Lecture 18

BT 632
Stem Cells, Cancer and Therapy
(3-0-0-6)

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Syllabus

Dr. Rajkumar P Thummer:

- Introduction to stem cells: Types, characteristics, potency, differentiation; Stem cell isolation and culture; Embryonic, tissue specific and germ line stem cells; Induced pluripotent stem cells: direct reprogramming, transcription factors and RNAi, Stem cell specification and trans-differentiation; Stem cell niche, signaling and metabolism; Epigenetics; Ethical guidelines and issues: embryonic and induced pluripotent stem cells;

Prof. Bithiah G Jaganathan:

- Cancer types, oncogenes and tumor suppressor genes; Cancer origin, progression and relapse; Cancer stem cells; Cancer and normal stem cells: common and shared pathways; Cancer microenvironment; Cancer therapy: Chemotherapy, radiation, cell and integrative therapy; Cancer multidrug resistance; Stem cells for cancer therapy; Degenerative diseases; Tissue repair and regeneration; Disease modeling and drug discovery; Pharmacogenomics and Personalized medicine.

Ethical guidelines and issues: embryonic and induced pluripotent stem cells

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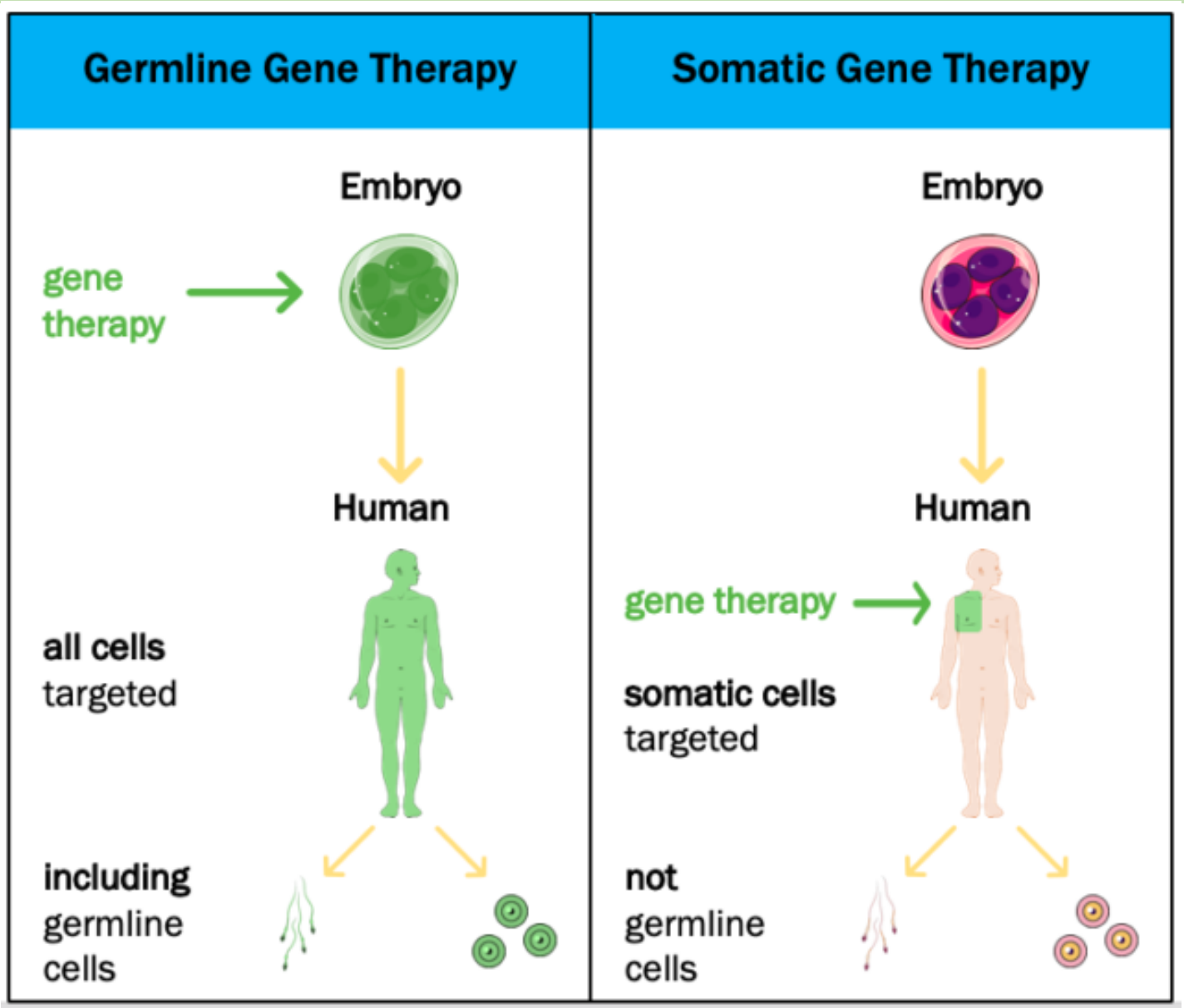

