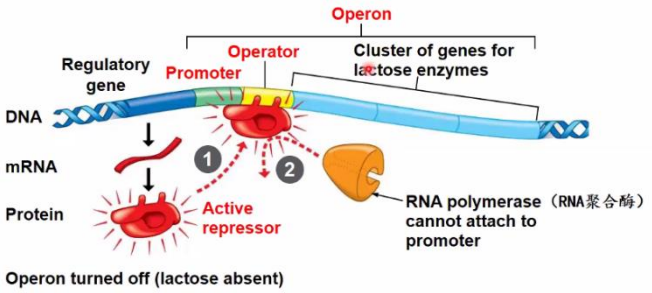
Gene regulation in prokaryotic cells

Natural selection favoured bacteria that express only genes whose products are needed by the cell.

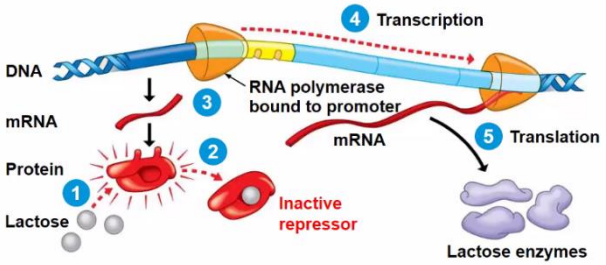
e.g., E. coli, when there are a lot of lactose in intestine (after drinking milk), the bacteria will turn on the lactose enzyme and absorb it until it's gone, and the gene is turned off

Gene regulation:

1. Proteins interact with DNA turn prokaryotic genes on or off in response to environmental changes.
2. DNA sequence that control them is called an **operon** [operator + promoter + gene], a cluster of genes with related function along with the control sequences (in this case, lactose *lac operon* coding for 3 lactose enzyme).
   Operator is a single "on-off" switch
   Promoter is the place for RNA polymerase to bind and transcript RNA
   Regulatory gene coding for repressor protein. When there's no lactose, the repressor will be activated and bind with the operator. If there's lactose in the environment, the repressor will bind with lactose and become inactive and thus can't bind to the operator.



Operon turned off (lactose absent)

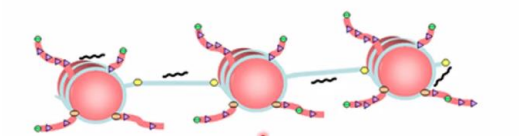


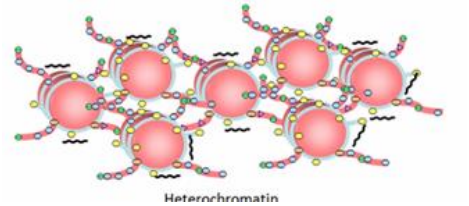
Operon turned on (lactose inactivates repressor)

   Addition of lactose will increase the enzyme thousandfold in just 15 minutes (very efficient)
   Gene regulation helps *E. coli* efficiently use the available resources, or utilize different nutrients.

Gene regulation in eukaryotic cells

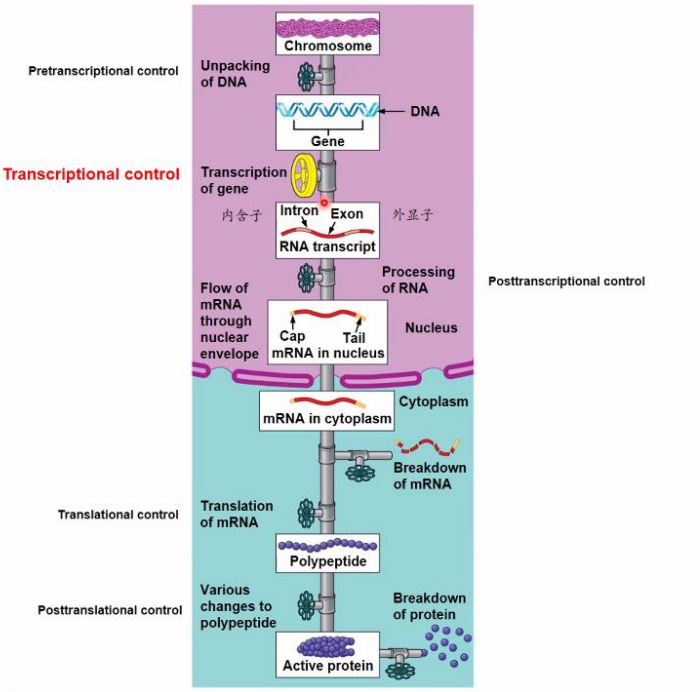
1) **Pre-transcriptional**
   DNA packing


