Epigenetics and Cell Differentiation

From Naïve to Antigen-Experienced Immune Cells

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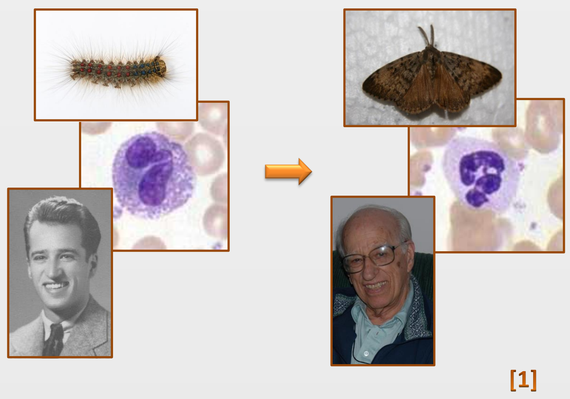
"Epigenetics: stably heritable phenotype without alterations in the DNA sequence."



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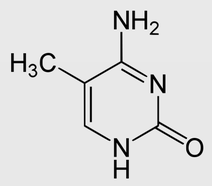
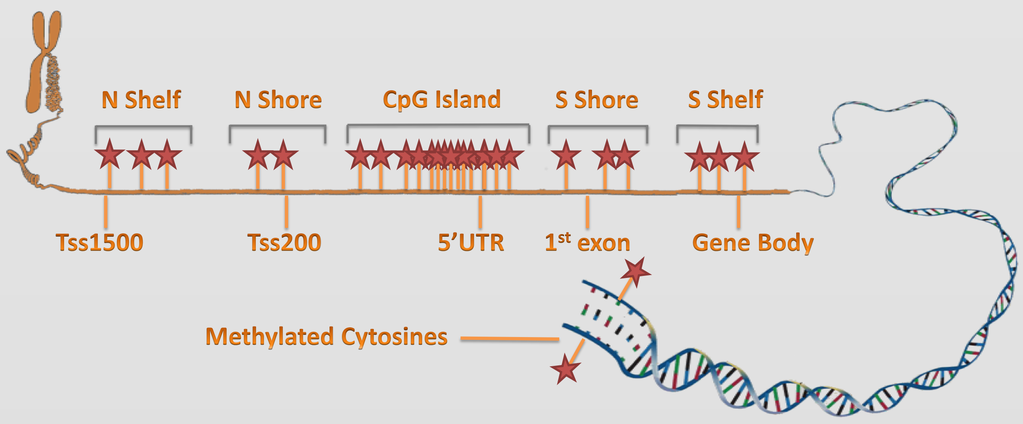
Epigenetics

Beside microRNA production and histone modification, **DNA methylation** is a well studied epigenetic modification that describes the covalent binding of a methyl group to a cytosine within a cytosine-guanine dinucleotide (CpG site). CpG dinucleotides can be **methylated**, **unmethylated**, and **hemimethylated**. Changes in methylation levels of CpG dinucleotides correlate with **transcriptional repression** and **gene silencing**, although not all sites have the same impact on gene expression. The approximately 28 million CpG sites in the human genome are not equally distributed and occur mainly in clusters of high CpG density, called **CpG islands** (CGI),[2] which can be found in generally 60% of all human gene promoters. They are also located in sections surrounding the transcription start site, gene body, and sections that follow the translation terminal codon.