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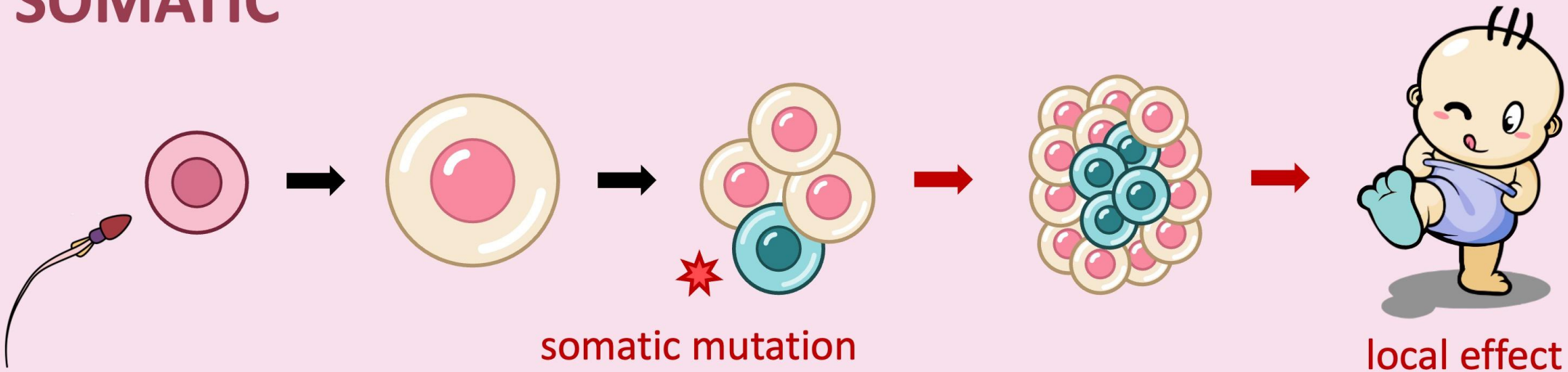
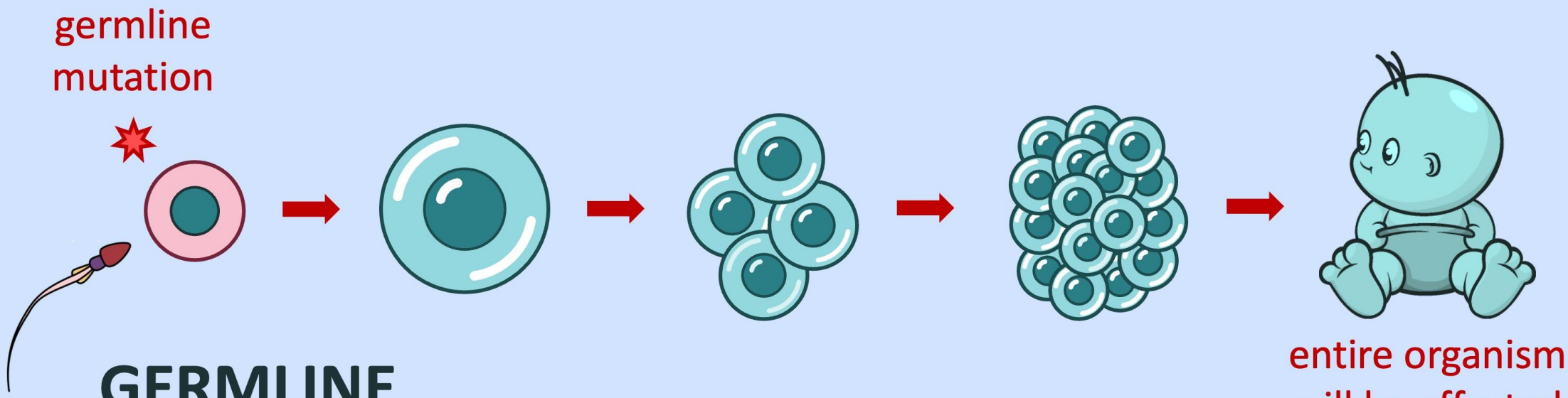
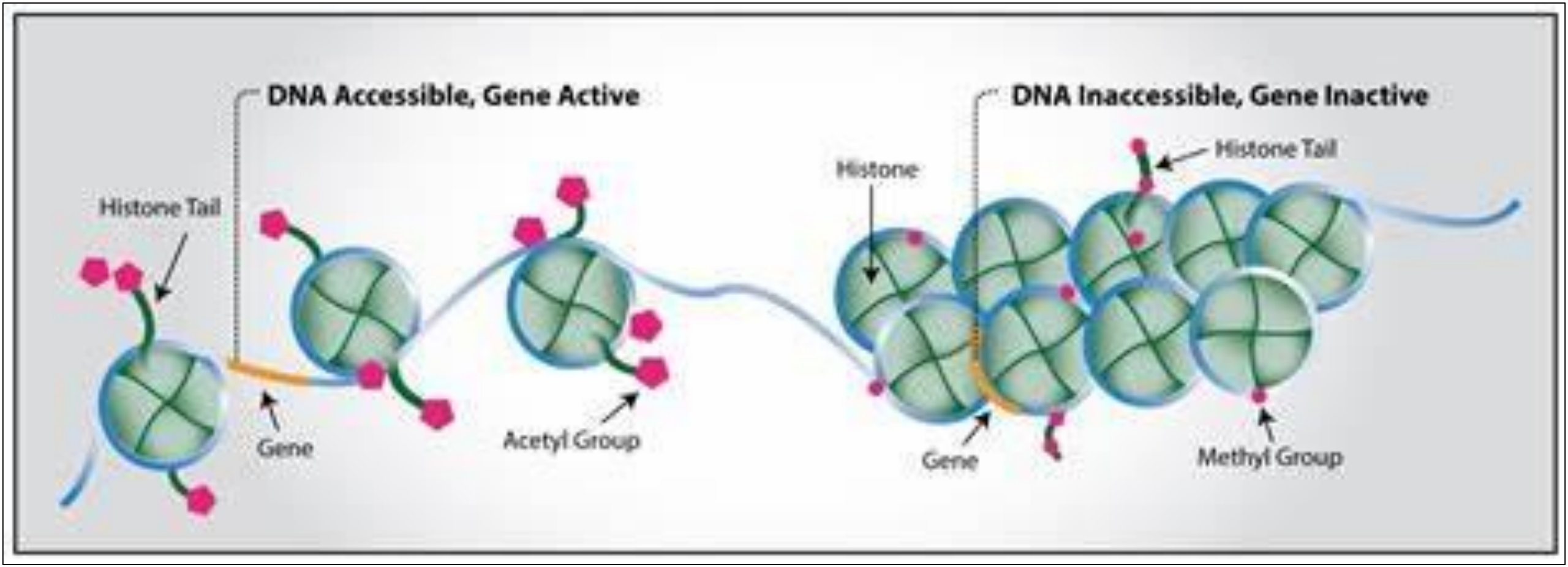