Euchromatin, gene-rich and transcriptionally active

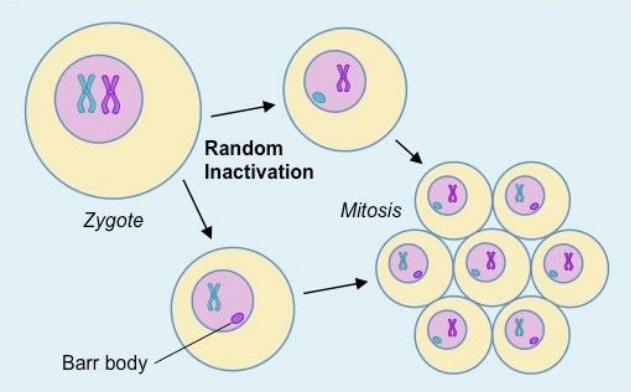


Heterochromatin, gene-poor and inactive

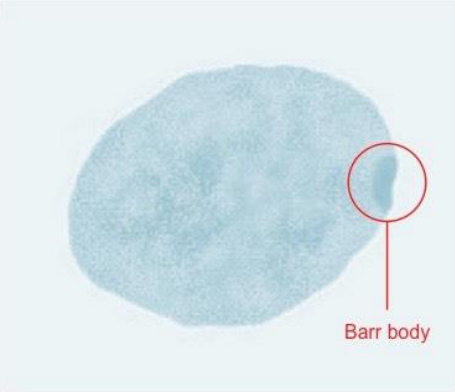
   Cell use DNA packing for long-term inactivation of genes (heterochromatin), e.g., Barr body, and tortoiseshell cats



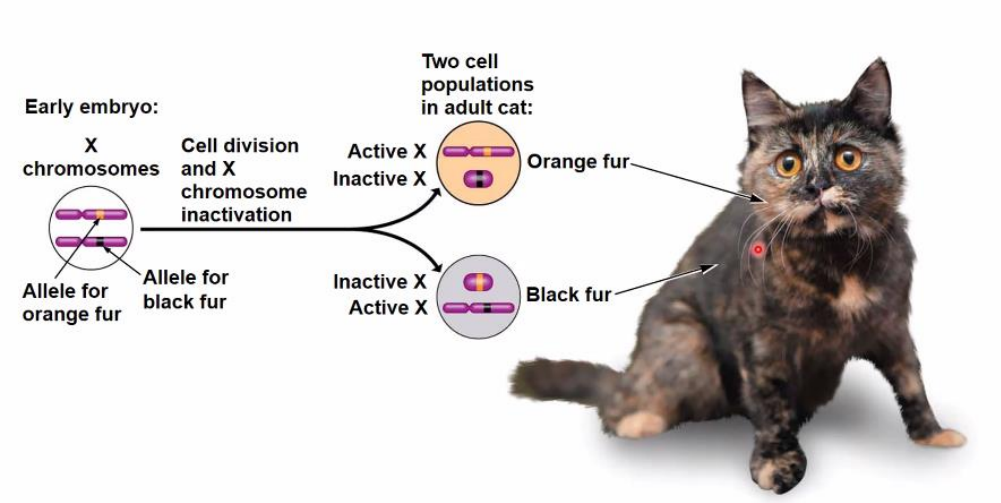
In human there's 22 pairs autosomes and 1 pair of gonosome (XX female, XY male)
The X inactivation occurred in embryonic cell, after division one X chromosome become barr body (random inactivation)