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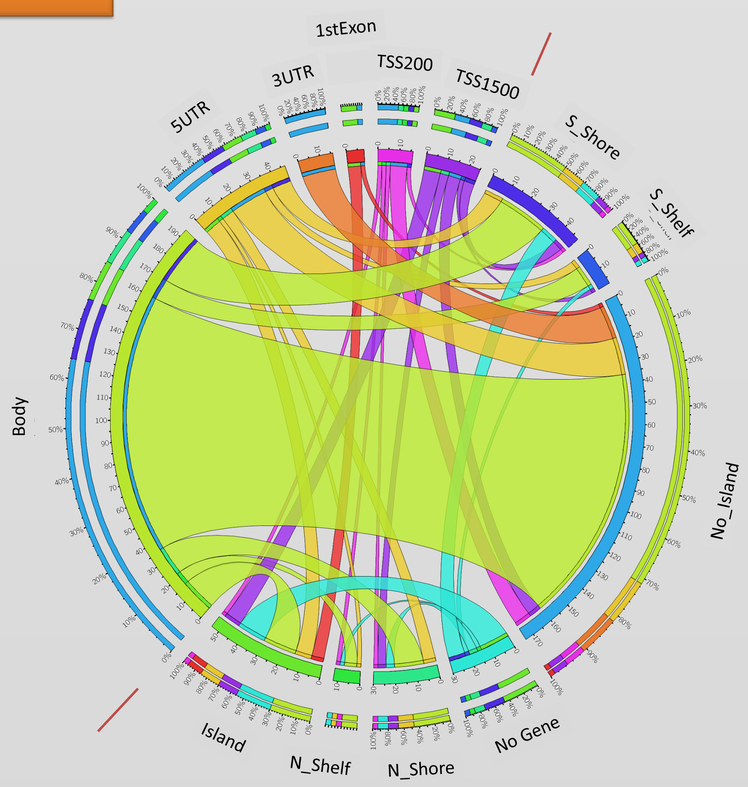
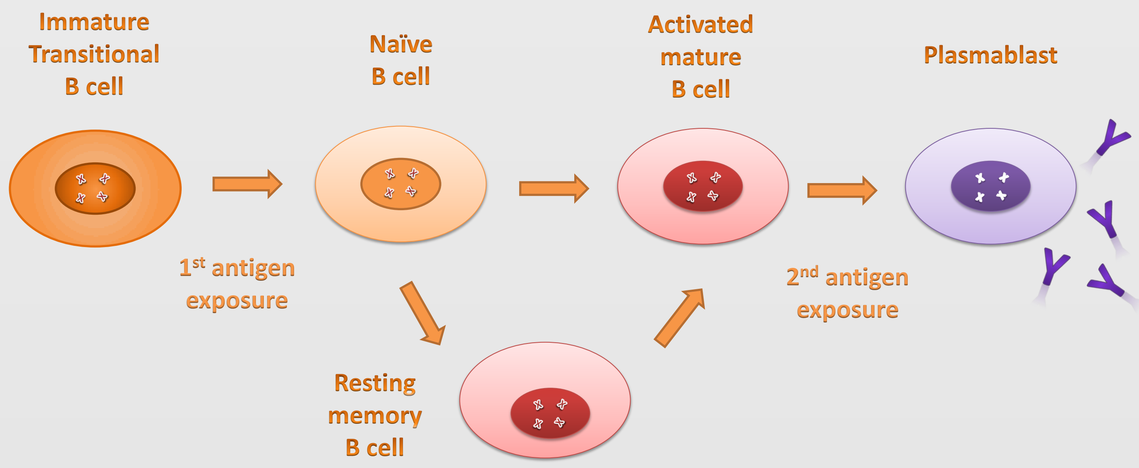
Annotation

Changes in DNA methylation occur mainly within islands and shores, which are located in the gene body section, but also surrounding the transcription start site (TSS) for coding genes. Genes which are hypomethylated in memory state and overexpressed in all three immune cell types are involved, e.g., in **myeloid cell differentiation**, **cell morpho genesis**, and **regulation of myeloid leukocyte differentiation.** Hypermethylated and underexpressed genes are involved in e.g., **cytoskeleton organization** and **regulation of cell growth**.



Study

The aim of this study is to analyse changes in DNA methylation due to cell **differentiation** from **naïve** to **memory** state in cytotoxic T cells, T helper cells, and B cells which may be involved in autoimmune diseases. Illumina **HumanMethylation450** BeadChip[3] platform was used to determine the DNA methylation state of cells from four healthy donors. These arrays provide a genome-wide coverage of more than 485,000 CpG methylation sites.



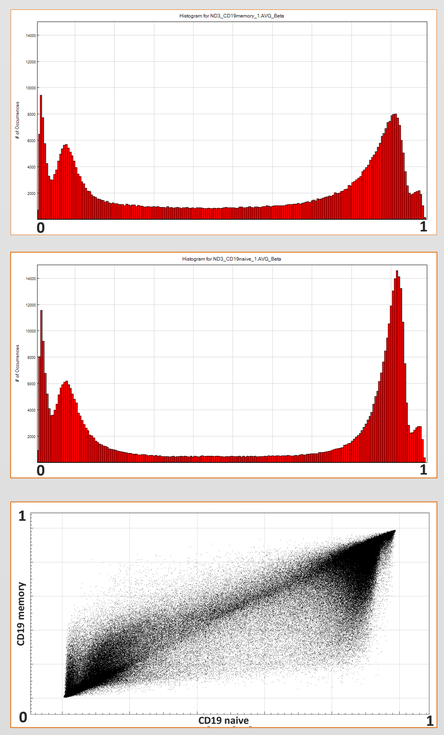
Differential Analysis

The methylation levels on single-nucleotide resolution are represented with a β **- value** as a quantitative measure ranging from 0 for completely unmethylated to 1 for completely methylated.

$$\beta = \frac{Intensity\ M}{Intensity\ U + Intensity\ M + 100}$$

Both **hyper-** and **hypomethylation** can be observed between naïve and memory cell types, even though hypo- predominates hypermethylation in differentiated cells. Comparison of gene expression between naïve and memory state shows an opposite trend and more **genes** are **overexpressed** than silenced. However, changes in DNA methylation do not always correlate with altered gene expression, indicating that other mechanisms have also an influence on gene regulation.

A



B

C

Cytotoxic T cells B-lymphocytes T-helper cells

(**A**) β-value distribution of B lymphocytes in naive and memory state and scatter plot of naive vs. memory (**B**) Number of genes which show hypo- or (**C**) hypermethylation in comparison when comparing cells in naïve and memory state (group diff. < 0.2, (|diff| > 0.6, BH-correction). Numbers in brackets: exclude mapping with expression data.

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http://www.pharmazeutische-bioinformatik.de

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[4] Darryl Leja (NHGRI), Ian Dunham (EBI)

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