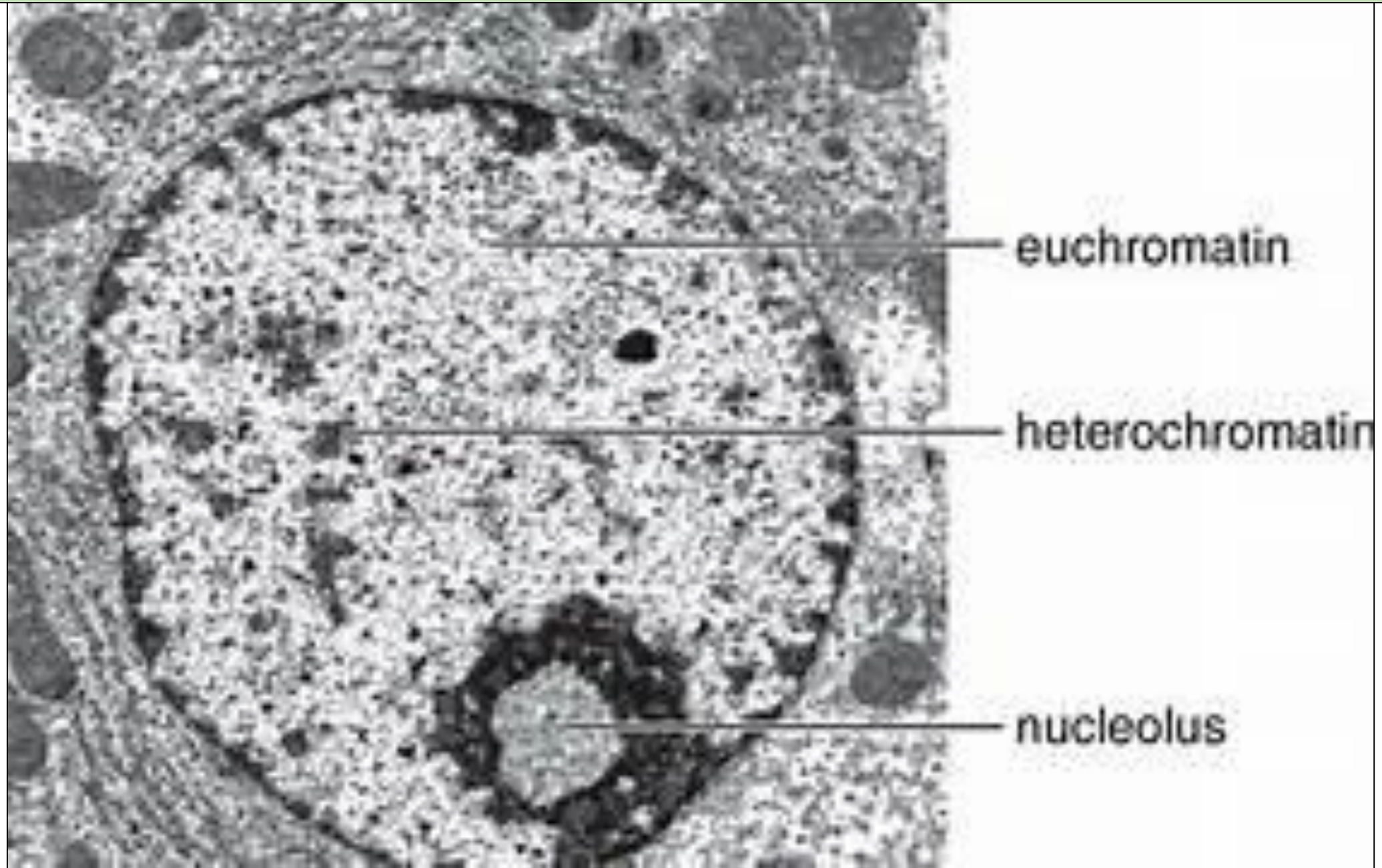
GERMLINE

Stem Cells and Epigenetics

Stem Cells and Epigentics



Stem Cells and Epigentics



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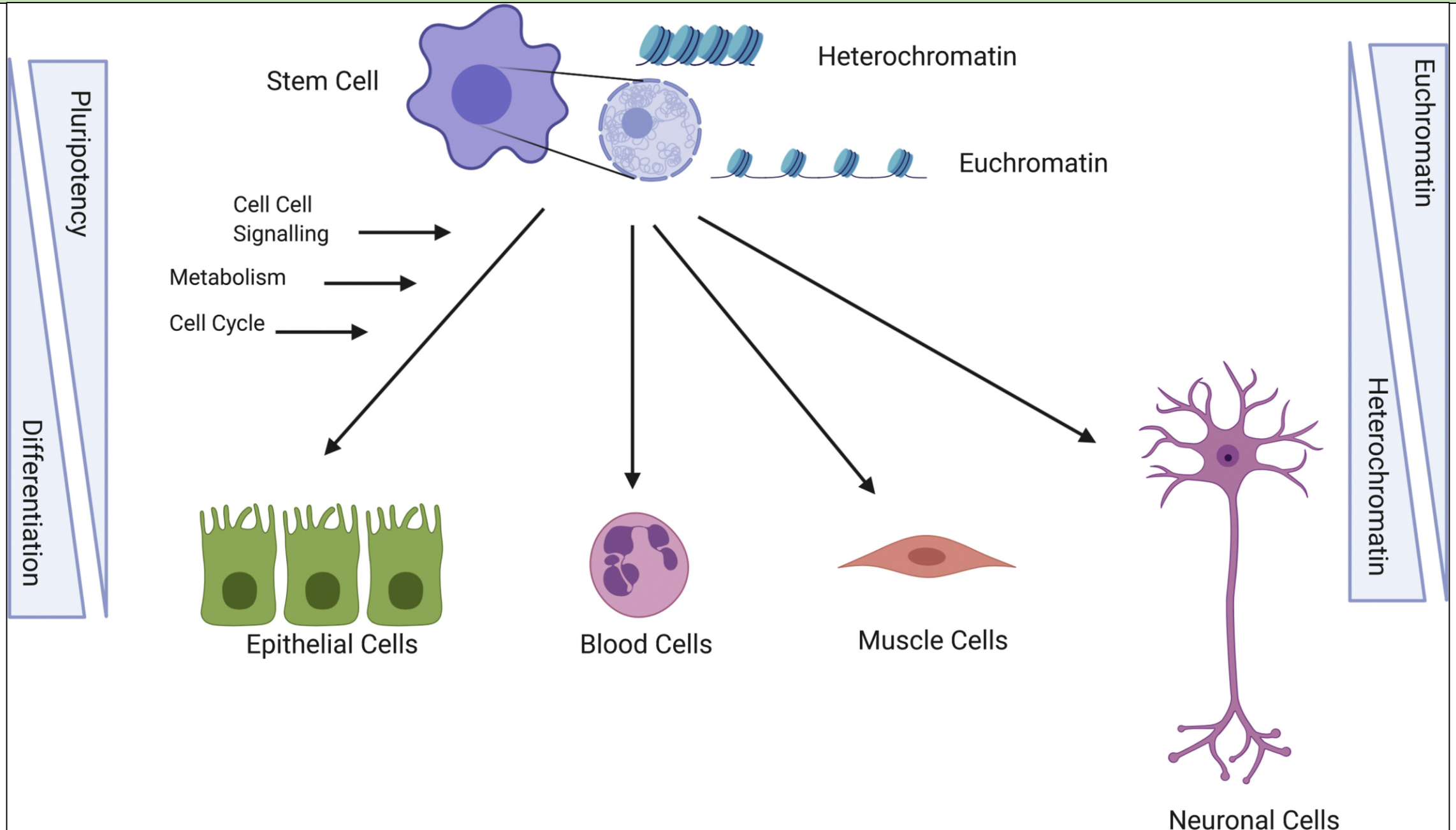