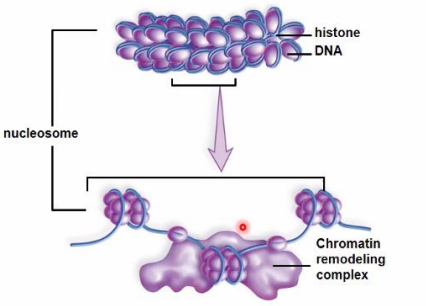
Summary of the Process of X-Inactivation



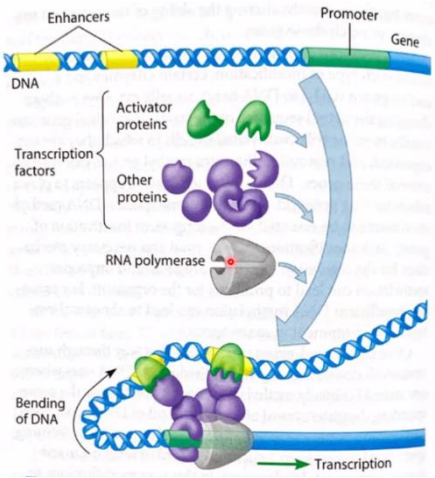
Barr Body in a Human Nucleus



Case: Red-green color blindness, results from cone cells' DNA damage. Recessive disease, B (normal), b (abnormal), located at x chromosome. X^By normal, X^by color blind, X^BX^B normal carrier, X^bX^b color blind, X^BX^b not perfectly normal, because in embryonic cell, one X will be randomly inactivated, some cells will have X^B o (normal) and X^b o (abnormal) (o = Barr body)



Euchromatin is a loosely packed areas of active genes, and still needs to be unpacked before it can be transcribed.
Chromatin remodelin complex push aside the nucleosome

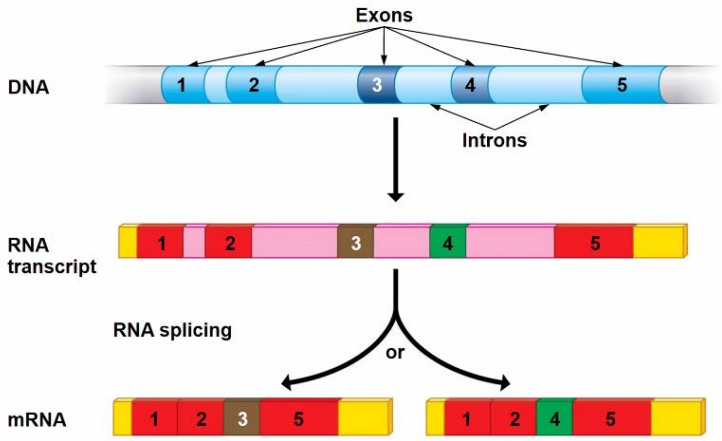


2) The Initiation of Transcription

RNA polymerase can bind with promoter with the help of other proteins (general transcription factors).
Activator protein will bind with enhancers and bend the DNA, bring the activator protein closer with the **promoter**.
Activator stimulate the transcription factors, making the RNA bind with promoter.
Activator (pr) + Enhancer (seq) → activate transcription
Represor (pr) + Silencer (seq) → avoid transcription

3) **RNA processing**

RNA processing includes addition of a cap and tail, remove introns splicing extrons
Alternative RNA splicing is used to make variants of protein



e.g., dopamine receptor-1, and dopamine receptor-2 acre quite similar, they are derived from the same genes but different RNA splices (different in one protein domain)

Components involved in gene regulation

- Promoter: RNA polymerase binding site; initiation of transcription.
- Operator: Repressor binding site; binded → off, unbinded → on.
- Operon: Promoter + Operator + Gene
- Activator: Bind to DNA (upstream/downstream); make RNA polymerase easier to bind.
- Repressor: bind to operator and silencer to turn off gene.
- Enhancer: protein bind to allow DNA bend; enhance transcription.
- Silencer: Repressor binding region; turn off gene expression.

