

Abstract

An initial microscopic model of epigenetic mechanisms is proposed, linking gene expression changes to cancer initiation. Emergent properties of complex tumours are influenced by aberrant modification of DNA methylation through the process of cell division. The objective here is to map the input for changes.

Introduction

Epigenetic mechanisms influence cell phenotype through heritable regulation of gene expression.[1]

The building blocks:

- *Chromatin = Cluster of DNA + Proteins(histones).*

Designed to package DNA into smaller volume in the cell and to control gene expression.

- *Nucleosome = Fundamental unit of chromatin.*

Each nucleosome unit consist of 147 base pairs of DNA and four base pairs of histone proteins(Fig 1).

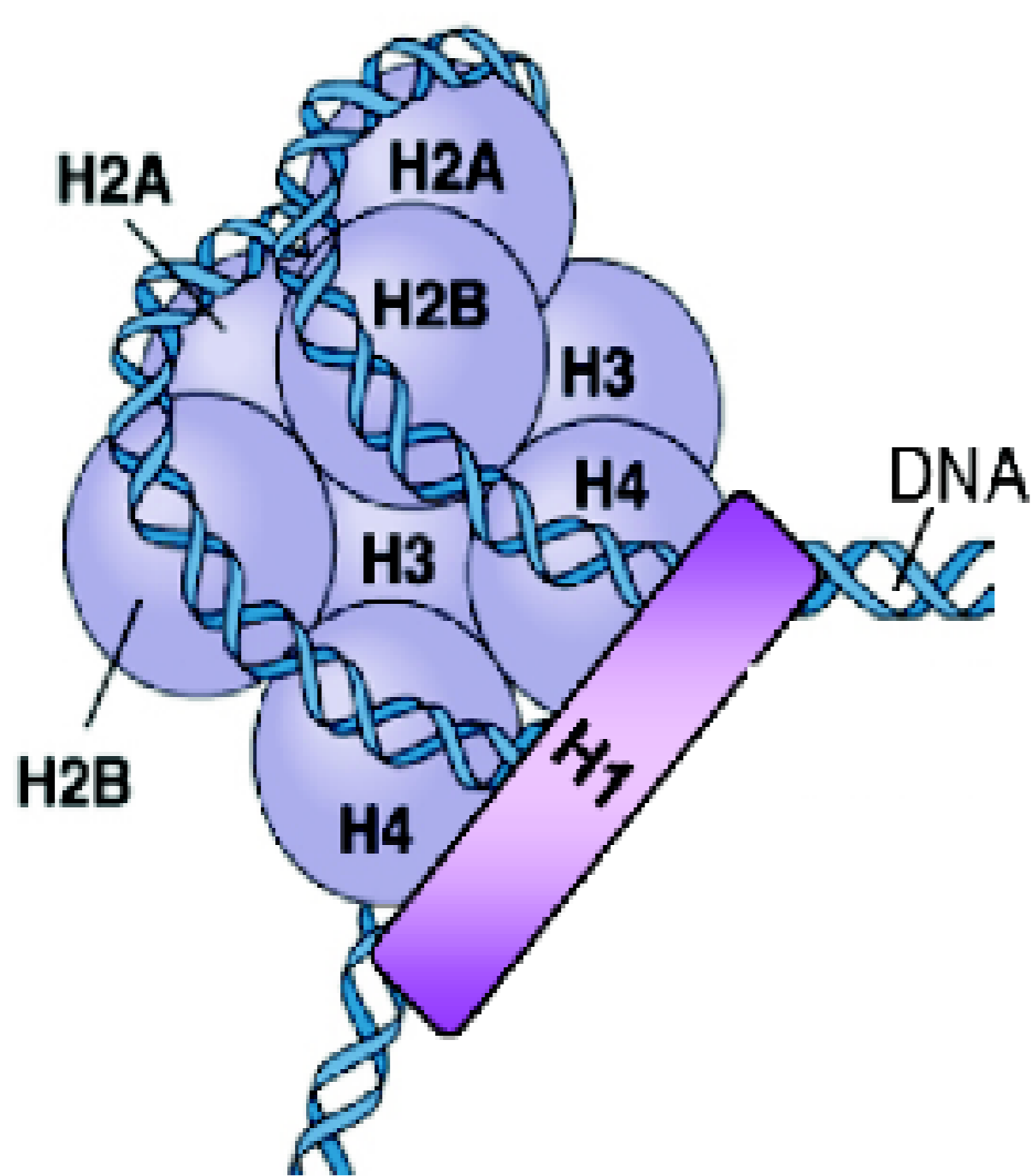


Figure 1: Nucleosome, fundamental unit of chromatin(adapted from C.Brenner,PhD thesis,Universite Libre de Bruxelles, 2005)

- *Epigenetic mechanisms = DNA methylation, Histone acetylation and Histone methylation.*

- Alterations in gene expression arise during development and cell proliferation and persist through cell divisions.
- DNA methylation is a post-replicative process of cytosine residues. CpG sequences are methylated during cell division.(C=cytosine, G=guanine, p=phosphate)
- Epigenetic changes result in DNA methylation errors; (Hypermethylation or Hypomethylation).