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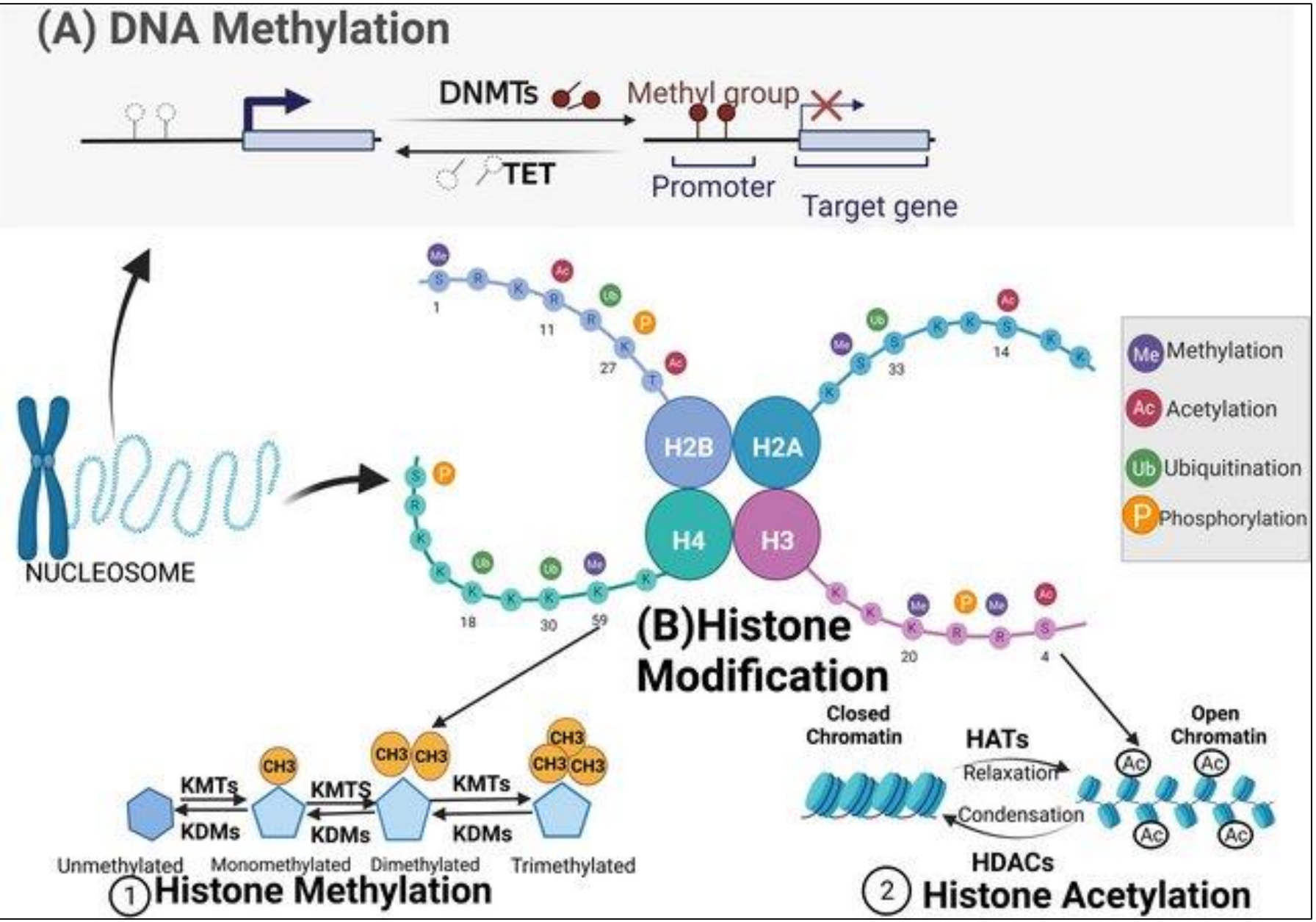


The mechanism of DNA methylation and histone modification in detail.