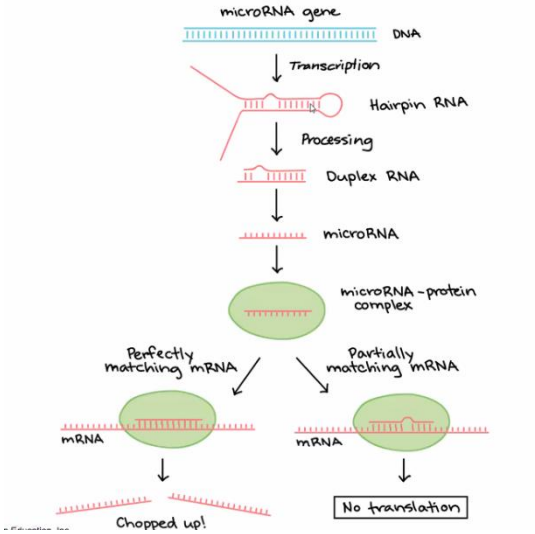
*upstream = located before the trasncripted DNA / *downstream = located after the transcripted DNA
*operator is located near with promoter. Repressor can bind with operator and silencer

4) **RNA Processing and Breakdown**

Start breakdown A' tail, and then start again from the G'

The exonuclease will chew down the nucleic acid from the two ends and attack the poly A tail first. It extend the life span of mRNA.

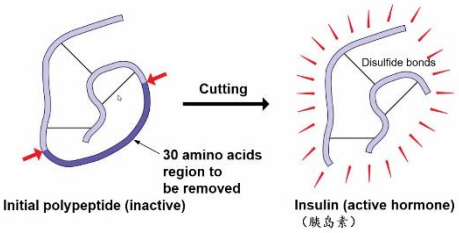
MicroRNA is used to check the gene expression, see the function of the gene. (about 20 nucleotides long, regulate half of human genes). MicroRNA = RNA interference, inject microRNA into a cell to turn off gene expression



5) **Protein Activation and Breakdown**

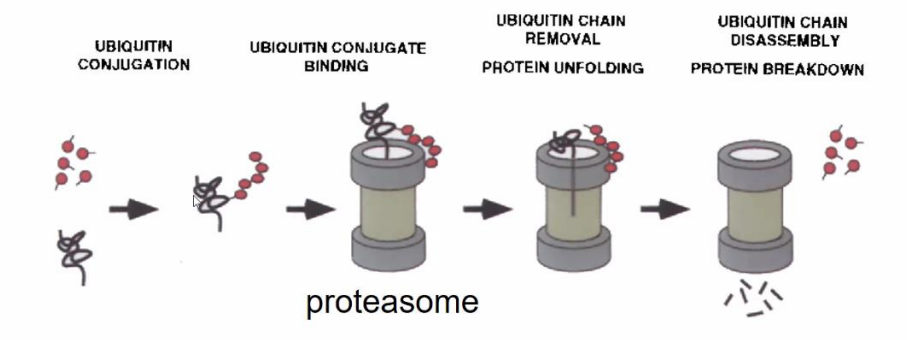
Maturation of Proteins

Protein need to be proceed further, (e.g., insulin need to be cut (30 amino acids are removed).



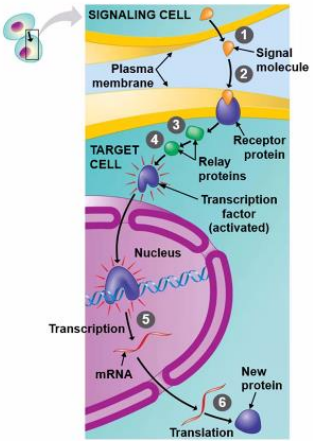
Selective protein degradation,

Junk protein will be taken to proteasome (tagged by ubiquitin)



