CHAPTER 12 : GENE REGULATION AND HUMAN DISEASE

TRANSCRIPTION AND DISEASE

- In most cases, mutations in gene regulation mechanisms are lethal and are not observed in the population – incompatible with survival (at least at birth)
- In observed cases, specific mutations have a dramatic effect on gene expression and produce severe disease.
- In other cases, changes in DNAs sequence can be more subtle, producing a quantitative change in the level of gene expression rather than severely reducing or abolishing transcription, processing and/or translation.
- ➢ DNA arrays / Gene chip analysis provide insight into the quantitative expression of different RNAs between normal and disease patients

Mutations in transcription factor coding genes, may result in:

- A functional TF that binds to DNA but fail to activate gene expression
- Example: Mutant Pit-1 → can bind to its DNA-binding site but cannot activate gene expression.

- Also act as a negative factor inhibiting expression by preventing wild-type protein from binding to DNA.

- Haploid insufficiency
- ➢ The amount of protein made is not sufficient, due to only one copy of the gene being mutated
- Failure to respond to signals
- ➢ E.g. members of nuclear receptor family such as steroids / glucocorticoids
- ➢ Cells do not respond to extracellular signals

- Mutations in DNA sequences to which TFs bind also cause disease
- ➢ Example: Promoter or enhancer
- ➢ Some mutations will abolish transcription of the target gene, OR
- ➢ This can be seen with GENE CHIP ANALYSIS (where the total RNA expression patterns in different normal human individuals has revealed quantitative differences in the expression of many different RNAs, which correlate with differences in promoter or enhancer sequences of corresponding genes in different individuals.)

- Rather than specifically causing a particular disease, such quantitative variations in gene expression are likely to enhance / reduce → risk of specific multifactorial diseases, which develop due to interaction of multiple genetic and environmental factors.

- An example: Mutations within enhancer → located 25 kB upstream, of the PF1A gene, cause human pancreatic agenesis in which the pancreas fails to develop.

- Interestingly the PTF1A gene itself encodes → basic helix turn helix TF → alterations in regulatory sequence can affect the production of TF → this will then produce abnormal expression of target genes for this factor.

- Sequence variation will only reduce the amount of gene transcription

- Mutations in transcriptional co-activators (e.g. CBP)
- To function effectively cell needs to have two intact genes encoding the CBP coactivator protein (Figure a)
- Lethal if no functional CBP is made, one functional gene will result in disease → most likely when CBP in normal cells is low with various transcription factors competing for it. → The CBP gene mutation is dominant because of inability of the one functional gene copy to produce the required amount of protein. (Figure b)
- Sometimes mutation cause incorrect protein -protein interactions by removing a functional co-activator e.g.→ CBP sequestration by Huntington protein (figure c)
- CAG sequence in coding sequence of Huntington protein has been expanded producing run of glutamine amino acids in Huntington protein. --> Abnormal form of this protein binds to Normal CBP protein and prevents it from regulating T/c → deposits it into insoluble aggregates

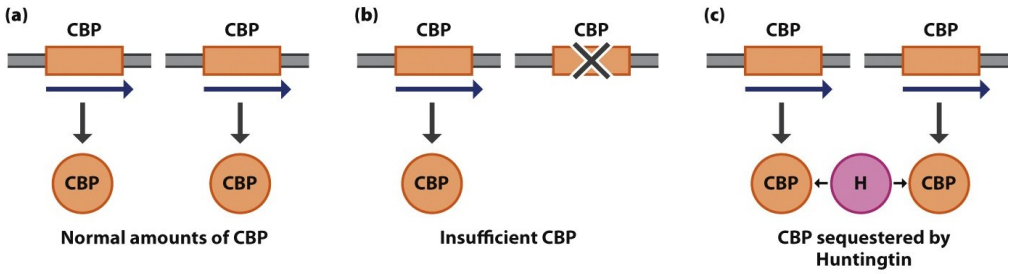

Figure 12.5 Gene Control (© Garland Science)

CHROMATIN STRUCTURE AND DISEASE

- Mutations in DNA methyltransferase enzymes cause:
- Incorrect methylation and recognition of genomic DNA
- Changes in methylation patterns