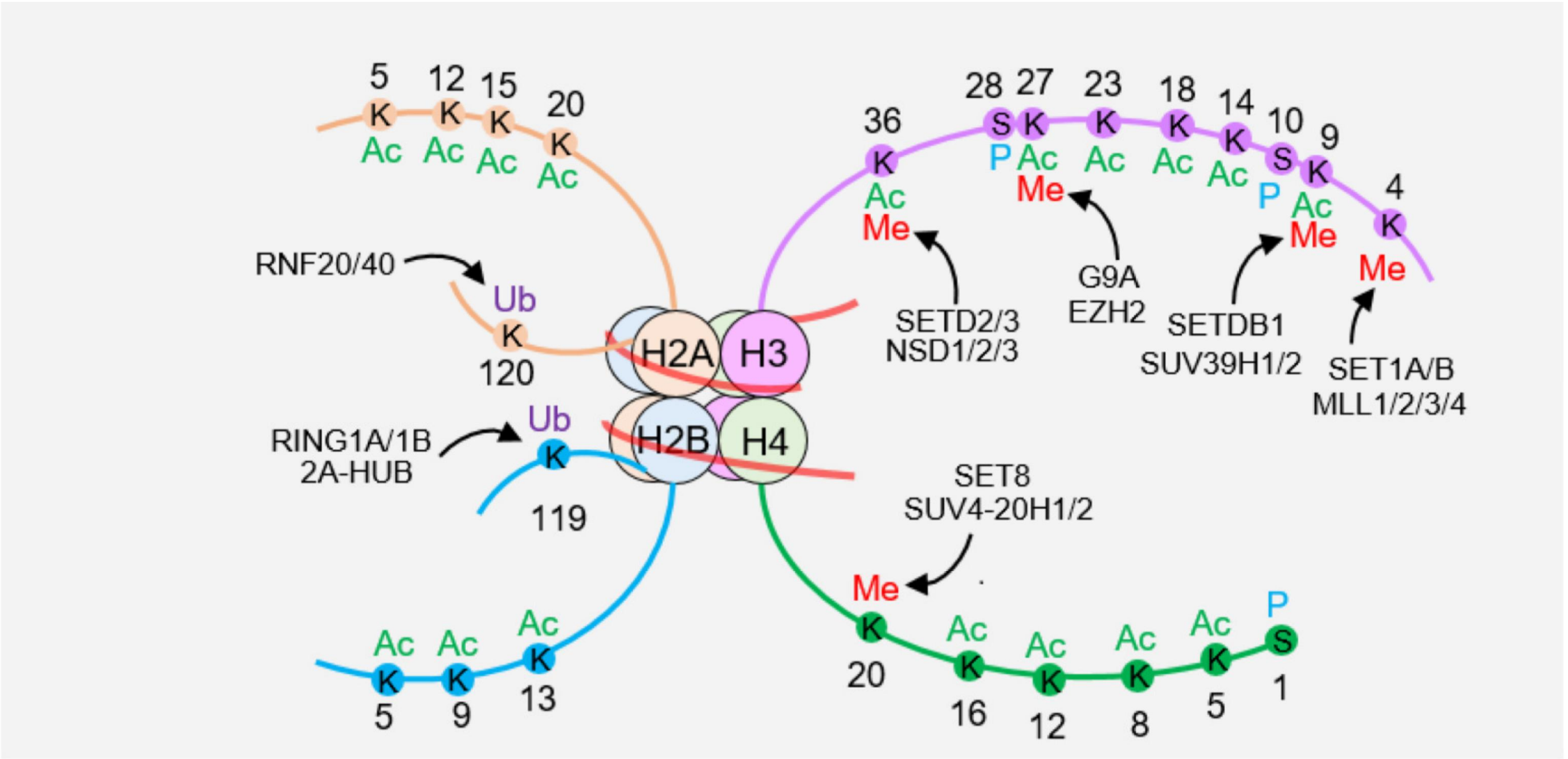
A) DNA Methylation: DNA methylation is regulated by two sets of enzymes DNMTs and TET. DNMTs leads to transcriptional repression while TET promotes the expression of specific genes.

B) Histone modifications: The fundamental unit of chromatin is called the nucleosome which consists of an octamer of four core histones (H3, H4, H2A, and H2B). Histone modification includes methylation, acetylation, ubiquitination, phosphorylation et al. The numbers indicate the positions of targeted lysine groups.

①Histone methylation is catalyzed by KMTs and reversed by lysine KDMs, and results in mono-, di- and trimethylation of lysine residues.

②Histone acetylation is regulated by two sets of enzymes HATs and HDACs. HATs alter the conformation of chromatin structure in nucleus by relaxing the chromatin and allowing transcriptional activation, while HDACs are the opposite

