The Concept of Epigenetics

The term 'Epigenetics' describes heritable genetic modifications that are not attributable to changes in the primary DNA sequence. Epigenetic modifications play a key role in regulating gene expression, and therefore are critical to the development, regulation and maintenance of the normal cell.
The Concept of Epigenetics

DNA methylation is involved in the regulation of many cellular processes, including X chromosome inactivation, chromosome stability, chromatin structure, embryonic development and transcription. Aberrant DNA methylation has been associated with many human diseases, including cancer. Patterns of DNA methylation are set during embryogenesis and re-established during early development by DNA methyltransferase and demethylase enzymes.

‘CpG islands’ (cytosine-phospho-guanine) are 300-3000 base pair stretches of DNA that are CpG rich. CpG islands are often located in the promoter regions of genes where in the normal cell they are typically unmethylated, thus allowing transcription. In contrast, CpGs found outside promoter regions are commonly methylated, and are believed to be responsible for silencing the transcription of repetitive sequences and parasitic sequence elements, such as viral DNA. Consequently, aberrant methylation can lead to either silencing of critical genes or increased expression of detrimental factors.
The Concept of Epigenetics

Consequently, aberrant methylation can lead to either silencing of critical genes or increased expression of detrimental factors.

Waterland RA, Jirtle RL. Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation
Mol Cell Biol 2003; 23: 5293-5300
The Concept of Epigenetics

Waterland RA, Jirtle RL. Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation

Mol Cell Biol 2003; 23: 5293-5300
The Concept of Epigenetics

Waterland RA, Jirtle RL. Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation

Mol Cell Biol 2003; 23: 5293-5300

- maternal dietary methyl-donor supplementation of agouti mice with folic acid, vitamin B12, choline and betaine shifts the coat colour distribution of the offspring
- mice developed a brown coat colour (pseudoagouti phenotype)
- the methyl-donor-induced shift in the phenotype was a result from an increase in DNA methylation at CpG sites in the upstream IAP transposable element
- the effect of a mothers diet during pregnancy on the phenotype of the offspring is directly linked to DNA-methylation changes
- the effects of maternal methyl supplementation can also be inherited in the F2 generation

The biological significance of methylation status does not seem to be even in the genome, and seems to be important at CpG islands, where CpG sites cluster. All the more so, when a CpG island is located in the 5' region of a gene, as it is known that its methylation status functions as a molecular switch that can turn-off or turn-on the expression of the downstream gene. For the majority of genes, the CpG islands in their 5' regions are not methylated, and they are ready to be expressed (A).

In some cancers, CpG islands in the 5' regions of tumor-suppressor genes are methylated, and their expressions are switched-off (B). This mechanism, gene silencing, is known to be one of the major mechanisms of tumor-suppressor gene inactivation.
Cancerogenesis

Initiation: The first step, more precisely the first mutation of a cell on its way to becoming cancerous marks the point of initiation. Initiation is very rare and affects only proliferating tissues. It gives the cell a small growth advantage but without the subsequent promotion, proliferation is hardly possible. As initiation is a genotoxic event it is passed on to the daughter cells and is not reversible.

Cancerogenesis

Promotion: After initiation promotion is the process that accelerates the development of a tumour. In particular, promotion supports the growth of initiated cells but it is a non-genotoxic event, which means that it does not cause any mutations. Several factors can act as a tumour promoter, endogenous substances like hormones and growth factors, but also exogenous ones like over-nutrition or environmental substances. The process of promotion is reversible, takes a long period, and has to exceed a threshold to be effective.
Cancerogenesis

Progression: Initially due to initiation and promotion preneoplastic foci and benign tumours are formed. The transformation to a malignant tumour is called progression. This stage is marked by accumulation of further mutations and selection of mutated cells and subclones. The mutations affect additional oncogenes and tumour suppressor genes. Several signalling pathways are effected which help in gaining the several traits of tumours (see above). One of the most important causes of progression is genetic instability which is often induced by mutations in genes for DNA repair.

Cancerogenesis

Tumor initiators: mutagens, carcinogens (aflatoxines, irradiation, ROS, cigarette smoke, etc)

Tumor promoters: promotes proliferation without being mutagenic (estrogens, phorbol esters, etc)
Cancerogenesis

a) Initiation
Aus einer veränderten Genetizelle
hervorgegangene Tumorzelle

b) Promotion
Achselung von Tumorzellen
(öffentlich bekannter benigner Tumor)

c) Progression
Invasive Tumorzellen

d) Invasion und
Metastasierung
Tumorzelzen
gelangen in die
Blutgefäße, wodurch
die Metastasierung
beginnt.

Cancerogenesis

Haustra
Semitunus fossa
Surface
epithelium

Crypt of
Latanichum
Lamina
propria
Muscularis
mucoeae
Submucosa
Circular
muscle of
muscularis
externa
Longitudinal
muscle of
muscularis
externa
Lymphoid node
(Peyer patch)
Cancerogenesis
Cancerogenesis
Cancerogenesis
NFκB and TNFα in Cancer Development

NF-κB is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival. As such, many different types of human tumors have misregulated NF-κB: that is, NF-κB is constitutively active. Active NF-κB turns on the expression of genes that keep the cell proliferating and protect the cell from conditions that would otherwise cause it to die. In tumor cells, NF-κB is active either due to mutations in genes encoding the NF-κB transcription factors themselves or in genes that control NF-κB activity (such as IκB genes); in addition, some tumor cells secrete factors that cause NF-κB to become active. Blocking NF-κB can cause tumor cells to stop proliferating, to die, or to become more sensitive to the action of anti-tumor agents. Thus, NF-κB is the subject of much active research among pharmaceutical companies as a target for anti-cancer therapy.

DBD: N-terminal DNA-binding domain
TRD: transrepression domain
TAD: transactivation domain

NFκB and TNFα in Cancer Development
NFκB and TNFα in Cancer Development

TNF is mainly produced by macrophages, but also by a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts and neuronal tissue. Large amounts of soluble TNF are released in response to lipopolysaccharide, other bacterial products, and Interleukin-1 (IL-1). It has a number of actions on various organ systems, generally together with IL-1 and Interleukin-6 (IL-6). Whereas high concentrations of TNF induce shock-like symptoms, the prolonged exposure to low concentrations of TNF can result in cachexia, a wasting syndrome. This can be found for example in tumor patients.

NFκB and TNFα in Cancer Development

Two receptors, TNF-R1 and TNF-R2, bind to TNF. TNF-R1 is constitutively expressed in most tissues, and can be fully activated by both the membrane-bound and soluble trimeric forms of TNF, while TNF-R2 is only found in cells of the immune system and respond to the membrane-bound form of the TNF homotrimer. Upon contact with their ligand, TNF receptors also form trimers, their tips fitting into the grooves formed between TNF monomers. This binding causes a conformational change to occur in the receptor, leading to the dissociation of the inhibitory protein SODD from the intracellular death domain. This dissociation enables the adaptor protein TRADD to bind to the death domain, serving as a platform for subsequent protein binding. Following TRADD binding, three pathways can be initiated:

- Activation of NF-kB
- Activation of the MAPK pathways
- Induction of death signaling