Fig 2 shows hypermethylation on CpG islands (>=200 base pairs of CpG dinucleotide) on promoter (regulatory region on the DNA).

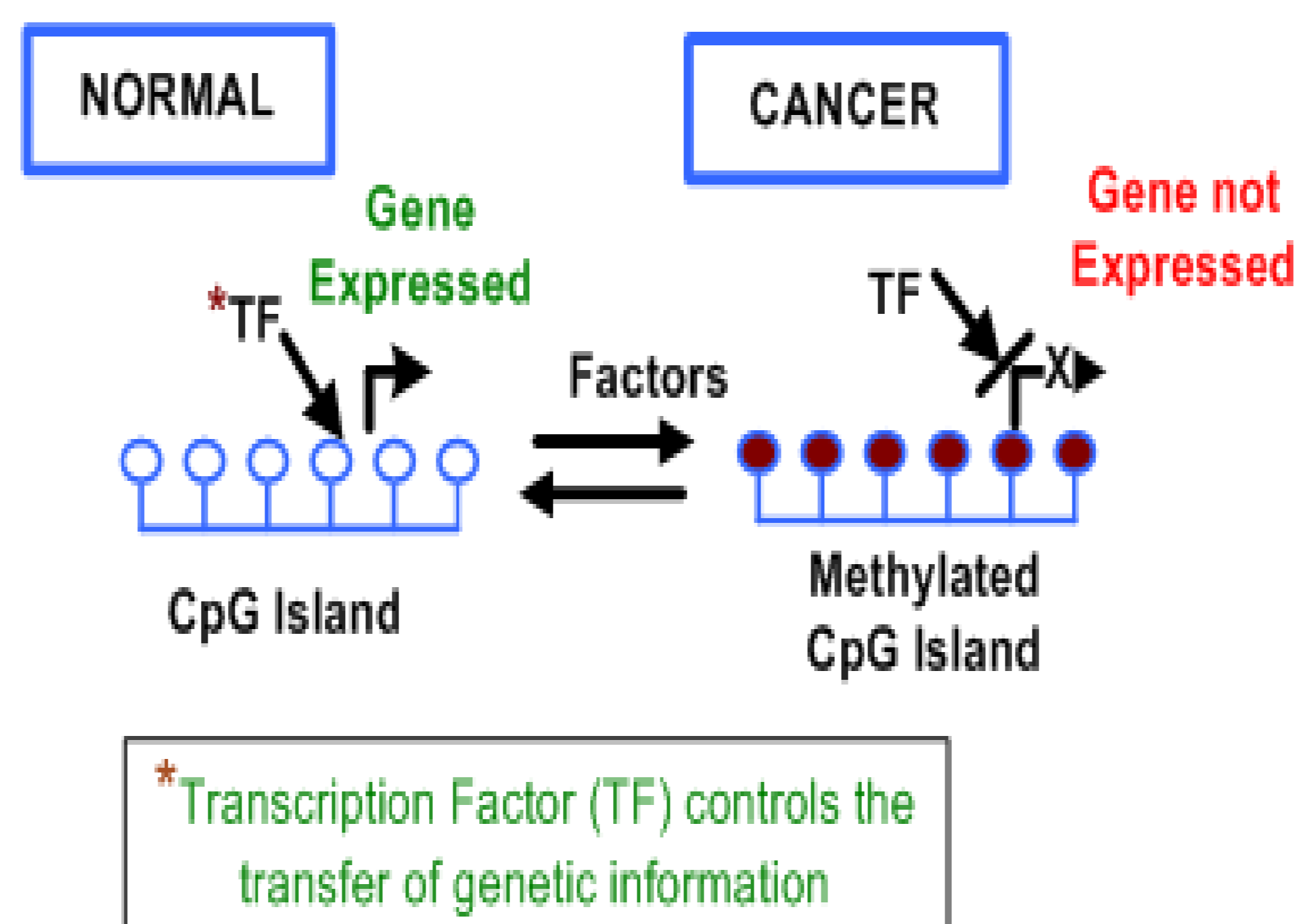


Figure 2: Change in DNA hypermethylation

Change of epigenetic factors directly impacts cell cycle in stem cell

- Environmental factors which alter epigenetic mechanisms include: smoking, radiation, nickel etc.[2][3]

Objective

Development of a microscopic representation of epigenetic mechanisms, providing hierarchy of changes and early detection of cancer initiation.

The Model

- An object-oriented model of epigenetic mechanisms focusing on individual nucleosomes and actual DNA sequences.

Fig 3 shows basic structure of the model.