Stem Cells and Epigentics



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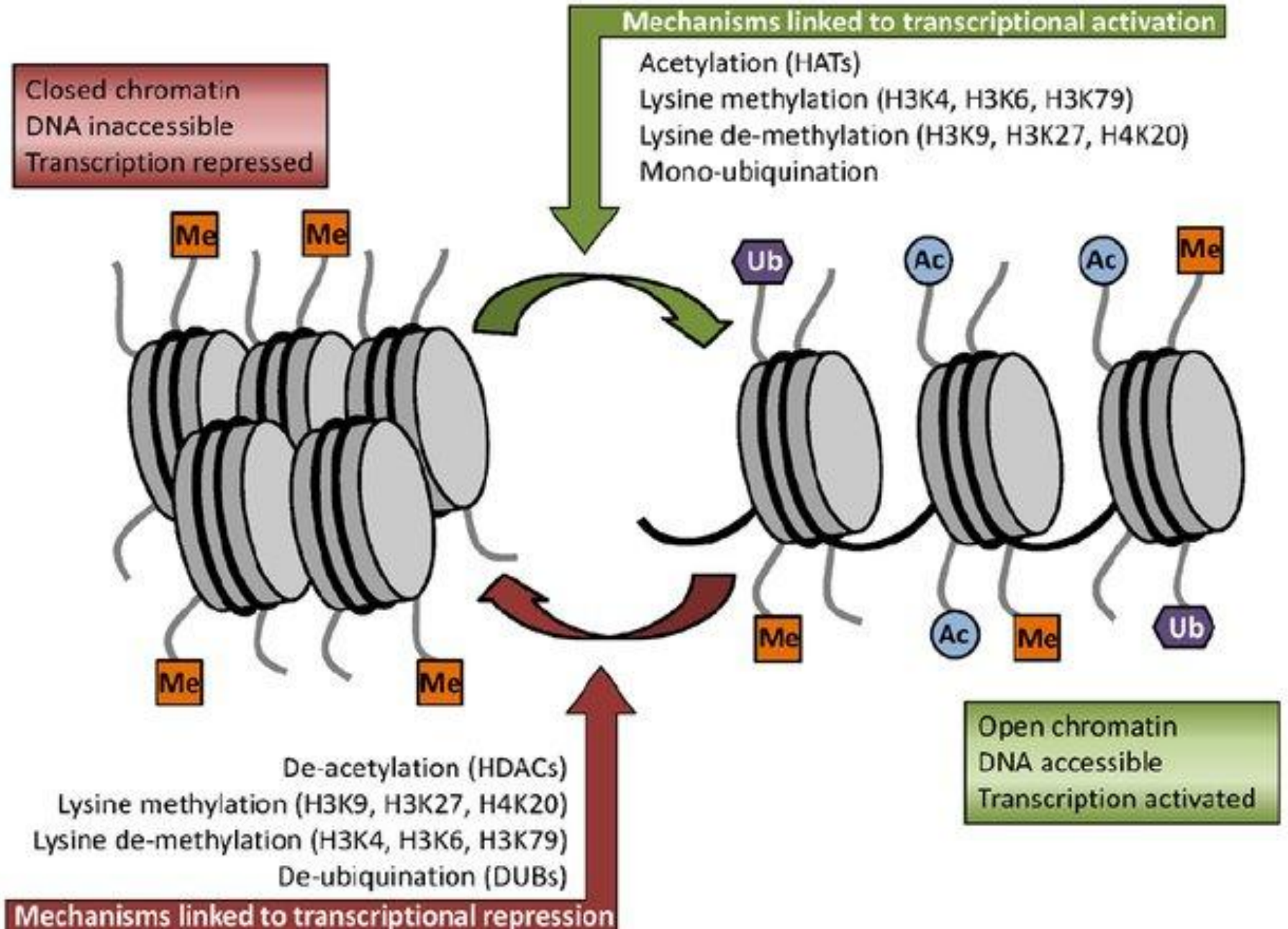
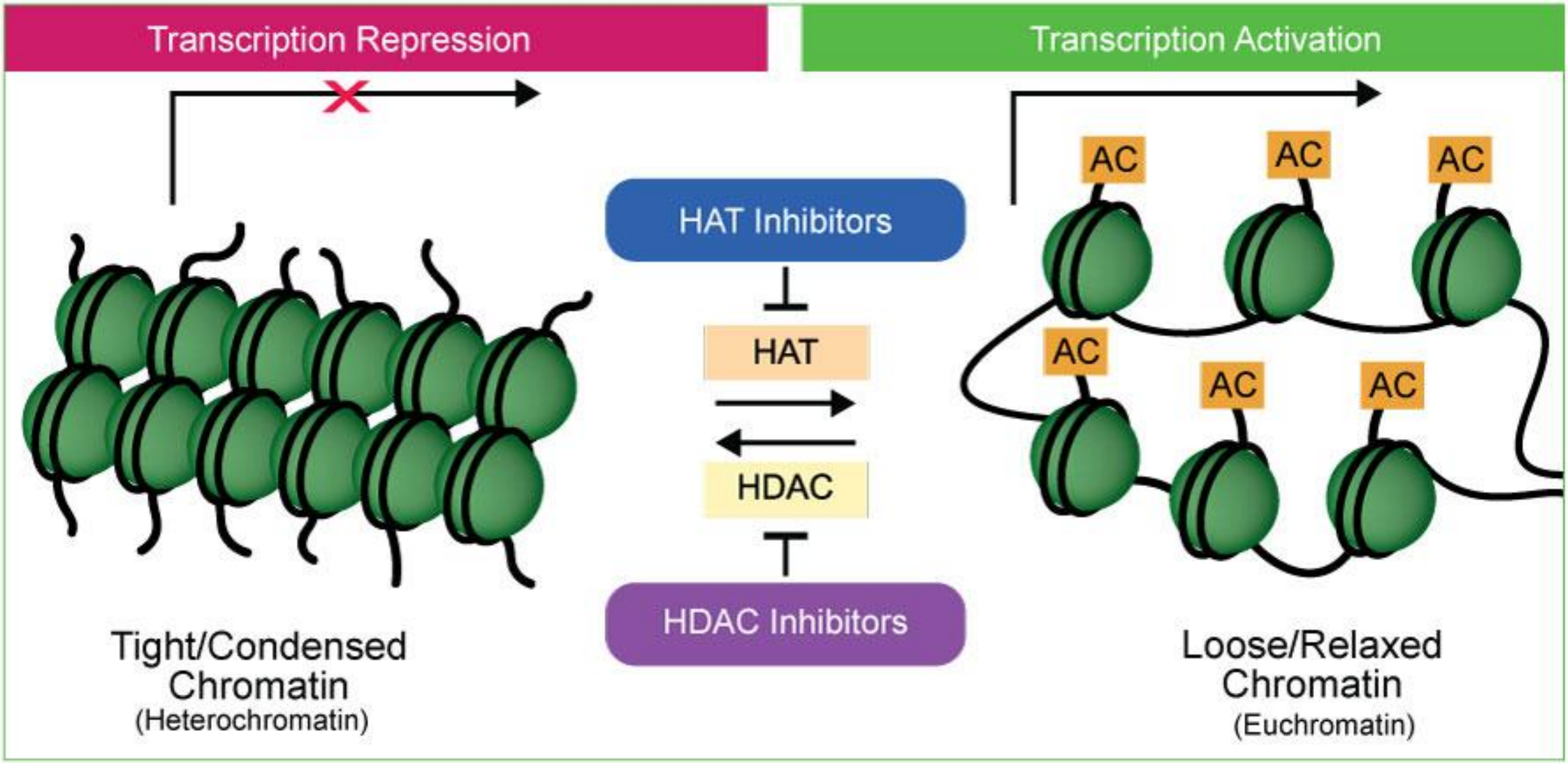


Some of the key histone modifications influencing gene expression. On the left is a representation of closed chromatin, in which the DNA is inaccessible to the transcriptional machinery and transcription is therefore repressed. Modifications to specific histone residues such as the addition of an acetyl group to a lysine residue (via a histone acetyl transferase, or HAT) lead to unfolding of the chromatin (as shown on the right hand side of the figure), which in turn allows the transcriptional machinery to access the DNA, resulting in transcriptional activation. Conversely, removal of this acetyl moiety (through a histone deacetylase, or HDAC) alters the histone configuration, once more returning the chromatin to the closed form. In the case of histone methylation, the effect on chromatin conformation depends on the specific lysine residue being methylated.

