Megakaryocytes

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- Megakaryocytes are large polyploid cells within the bone marrow that produce circulating platelets.
- Platelets are small anucleate cells that play an essential role in hemostasis, serving to plug holes in blood vessels and initiate coagulation.
- Based on the adult blood volume (5 L), the number of platelets per microliter of blood **($\sim 2 \times 10^5$)**, and their circulatory half-life (10 days), it can be calculated that each day an adult human produces **1×10^{11}** platelets, although in times of increased demand, platelet production can rise tenfold or more.

To function in this role, platelets have unique properties, including:

- the ability to adhere to injured blood vessels and to other platelets.
- undergo dramatic shape change.
- release granules containing vasoactive and thrombogenic substances, and modulate the phospholipid content of their external membrane.
- Platelets also release agents that promote wound healing.

Megakaryopoiesis and the Hematopoietic Stem Cell

- Although megakaryocytes are terminally differentiated cells, they share a number of characteristics with HSCs.
- For example, both megakaryocytes and HSCs express the integrins CD41 (integrin *a*2b) and CD61 (integrin *b*3)
- The integrin *a*2b*b*3 complex forms a fibrinogen receptor that is one of the defining markers of the megakaryocyte lineage, but is now known to be expressed much earlier in hematopoiesis, including on HSCs.
- In addition to similarities in cell surface protein and gene expression patterns, both HSCs and megakaryocytes require thrombopoietin TPO for their growth and survival.

Megakaryocyte Development

- In current models of hematopoiesis, the HSC can either undergo symmetric divisions, resulting in self-renewal, or asymmetric divisions, in which the daughter cells become progressively committed to a specific hematopoietic lineage.
- Lineage commitment is marked by characteristic gene expression patterns and modulated by hematopoietic cytokines.

- Precursors that are committed to the megakaryocyte lineage undergo further maturation before they are capable of platelet production. As they differentiate, megakaryocytes express specific cell surface proteins, become polyploid, develop a complex cytoplasm containing granules and a system of demarcation membranes, and ultimately form proplatelet processes.

- Historically, the developmental stages of megakaryocytes have been described based on morphologic criteria including the quality and quantity of the cytoplasm and the size, lobulation, and chromatin pattern of the nucleus. Thus, cells can be categorized as promegakaryoblasts and stage I megakaryoblasts, stage II promegakaryocytes, stage III mature megakaryocytes, and stage IV megakaryocytes preparing to release platelets from their cytoplasm.