Each unit represents a class.

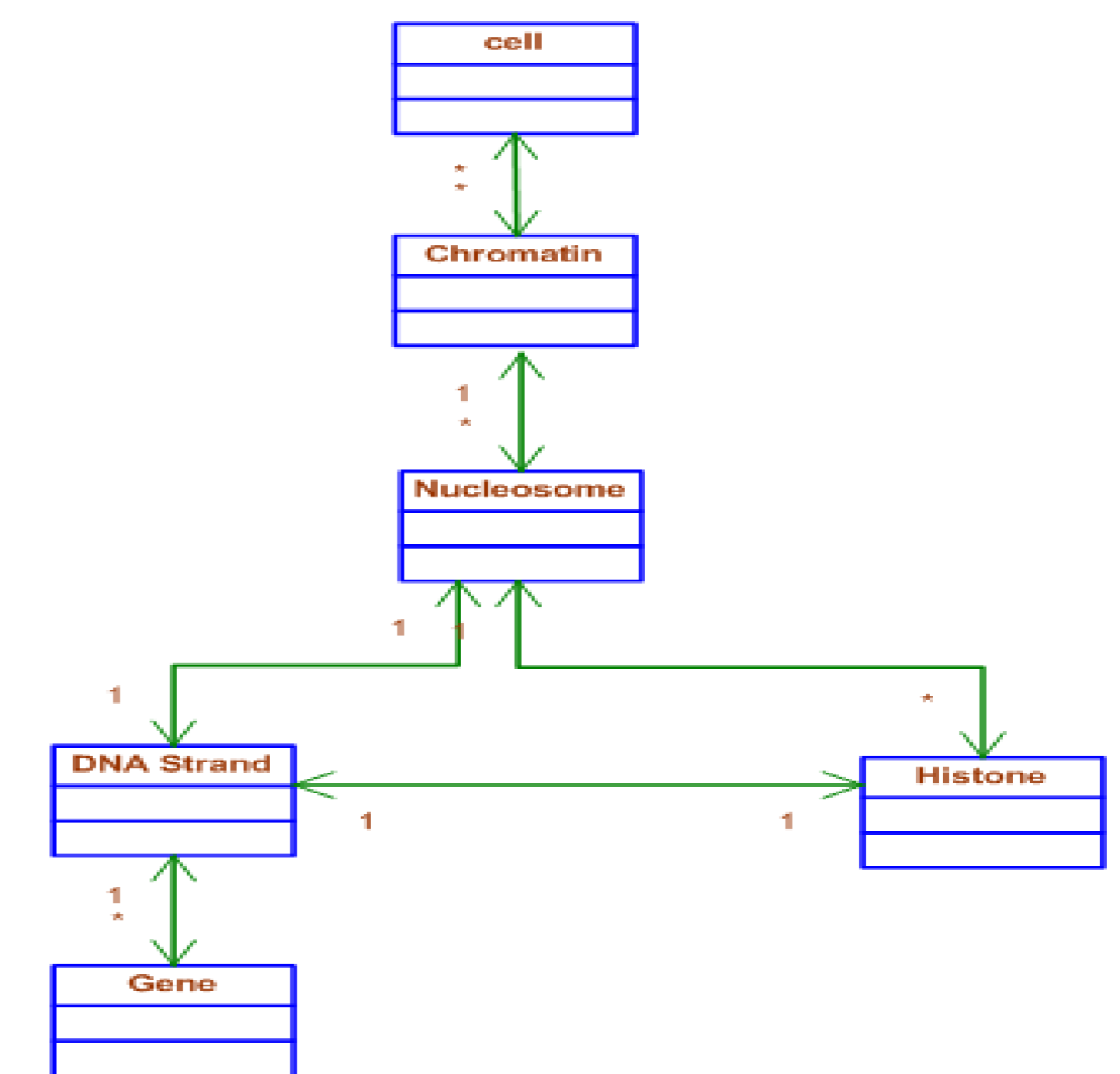


Figure 3: Structure of Model

- Model Layers:

$$P = G + E + EpiG \quad (1)$$

Where P = phenotype (An organism behaviour); G = Genetic factors; E = Environmental factors; EpiG = Epigenetics(changes in gene expression stable between cell divisions)[4]

$$EpiG = E_g + G_{env} \quad (2)$$

where E_g is the presence of an enzyme group with certain characteristics, G_{env} is a set of genes affected by environmental factors.

- Each environmental entity is represented by specific agents. Types of agents are inherited from a common class. Interactions are implemented by various C++ classes.

Conclusion

It is possible for low level changes to be modelled such that high level phenomena can be attributed to epigenetic events.

References

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3. Herceg Z., "Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors", Mutagenesis, 22:91-103, 2007.
4. Perrin D., Ruskin H.J., Crane M., Walshe R., "Epigenetic Modelling", ERCIM NEWS, 72:46, 2008.