Stem Cells and Epigentics



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- Histones are the most eminent DNA-interacting proteins. As the primary protein constituent of chromatin, they form complexes with DNA to compact our large genome for efficient nuclear organization. Histones support critical cellular processes, such as transcription, DNA replication, and DNA repair, via diverse post-translational modifications that moderate their interactions with DNA and other nuclear proteins. Histone marks come in a variety of chemistries, collectively constituting a so-called “histone code” involved in the epigenetic regulation of chromatin. Covalent modifications to histone tails, including methylation, acetylation, ubiquitination, sumoylation, citrullination, and phosphorylation, are well-correlated with chromatin structure and accessibility, which in turn impact transcriptional activation/silencing.

Stem Cells and Epigentics

- Among these modifications, histone acetylation stands out as a prominent mechanism that can profoundly influence chromatin structure and function. Acetylated histones, like H3K9ac, H3K14ac, and H3K27ac, have been linked to an open chromatin configuration and active gene expression state. The transfer of acetyl groups to histone proteins is catalyzed by enzymes known as histone acetyltransferases (HATs). By adding acetyl groups to histones, HATs loosen the tight packaging of DNA around histones, allowing for easier access by transcriptional machinery. This relaxed chromatin structure promotes gene expression, making HATs crucial regulators of transcription.

- HATs are involved in various cellular processes, including embryonic development, differentiation, and cell cycle control. They orchestrate the activation of genes essential for proper growth and development. Histone deacetylases (HDACs), on the other hand, play a counteracting role to HATs. They remove acetyl groups from histones, resulting in a more condensed chromatin structure that restricts access to DNA. This repression of gene expression is crucial for maintaining proper cellular function, regulating cell proliferation, and preventing uncontrolled growth.

- Anomalous changes in histone acetylation can lead down the road to assorted pathological conditions, making this modification and its associated modifying enzymes suitable diagnostic, prognostic, and therapeutic tools in the fight against human disease.

Stem Cells and Epigentics

- Indeed, the dynamic balance between HAT and HDAC activity is fundamental to cellular health. This balance is frequently disrupted in various disease conditions, leading to aberrant gene expression profiles. A classic example is seen in cancer, where an abnormal increase in HDAC activity or a decrease in HAT activity can silence tumor suppressor genes, promoting unchecked cell proliferation and tumorigenesis. Similarly, neurodegenerative disorders like Alzheimer's disease and Huntington's disease have been linked to changes in histone acetylation, with implications for both disease progression and therapeutic strategies.

- Moreover, dysregulated histone acetylation has also been implicated in inflammatory diseases and psychiatric disorders. In these conditions, aberrant gene expression resulting from disrupted HAT and HDAC activities can alter immune responses or neuronal signaling, leading to disease. Thus, the role of histone acetylation in regulating gene expression is critical across a wide spectrum of biological processes and diseases, further underlining the importance of monitoring HAT and HDAC activities.