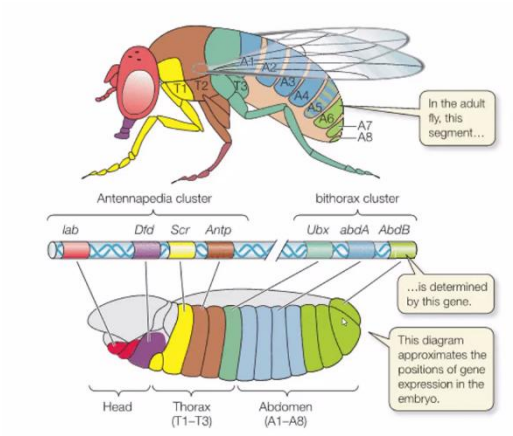
Cell Signaling

Induce the initiation of transcription of the gene. First signaling cell secretes the signal molecule, bind with a specific receptor protein embedded in the target cell's plasma. It activates I1 (enzympe). I1 = *Kinase* adds phosphate group to I2, producing I2. Then the signal is amplified. The last relay molecule activates a transcription factor that triggers the transcription of a specific gene, creating a protein that can perform the function originally called for by the signal.



Homeotic Genes (master gene)

Regulate groups of other genes that determine what body parts will develop in which locations (regulate the development of anatomical structures). It is master gene encodes for factor that regulates batteries of other genes that determine the anatomy of the body



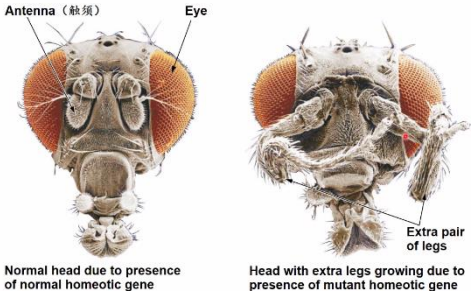
e.g., cell on the head turn on the Anty gene, will grow an extra leg on the head

Same structure → same set of homeotic gene: proof of same common ancestor

DNA Microarrays

Determining gene expression

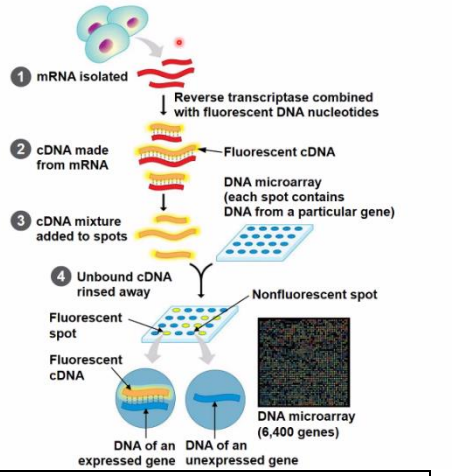
DNA Hybridization:



e.g., Cancerous breast cell, normal breast cell

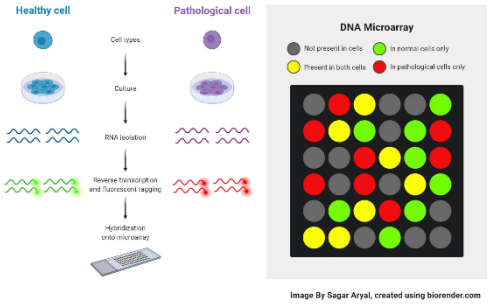
gene1: c > n, gene 2: n > c, gene 3: ~ gene 4:no expression in both

1. Isolate the mRNA from two kind of cells,
2. Take off the mRNA from the cell sample, add structure of T base to ????



Cancerous cell				Normal breast cell			
Gene 1	Gene 2	Gene 3	Gene 4	Gene 1	Gene 2	Gene 3	Gene 4
+++++	+	+++	-	+++	+++	+++	-

mRNA is not stable, so we use reverse transcription (reverse transcriptase) make the cDNA (complementary DNA). Use fluorescent DNA nucleotide to tag the DNA. Red color for cancerous cell and green color for normal cell, then remove the mRNA



Cancerous cell				Normal breast cell			
Gene 1	Gene 2	Gene 3	Gene 4	Gene 1	Gene 2	Gene 3	Gene 4
+++++	+	+++	-	+++	+++	+++	-

