Cancer Biology

Lecture No. 4

Presented by

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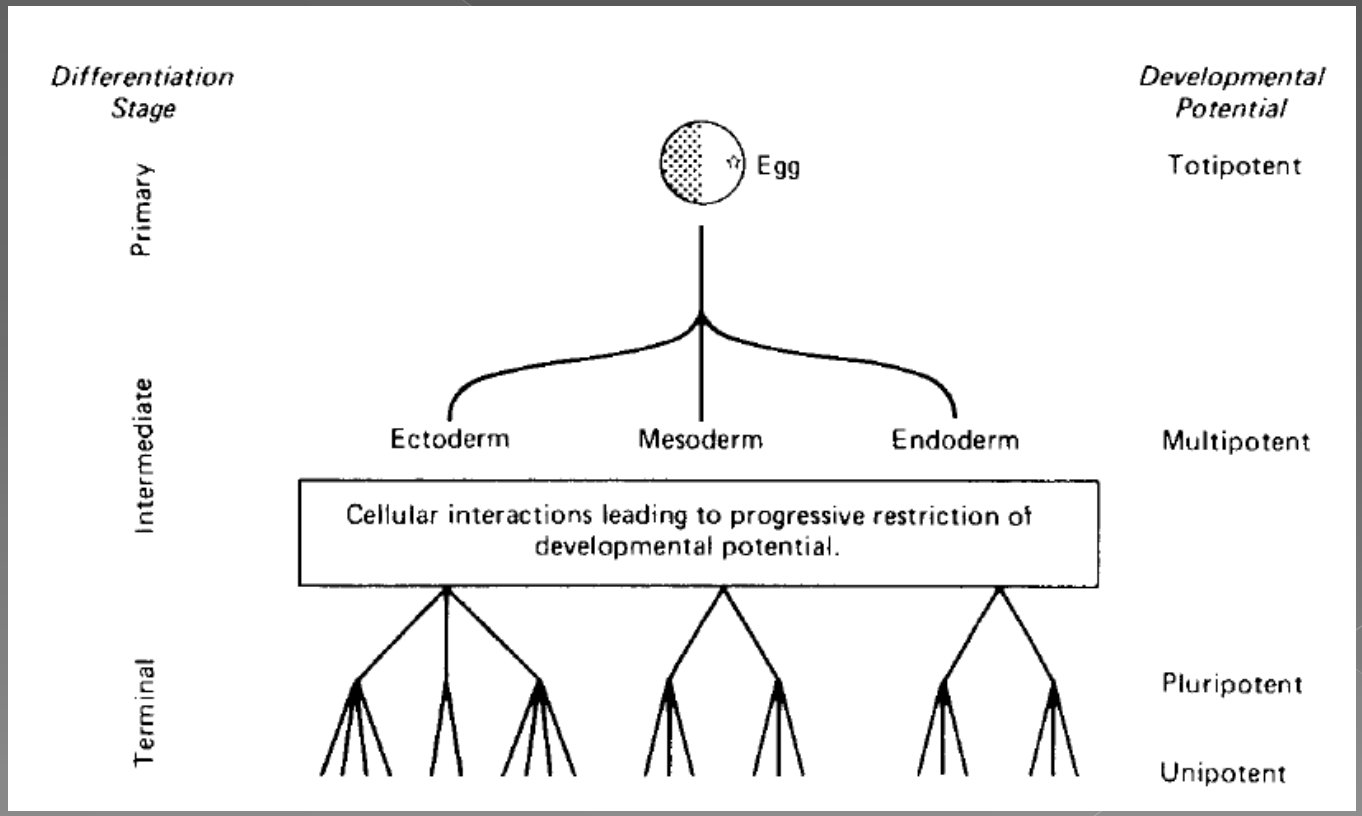
Definition of Cell differentiation

Differentiation is the sum of all the processes by which cells in a developing organism achieve their specific set of structural and functional characteristics.



Cell Differentiation

Differentiation requires a progressive restriction
of genomic expression.

The totipotentiality of cells starts to change very early
after fertilization as the developing embryo proceeds through the blastula stage.

Internal reprogramming and external stimuli by neighboring cells

Differentiation appears to be fairly permanent in that, as tissues develop, some cells retain the capacity to divide.

Balance between Cell Proliferation and cell differentiation

Adult tissues generally express a variety of factors that act to maintain both the proliferation and the differentiation status of the cells.

For example, myoD and c/EBP-a are nuclear factors that activate the transcription of muscle- and adipocyte-specific genes, respectively; in addition, both proteins are potent inhibitors of cell proliferation

Embryonic development

Vigorous Proliferation

Extensive migration

Increased local supply of blood

Capability of degrading basement membranes.