Stem Cell Metabolism

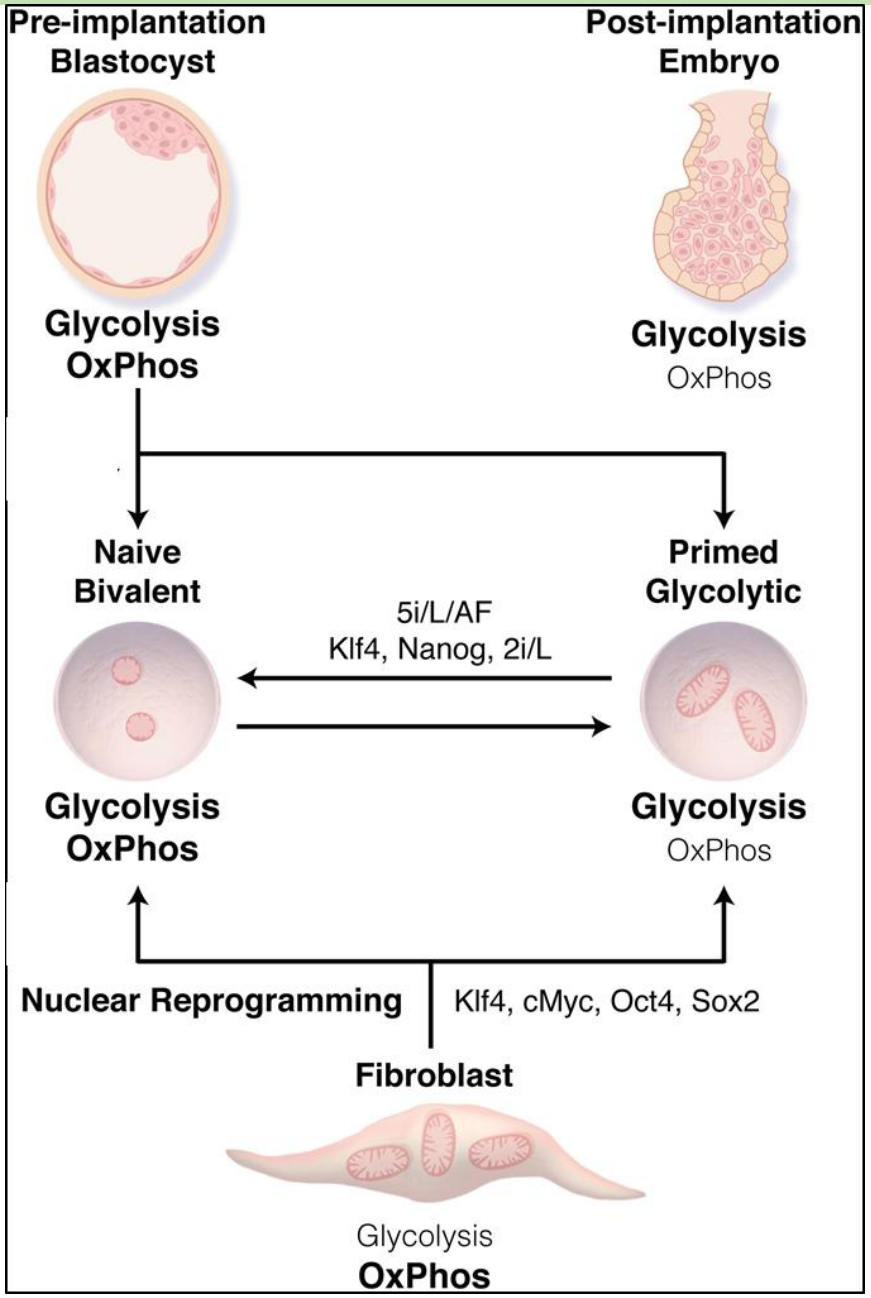
Stem Cell Metabolism

- **Stem cell metabolism** is the process by which stem cells generate energy and produce molecules that help them proliferate, differentiate, and maintain their stemness. Stem cell metabolism is tightly regulated and can be influenced by environmental factors.

- **How stem cell metabolism works:**

- **Quiescent stem cells:** Rely on glycolysis to prevent oxidative stress
- **Proliferating stem cells:** Rely on glycolysis to fuel cell growth, while maintaining low oxidative phosphorylation (OxPhos) levels
- **Stem cells during commitment:** Shift their metabolism to alter cell function.

Stem Cell Metabolism



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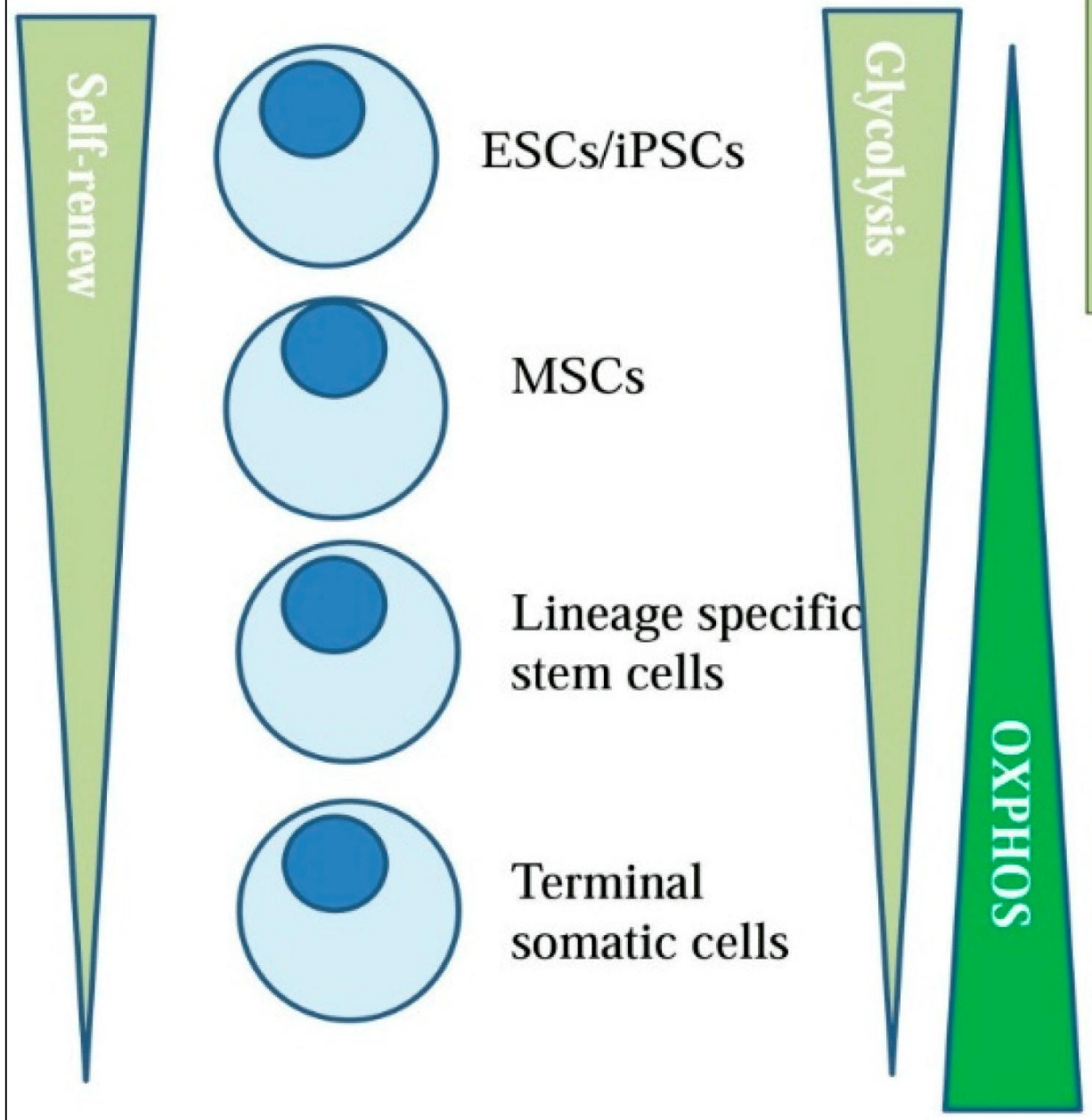

Spherical and cristae-poor mitochondria
Increased expression of LDH
Relative low level of ATP
Elevation in glycolytic key enzymes
Elevation in antioxidant defenses

Tubular and cristae-rich mitochondria
Elevation in TCA cycle
Abundant ATP
Up-regulation of mtDNA
Elevation in mitochondrial key enzymes
Increased ROS production
Increased lipid biosynthesis

Stem Cell Metabolism

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