Mix those samples together to generate the microarray

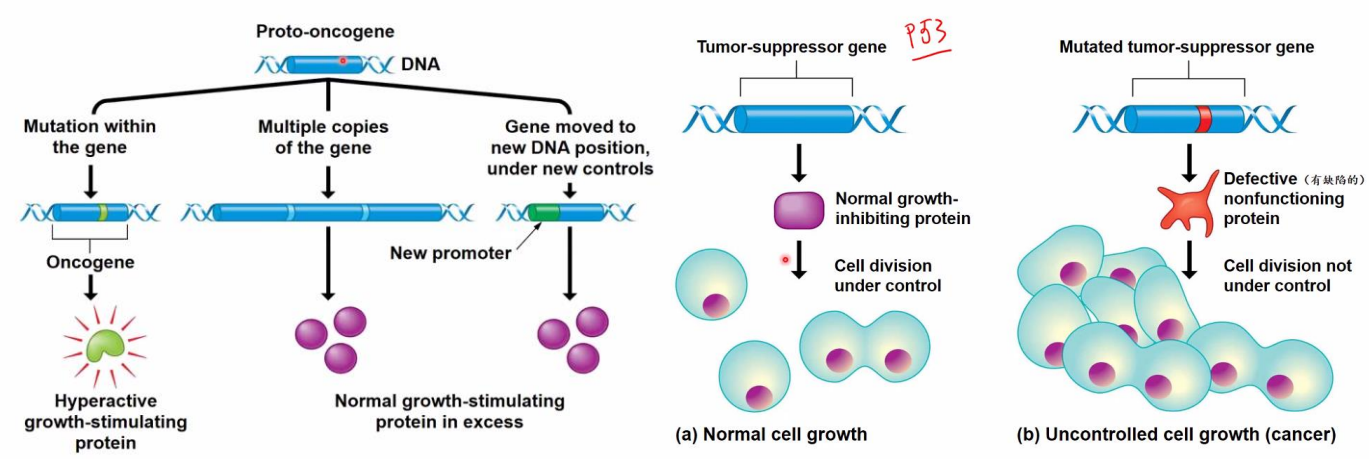
Gene 1	Gene 2	Gene 3	Gene 4
Red	**Green**	**Yellow**	**Black**

Cell Division

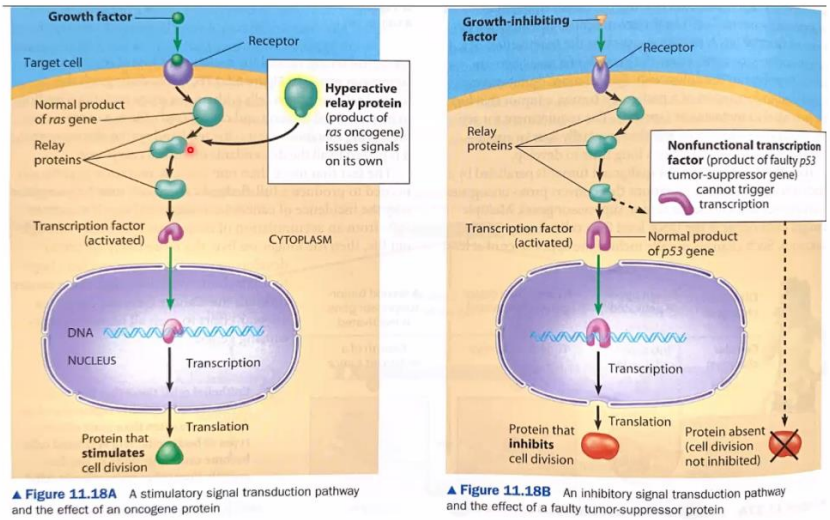
Genetic Basis of Cancer

- **Pro-oncogenes** encode for proteins that stimulate cell cycle mutate to become oncogene that become oncoprotein. It often induces uncontrolled cell proliferation
- **Tumour suppressor genes** stop cell cycle and promote apoptosis, e.g., p53 gene

These two genes control the cell division. If there's any mutation, pro-oncogenes become oncogenes (unlimited cell division)