These traits also are characteristic of tumor cells

Embryonic development

Tumor angiogenesis is an important, negative prognostic indicator for carcinomas and leukemias.

Mutations or conditions that activate portions of embryonic programs for gene expression or inactivate portions of the adult program can produce cells with many properties of malignant tumor cells.

Stem Cells

Capacity for both self-renewal and differentiation

Stem cell differentiation
Two types of changes:

1- The expression of specialized, differentiation-specific gene products

2- Partial complete restriction of the cell's capacity for further proliferation.

Note: Tumor cells might arise through mutations that render a stem cell partly or wholly unable to differentiate.

Mechanisms of Cellular Differentiation

Extracellular Factors That Control Differentiation

Insoluble factors such as ECM and both the proximity and type of neighboring cells as well as a growing list of soluble factors.

Cell-cell and cell-ECM interactions

Mechanisms of Cellular Differentiation

Cell surface receptors

The soluble factors are classified into two classes:

1- Bind to cell surface receptors

2- Freely cross the plasma membrane and bind to cytoplasmic or nuclear receptors.

Mechanisms of Cellular Differentiation

Intracellular signal transduction pathways.

Then Gene expression Regulation

DNA Methylation

DNA methylation

DNA methylation is an essential epigenetic mark that controls gene expression.

It is borne by the genetic material but does not influence its sequence.

It can regulate genomic activities and can be maintained through mitosis and meiosis.

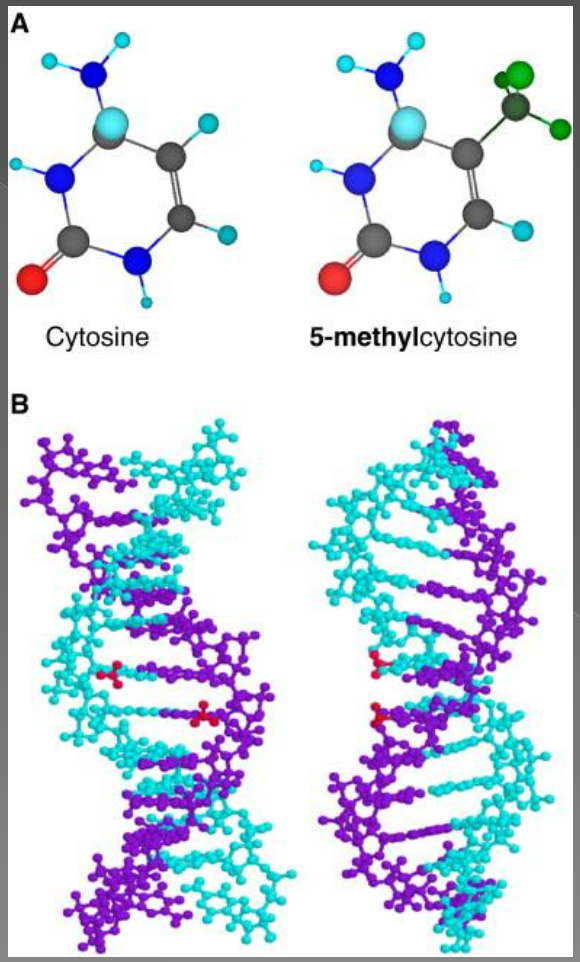
DNA methylation

*Absolutely required for embryonic development.

*The key role of DNA methylation is to control gene expression.

*The DNA of mammals can be methylated on cytosines within the CpG dinucleotides

DNA methylation



DNA Methylation

DNA methyltransferases (DNMTs).

De novo	Maintenance	Cofactor
DNMT3a	DNMT1	DNMT3L
DNMT3b		

DNA Methylation

Proteins that recognize methylated DNA:

Group 1: Methyl-binding Domain (MBD)

Group 2: contains the Zinc-finger proteins.
These proteins are bifunctional: they bind methylated DNA, but also some non-methylated consensus sequences.

Group3: bind through their SET-and-RING-Finger-Associated (SRA) domain

All these proteins inhibit gene expression by creating a repressive chromatin structure

DNA Methylation

Targets of DNA methylation differ in normal and cancer cells:

First: Parentally imprinted genes.

Second: the transposons.

Third: a number of genes are methylated in a tissue-specific manner.

DNA methylation and Cancer

*DNA methylation is deregulated in cancer

*Abnormal DNA methylation is an early causal event during cellular transformation.

*Demethylating agents can re-establish the expression of silenced tumor suppressor genes and have been approved for clinical use against some leukemias.