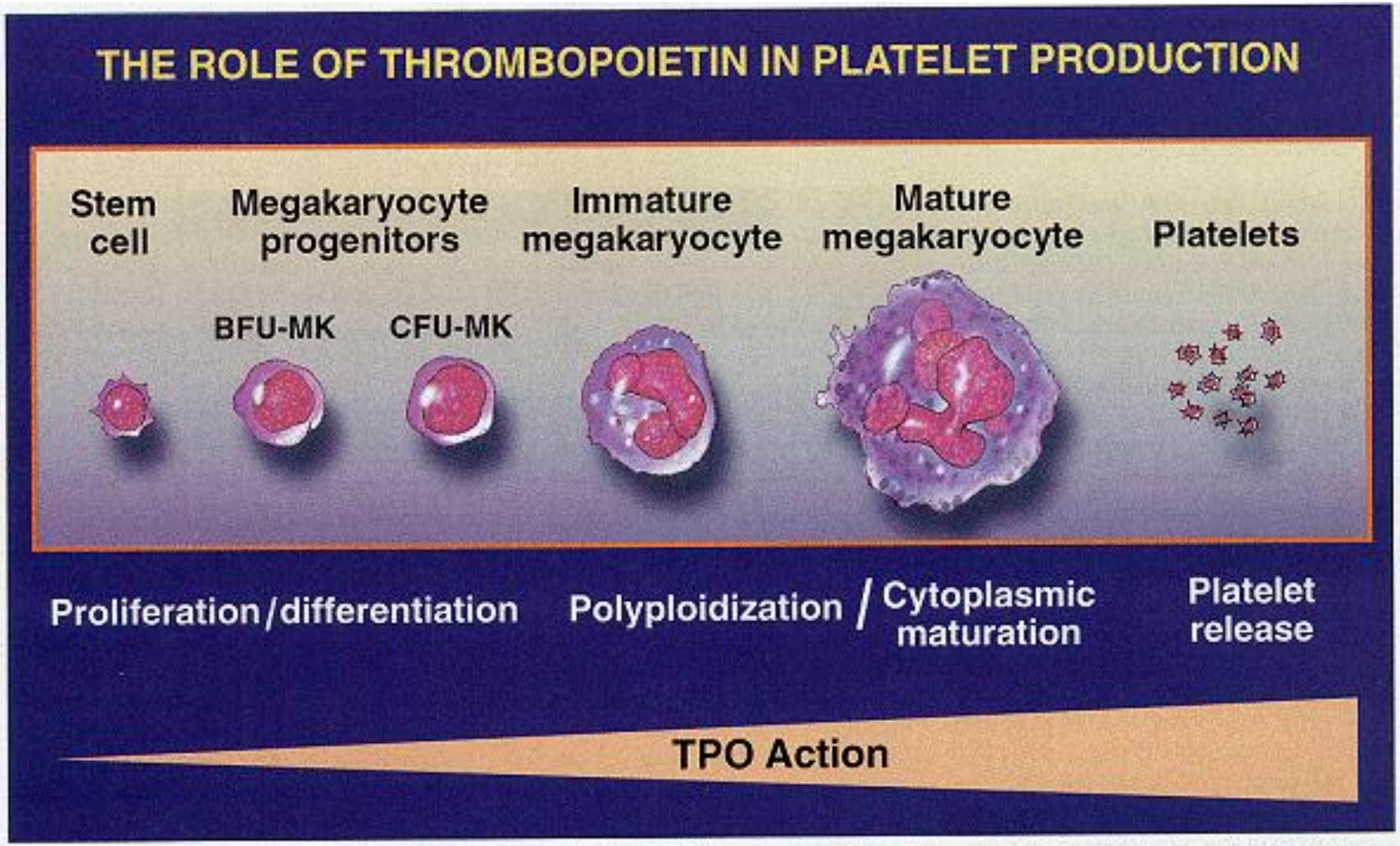
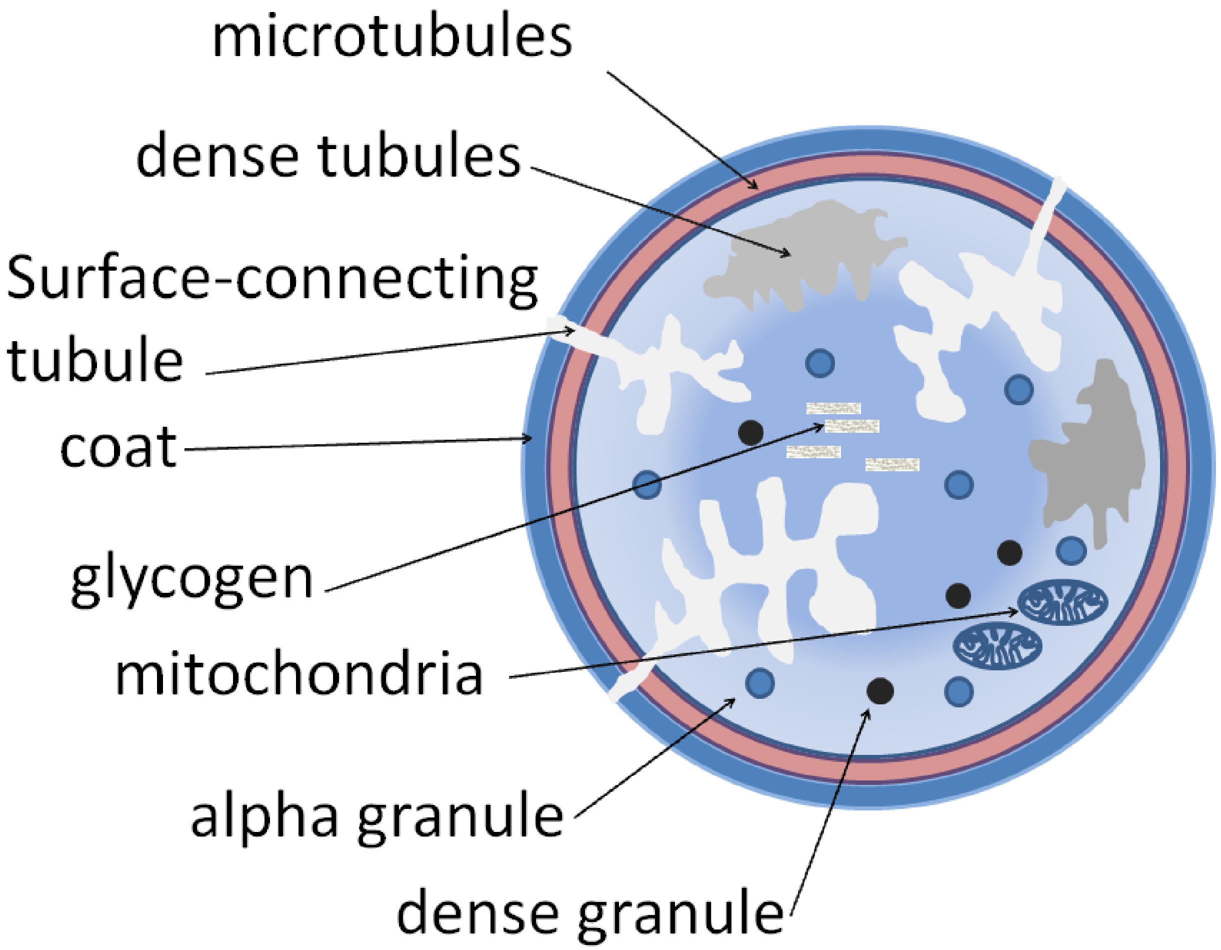


Figure 2: Regulation of Megakaryocytopoiesis by Thrombopoietin—Thrombopoietin acts at multiple levels, including proliferation and differentiation of megakaryocyte (MK) progenitors and maturation of MKs into large polyploid cells capable of producing platelets.[37,40]

- One of the most characteristic and intriguing features of megakaryocyte maturation is the development of polyploidy. As they mature, megakaryocytes switch from mitotic cell cycling to endomitosis, or DNA replication in the absence of nuclear or cytoplasmic division .
- Endomitosis begins late in stage I megakaryoblasts, after sufficient diploid cell divisions have occurred to expand the number of megakaryocytic precursor cells, and is completed by the end of stage II megakaryocyte development.

Platelet Structure

- Light microscopy of Wright-stained smears reveals platelets as small, anucleate (i.e., lacking a nucleus) fragments with occasional reddish granules, measuring approximately 2 μm in diameter with a volume of approximately 8 fl and exhibiting considerable variation in size and shape.
- Platelets released from the marrow under "conditions of stress" such as thrombocytopenia and termed *stress platelets* are large and often beaded in shape, whereas young platelets, recently released from the marrow, are termed *reticulated* in reference to their RNA content and in analogy to young red cell reticulocytes.


microtubules
dense tubules
Surface-connecting
tubule
coat
glycogen
mitochondria
alpha granule
dense granule