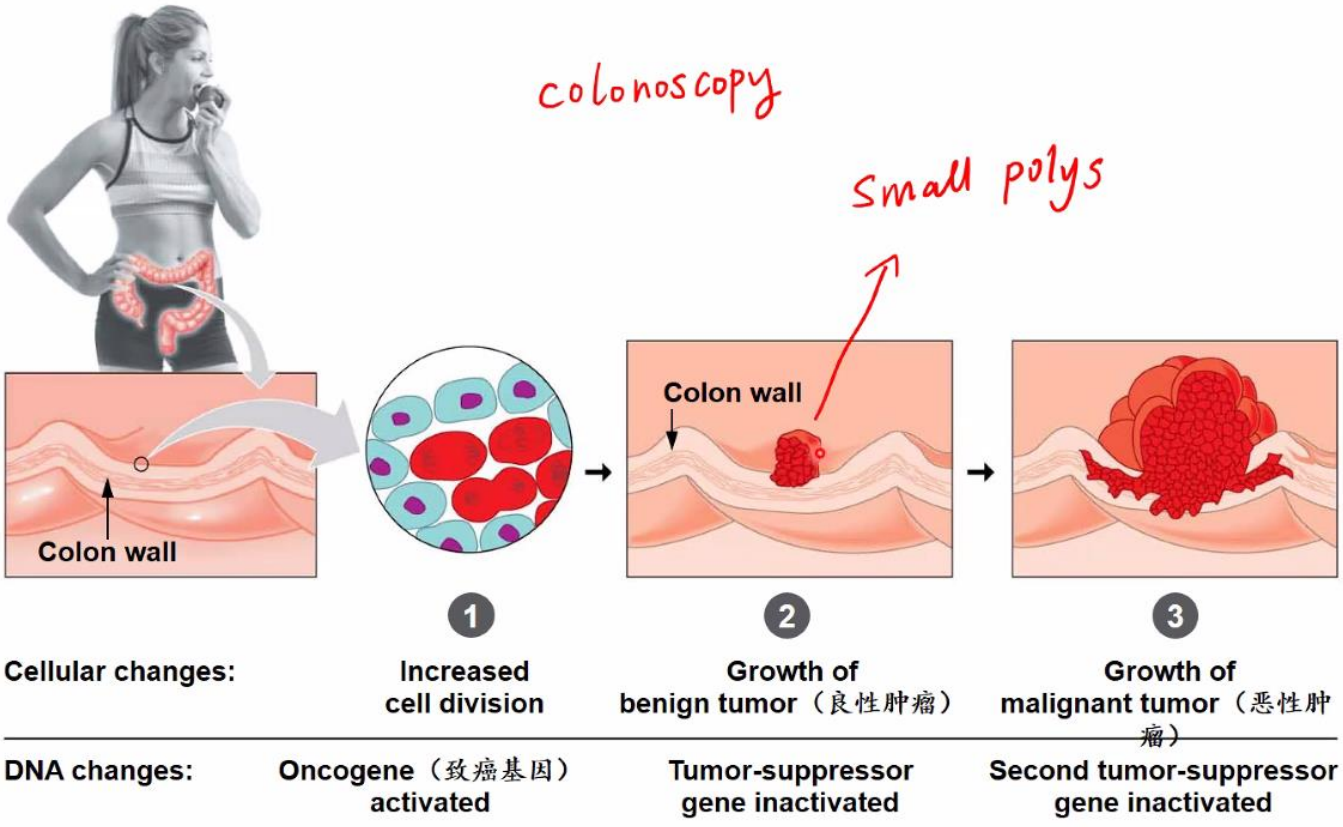


These two is controlled by growth factor. For mutated pro-oncogene, hyperactive relay protein does not need growth factor, it can signal division on its own. Non-functional transcription factor cannot trigger transcription for protein that inhibits cell division.



▲ Figure 11.18A A stimulatory signal transduction pathway and the effect of an oncogene protein

▲ Figure 11.18B An inhibitory signal transduction pathway and the effect of a faulty tumor-suppressor protein



- Small polys is not yet cancer, it is still a benign tumor, and not grow and spread to another part of the body.
- Pancreatic cancer is difficult to be cured (lowest lifespan), and nearly impossible to remove the tumor.